



EUROPEAN COMMISSION
DIRECTORATE-GENERAL RESEARCH & INNOVATION



AMENDMENT Reference No AMD-754688-7

Grant Agreement number: 754688 — Systems Medicine of Metabolic-Signaling Networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)

The parties agree to amend the Grant Agreement as follows ('Amendment'):

1 . Removal of a beneficiary whose participation was terminated (for other reasons)

The participation of the following beneficiary has been terminated:

- UNIVERSITY OF DURHAM (UDUR) - on 1 February 2019

This implies the **following changes** to the Grant Agreement:

- The 'termination date' is added, for the beneficiary, in the **Preamble**:

UNIVERSITY OF DURHAM (UDUR), established in STOCKTON ROAD THE PALATINE CENTRE, DURHAM DH1 3LE, United Kingdom, VAT number: GB675542510,
- until 1 February 2019

In accordance with Article 50 of the Grant Agreement, the beneficiary's obligations continue to apply after termination.

2 . Addition of a new beneficiary

The following new beneficiary is added:

- UNIVERSITAET INNSBRUCK (UIBK) — as from 1 February 2019

This implies the **following changes** to the Grant Agreement:

- The new beneficiary and the 'accession date' is added to the **Preamble**:

"UNIVERSITAET INNSBRUCK (UIBK), established in INNRAIN 52, INNSBRUCK 6020, Austria, VAT number: ATU57495437, represented for the purposes of signing the Agreement by Head of Department, Eduard STEFAN — as from 1 February 2019"

3. Change of coordinator

As from 1 February 2019, ACADEMISCH ZIEKENHUIS GRONINGEN will no longer assume the role of coordinator and will be replaced by UNIVERSITAET INNSBRUCK.

This implies the **following changes** to the Grant Agreement:

- The 'handover date' and the new role are added to the **Preamble**:

“1. ‘the coordinator’:

ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG), established in HANZEPLEIN 1, GRONINGEN 9713 GZ, Netherlands, VAT number: NL800866393B01, represented for the purposes of signing the Agreement by Loket LCR — as coordinator until 31 January 2019

UNIVERSITAET INNSBRUCK (UIBK), established in INNRAIN 52, INNSBRUCK 6020, Austria, VAT number: ATU57495437, represented for the purposes of signing the amendments to the Agreement by Head of Department, Eduard STEFAN — as from 1 February 2019".

4. Change of Annex 1 (description of the action)

Annex 1 is changed and replaced by the Annex 1 attached to this Amendment.

5 . Changes of Annex 2 (estimated budget)

Annex 2 is changed and replaced by the Annex 2 attached to this Amendment.

6. Change of bank account for payments

The bank account for payments is changed.

This implies the **following changes** to the Grant Agreement:

- The bank account is replaced in **Article 21.8**:

"Name of bank: HYPO TIROL BANK AG GEST.UNIVERSITAETSKLINIK
Full name of the account holder: UNIVERSITAT INNSBRUCK BANKKONTO FUR 27 UG
FORSCHUNGSPROJ P7190 029 011
Full account number (including bank codes):
IBAN code: AT475700021011130470"

All other provisions of the Grant Agreement and its Annexes remain unchanged.

This Amendment **enters into force** on the day of the last signature.

This Amendment **takes effect** on the date on which the amendment enters into force, except where a different date has been agreed by the parties (for one or more changes).

Please inform the other members of the consortium of the Amendment.

SIGNATURES

For the coordinator

For the Commission

Enclosures:

Annex 1

Annex 2



EUROPEAN COMMISSION
DIRECTORATE-GENERAL RESEARCH & INNOVATION
Innovative tools, technologies and concepts in health research



ANNEX 1 (part A)

Research and Innovation action

NUMBER — 754688 — MESI-STRAT

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1.1. The project summary

Project Number ¹	754688	Project Acronym ²	MESI-STRAT
One form per project			
General information			
Project title ³	Systems Medicine of Metabolic-Signaling Networks: A New Concept for Breast Cancer Patient Stratification		
Starting date ⁴	01/01/2018		
Duration in months ⁵	57		
Call (part) identifier ⁶	H2020-SC1-2017-Two-Stage-RTD		
Topic	SC1-PM-02-2017 New concepts in patient stratification		
Fixed EC Keywords	Systems medicine		
Free keywords	patient stratification; systems bio-medicine; breast cancer; cancer metabolism; cancer signaling		
Abstract ⁷			
Breast cancer (BC) is a complex disease with high prevalence in the EU. 75% of the tumors are estrogen receptor-positive (ER+), and are treated with endocrine therapies (ET). MESI-STRAT will develop new concepts for knowledge-based stratification of patients into subgroups with different ET resistance mechanisms. We will establish predictive models for (1) patient stratification prior and during ET; (2) recurrence risk assessment when ending ET; (3) marker panel development to guide targeted therapies for ET-resistant patients; (4) novel ET resistance mechanism-based therapy design. The unique collection of matched BC tissue, serum, and >10 years follow-up from the patient organization PATH is essential for the longitudinal analysis of ET resistance and relapse. Our team of oncologists, modelers, bioinformaticians and experimentalists will develop new computational models in combination with network analyses and pharmacogenomics, to integrate multi-omics data and explore metabolic and signaling (MESI) networks driving ET resistance. Metabolite marker panels measured in biological fluids will enable patient stratification, resistance monitoring and clinical decision-making. This is a new concept as BC metabolism is poorly explored for diagnostics and therapy. Upon successful validation in preclinical models, the predictive marker panels and related treatments will be jointly investigated by our clinical and industrial partners in clinical studies. Our 3 SMEs will closely co-develop the research, and directly exploit the MESI-STRAT results. BC accounts for the highest cancer-related health-care costs in the EU. Our stratification concepts will increase cost effectiveness and the patients' quality of life by (1) avoiding ineffective therapies, (2) marker detection in body fluids without surgical interventions, and (3) reducing clinical trial cohorts by improved stratification. This will accelerate the translation of MESI-STRAT results into medical use.			

1.2. List of Beneficiaries

Project Number ¹	754688	Project Acronym ²	MESI-STRAT
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List of Beneficiaries

No	Name	Short name	Country	Project entry date ⁸	Project exit date
1	UNIVERSITAET INNSBRUCK	UIBK	Austria	01/02/2019	
2	STIFTUNG PATIENTS TUMORBANK OF HOPE- DIE PATIENTENEIGENE TUMORGEWEBEBANK DER HOFFNUNG (PATH)	PATH Biobank	Germany		
3	UNIVERSITAETSKLINIKUM HEIDELBERG	UKL-HD	Germany		
4	DEUTSCHE KREBSFORSCHUNGSZENTRUM HEIDELBERG	DKFZ	Germany		
5	FUNDACIO PRIVADA INSTITUT D'INVESTIGACIO ONCOLOGICA DE VALL-HEBRON	VHIO	Spain		
6	DE DUVE INSTITUTE	DDI	Belgium		
7	UNIVERSITETET I BERGEN	UiB	Norway		
8	UNIVERSITETET I TROMSOE	UiT	Norway		
9	UNIVERSITY OF NEWCASTLE UPON TYNE	UNEW	United Kingdom		
10	CHARITE - UNIVERSITAETS MEDIZIN BERLIN	Charité	Germany		
11	UNIVERSITY OF DURHAM	UDUR	United Kingdom		01/02/2019
12	NEUROIMMUN GMBH	Neuroimmun GmbH	Germany		
13	SYSBIOSIM BV	SysBioSim B.V.	Netherlands		
14	HITS GGMBH	HITS	Germany		
15	ACADEMISCH ZIEKENHUIS GRONINGEN	UMCG	Netherlands		

1.3. Workplan Tables - Detailed implementation

1.3.1. WT1 List of work packages

WP Number ⁹	WP Title	Lead beneficiary ¹⁰	Person-months ¹¹	Start month ¹²	End month ¹³
WP1	Data survey of existing patient samples and materials	2 - PATH Biobank	27.00	1	57
WP2	Setup and maintenance of MESI-SEEK data and model management platform	14 - HITS	31.00	1	57
WP3	Assess SIGNALLING NETWORKS for model parameterization & validation	10 - Charité	121.00	7	57
WP4	Assess METABOLIC NETWORKS for model parameterization and validation	7 - UiB	112.00	7	57
WP5	Integrative MESI network modeling and network analyses	9 - UNEW	172.00	7	57
WP6	Preclinical and clinical trials without drug treatments in ER+BC patient-derived models and the longitudinal PATH cohort	4 - DKFZ	58.50	1	57
WP7	Preclinical and clinical trials with drug treatments: preclinical drug tests, WOO, ET Termination and Intervention Validation Trials	3 - UKL-HD	104.00	1	57
WP8	Project coordination: management and communication	1 - UIBK	38.00	1	57
WP9	Dissemination, exploitation, and communication	13 - SysBioSim B.V.	30.50	1	57
WP10	Ethics requirements	1 - UIBK	N/A	1	57
Total			694.00		

1.3.2. WT2 list of deliverables

Deliverable Number¹⁴	Deliverable Title	WP number⁹	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
D1.1	Data management plan	WP1	14 - HITS	ORDP: Open Research Data Pilot	Confidential, only for members of the consortium (including the Commission Services)	6
D2.1	Omics data in public resources (EMBL-EBI & others)	WP2	14 - HITS	Other	Confidential, only for members of the consortium (including the Commission Services)	57
D3.1	Signaling time course datasets for ER+BC cell lines	WP3	10 - Charité	Report	Confidential, only for members of the consortium (including the Commission Services)	18
D3.2	Signaling marker panels for patient derived models and samples measured	WP3	10 - Charité	Report	Confidential, only for members of the consortium (including the Commission Services)	57
D4.1	Metabolite time course datasets for ER+BC cell lines	WP4	7 - UiB	Report	Confidential, only for members of the consortium (including the Commission Services)	18
D5.1	Computational signaling and metabolic models for ER+BC cell lines	WP5	9 - UNEW	Other	Confidential, only for members of the consortium (including the Commission Services)	18
D5.2	First MESI model parametrized for patient samples	WP5	9 - UNEW	Other	Confidential, only for members of the consortium (including the Commission Services)	27
D5.3	First customized model for pharma	WP5	13 - SysBioSim B.V.	Other	Confidential, only for members of the consortium (including the Commission Services)	36

Deliverable Number¹⁴	Deliverable Title	WP number⁹	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
D6.1	Preclinical Model-Subgroup Assignment	WP6	4 - DKFZ	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D7.1	WOO trial: First study subject approvals package	WP7	3 - UKL-HD	Report	Confidential, only for members of the consortium (including the Commission Services)	6
D7.2	ET termination trial: First study subject approvals package	WP7	2 - PATH Biobank	Report	Confidential, only for members of the consortium (including the Commission Services)	6
D7.3	WOO trial: Midterm recruitment report	WP7	3 - UKL-HD	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D7.4	ET termination trial: Midterm recruitment report	WP7	2 - PATH Biobank	Report	Confidential, only for members of the consortium (including the Commission Services)	30
D7.5	WOO trial: Report on status of posting results	WP7	3 - UKL-HD	Report	Public	57
D7.6	ET termination trial: Report on status of posting results	WP7	2 - PATH Biobank	Report	Public	57
D8.1	Management plan	WP8	1 - UIBK	Report	Confidential, only for members of the consortium (including the Commission Services)	3
D9.1	Dissemination & exploitation plan	WP9	13 - SysBioSim B.V.	Report	Confidential, only for members of the consortium (including the Commission Services)	3
D9.2	Communication plan	WP9	2 - PATH Biobank	Report	Confidential, only for members	3

Deliverable Number¹⁴	Deliverable Title	WP number⁹	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
					of the consortium (including the Commission Services)	
D9.3	MESI-STRAT website with continuous updates	WP9	1 - UIBK	Websites, patents filling, etc.	Public	6
D10.1	NEC - Requirement No. 1	WP10	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D10.2	POPD - Requirement No. 2	WP10	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D10.3	H - Requirement No. 3	WP10	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D10.4	HCT - Requirement No. 4	WP10	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D10.5	A - Requirement No. 5	WP10	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D10.6	GEN - Requirement No. 7	WP10	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	3
D10.7	H - Requirement No. 8	WP10	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	3

1.3.3. WT3 Work package descriptions

Work package number ⁹	WP1	Lead beneficiary ¹⁰	2 - PATH Biobank
Work package title	Data survey of existing patient samples and materials		
Start month	1	End month	57

Objectives

The overall aim of WP1 is to provide the biological samples, pre-clinical models, clinical samples (for details see clinical annex), and data to derive model-based MESI marker panels allowing the prediction and monitoring of ET responses, and the validation of established and novel (combinatorial) therapies for newly identified ER+BC subgroups. The specific objectives of WP1 are to provide

1. a comprehensive overview of pseudonymized clinical data, patient materials and patient-derived cell and PDX models in the MESI-REPOSITORY
2. ER+BC cell lines, PDX, matched cultures and patient material for preclinical trials
3. matched fresh frozen ER+BC tissue, serum, and pseudonymized patient data from the PATH collection.
4. longitudinally collected serum and urine from ER+BC patients at relapse and under intensified treatments (PATH and clinical studies performed by partners and collaborators)
5. biobanking of samples and pseudonymized clinical data from our WOO and ET Termination trials

Description of work and role of partners

WP1 - Data survey of existing patient samples and materials [Months: 1-57]

PATH Biobank, UIBK, UKL-HD, DKFZ, VHIO, DDI, HITS

WP1 will provide a searchable database (MESI-REPOSITORY) of fresh frozen and FFPE tissue, se-rum/plasma, urine, and pseudonymized patient data (treatment and follow-up) from BC patients from existing clinical cohorts (PATH, observational studies UKL-HD, UMCG, VHIO), blood, and urine from longitudinal collection in the framework of MESI-STRAT and from relevant BC clinical trials. In addition, this repository will incorporate patient-derived model systems (matched cultures of primary human BC cells and PDX models) (VHIO & DDI). WP1 thus provides the basis for the analyses performed in WPs 2–7 of MESI-STRAT and will also incorporate pseudonymized clinical data and biological samples of WP7 into the MESI-REPOSITORY.

As the MESI-STRAT marker panels to be derived are hitherto unknown, our sample collection will need to allow a variety of measurements. Therefore, patient cohorts will be built up in a comprehensive way using the biobanks (fresh frozen and FFPE tissue, blood, serum, urine) and sample collections from studies for later validation of all potential markers. Clinical data to be collected will/can include: (i) clinical-pathological characteristics of the patients (age, tumor type, grading, staging, imaging, TNM status, Ki67 status); (ii) therapy and response (follow-up); (iii) amount and type of material present at either the clinics or biobanks; (iv) sufficient material to determine molecular features (e.g., mutations status by panel sequencing).

MESI-STRAT partners will provide patient samples for MESI-STRAT

(see clinical annex for details on the clinical trials). Their existing sample collections include:

- PATH BC biobank: 4022 matching fresh frozen ER+BC tissues, adjacent normal tissues and sera from BC patients with full documentation; >80 postmenopausal and >50 premenopausal with high-risk BC, (as defined below, task 1.1) respectively; 106 samples of patients who developed distant metastasis during follow-up; 1847 patients stable >5 years; 451 patients having received 5 years of ET in the MESI-STRAT study period.
- UKL-HD: >300 longitudinal serum/plasma samples from the PRAEGNANT study (patients with advanced, incurable, metastatic breast cancer under intensified treatments, sampled at each progression); samples from 5 interventional clinical trials with ET, CDK4/6 inhibitors or HER2 inhibitors, >70 serum, plasma, and urine samples as well as tissues of patients from the GEKKO study (at diagnosis); Male cohort: approx. 100 FFPE samples from male BRCA mutant BC patients.
- UMCG: 200 samples from the IMPACT Breast trial (non-rapidly progressive MBC patients eligible for first-line systemic therapy undergoing molecular imaging); 20 samples from FDHT PET AND BICALUTAMIDE IN MBC trial; Male cohorts: 200 serum/plasma samples & fresh frozen BC tissue prospectively collected from males with BC; 800 FFPE samples retrospectively collected from males with BC.
- VHIO: samples from 9 interventional clinical trials with CDK4/6 inhibitors, PI3K inhibitors, Akt inhibitors, tyrosine kinase inhibitors, or mTOR inhibitors (Everolimus, dual inhibitors)

Feasibility of sample provision and biobanking

PATH Biobank, UKL-HD/NCT, and UMCG have longstanding expertise in biobanking and contribute to the European Biobanking and Biomolecular Resource Research Infrastructure (BBMRI-ERIC) initiative. Thus, our partnering biobanks will immediately contribute to our project by providing retrospective samples and actively banking the prospective samples collected in the frame of MESI-STRAT (see letter from the UKL-HD/NCT biobank). This will ensure that the biological samples collected in the frame of MESI-STRAT will be available for the scientific community.

Task 1.1 Provision of sera and selected BC tissues at diagnosis from high-risk and low-risk ER+ BC patients. Partners: PATH

High-risk and low-risk ER+BC patients will be selected according to the criteria below. 50 sera of each pre- and postmenopausal high- and low-risk ER+BC patients will be provided (200 sera in total) and corresponding BC tissues of approx. 5 patients per group (20 BC tissues in total).

Selection of ER+BC patients (see table in Section 3.1.3 of Part B)

>80 postmenopausal and >50 premenopausal patients that fulfil these criteria are available per group in the PATH cohort. To harmonize the collections, we will include the following most common histopathological tumor types: invasive carcinoma of no special type (NST, also known as invasive ductal carcinoma) and invasive lobular carcinoma.

Task 1.2 Provision of sera and selected ER+BC tissues at diagnosis of patients who remained stable for >5 years and of patients who developed relapse/distant metastasis. Partners: PATH

75 sera of ER+ BC patients who developed distant metastasis during follow-up and 150 sera of patients who remained stable for >5 years will be provided. The tumors at diagnosis will be matched for tumor size, lymph node affection, and grade. Representative BC tissues, approx. 10 for the ones with distant metastasis during follow-up and 20 for the controls, will be provided for the analysis of the mechanisms underlying the MESI marker panel differences in BC tissue.

Task 1.3 Biobanking and provision of sera and urine from ER+BC patients before and after termination of ET and from ER+BC patients at relapse and under intensified treatment. Partners: PATH, UKL-HD, UIBK VHIO

Provision of serum and urine and pseudonymized clinical data of patients at relapse and under intensified treatments in the frame of clinical studies performed by MESI-STRAT partners (UKL-HD, VHIO). Provision of serum and urine from stable patients matched to the patients from which samples were obtained in the frame of the above studies (PATH).

Task 1.4 Survey of ER+BC cell lines and of matched patient-derived cell and PDX models and corresponding clinical samples. Partners: VHIO, DDI UIBK

ER+ BC cell lines: Suitable ER+BC cell lines are widely used in cancer research and will be used by MESI-STRAT for the basic parameterization of dynamic computational models specific for ER+ BC (WPs 3-5). They will be obtained from ATCC and distributed across the MESI-STRAT consortium and will be regularly genotyped to ensure that all partners work with the same material. We will work primarily with MCF-7, ZR-75-1, and BT474 cells. Further ER+BC cell lines such as T47D and others will be considered as needed.

ER+BC PDX models, matched cultures, and patient samples: Nine ER+BC PDX models from VHIO (2 from primary, 5 from metastatic and 2 from both primary and metastatic tumors) (VS), 35 PDX models from the EuroPDX consortium (VS), matching 3D cell cultures for 9 ER+BC PDX models (VS), immunocompetent ER+BC PDX models (DDI, BE). Further ER+BC models can be established by VS if needed.

Task 1.5 Setup of the MESI-REPOSITORY encompassing all patient materials, pseudonymized clinical data, and models. Partners: DKFZ, PATH, UKL-HD, UMCG, VHIO, HITS, UIBK

The MESI-REPOSITORY will enable all consortium members to gain insight into the available patient-derived cell and PDX models, pseudonymized patient samples and clinical data. WP1 will document pseudonymized patient data including age, BC type, grading, staging, receptor expression, clinical parameters and partner site from existing collections as well as from patients that will be prospectively recruited (WP7). The available data will be used by other WPs for selection of tissue/serum/urine samples for signaling, omics (WP3) and metabolic analyses (WP4), and of tumor samples/PDX for model verification and clinical validation analyses (WPs 3, 4, 7). The MESI-REPOSITORY will be set up at the central DataCenter of the IT Core Facility of the DKFZ, which complies with all regulations of data safety necessary for storage of personal data and protection of confidentiality of individual records (for details, see section 5.1.4 Personal Data).

Participation per Partner

Partner number and short name	WP1 effort
1 - UIBK	1.00

Partner number and short name	WP1 effort
2 - PATH Biobank	9.00
3 - UKL-HD	10.00
4 - DKFZ	1.00
5 - VHI	3.00
6 - DDI	1.00
14 - HITS	2.00
Total	27.00

List of deliverables

Deliverable Number¹⁴	Deliverable Title	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
D1.1	Data management plan	14 - HITS	ORDP: Open Research Data Pilot	Confidential, only for members of the consortium (including the Commission Services)	6

Description of deliverables

D1.1 : Data management plan [6]

Data management plan

Schedule of relevant Milestones

Milestone number¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
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Work package number⁹	WP2	Lead beneficiary¹⁰	14 - HITS
Work package title	Setup and maintenance of MESI-SEEK data and model management platform		
Start month	1	End month	57

Objectives

Key property of MESI-STRAT data management is the adherence to the H2020 Programme Guidelines on FAIR Data Management, and participation in the open data pilot. The overall aim of WP2 is to curate and preserve the generated data and make it available to all MESI-STRAT partners and external users in a user-friendly and securely accessible format. The specific objectives of WP2 are the

1. creation of the MESI-STRAT data management plan (DMP, outlined in section 2.2.2), according to the consortium agreement
2. setup and maintenance of the MESI-SEEK data management platform which implements the DMP and allows compliant and simple management of scientifically relevant pseudonymized patient data; of raw data from sequencing, proteomics, and metabolomics (WP3 and 4) including their deposition into publicly hosted databases; and analyzed data from sequencing, proteomics, metabolomics, molecular kinetic measurements and computational models, using MIBBI-compliant templates

Description of work and role of partners

WP2 - Setup and maintenance of MESI-SEEK data and model management platform [Months: 1-57]

HITS, UIBK, PATH Biobank, UKL-HD, DKFZ, UiB, UNEW, Charité

In collaboration with EMBL-EBI and FAIRDOM, as well as ELIXIR where appropriate.

WP2 interacts with all other WPs and coordinates the management of research data arising from MESI-STRAT. All WPs have the primary responsibility to manually upload their data and models according to agreed standards as soon as they are available. This will be supported by the FAIRDOM team, and the scientists appointed at HITS gGmbH and UiB. They will represent MESI-STRAT in the FAIRDOM PALS team and attend the PAL focus group meetings that FAIRDOM holds twice a year. Furthermore, they will have visitor status at EMBL-EBI (see letters of support), and will interact closely with the IntAct and ATLAS teams at EBI.

Task 2.1 Setting up the data management plan (DMP)

The agreement with all WP leaders on data management, detailed in section 2.2.2 and formalized in the consortium agreement, is already in place and will be implemented upon project start. Within the first six months a detailed DMP will be setup together with the other WP leaders, to establish a data management framework tailored to the needs of each WP. The DMP will (i) ensure efficient and accurate standardized data exchange within MESI-STRAT and facilitates data release and sharing with the scientific community in line with patient privacy regulations and H2020 guidelines on open access to research data; and (ii) coordinate the primary analysis of all omics datasets and their conversion to formats easily accessible to modelers and bioinformaticians.

The MESI-STRAT DMP is based on the outcomes of the FAIRDOM project (FAIR Data Operations Mod-els, <http://www.fair-dom.org>) and will be run by HITS, one of the core FAIRDOM partners. FAIRDOM provides the FAIRDOMHub site for data sharing and the openSEEK platform – a user-friendly, public hosted service which allows sharing of data and computational models. The FAIR (Findability, Accessibility, Interoperability, Reusability) data management guidelines will be the basis for our DMP and require definition of (i) the data standards applied (see 2.2.2, Table 7); (ii) data exploitation and sharing/ accessibility for verification and reuse. As detailed in 2.2.2 MESI-STRAT will provide open access whenever possible legally, ethically, and without compromising IPR and patient privacy regulations. The data will be citable using DOIs, Research Objects and Combine Packages can easily be generated and exported into OpenAIRE Zenodo website. (iii) data curation and preservation. Curation services is a HITS core activity, and data will be preserved for at least 10 years beyond the end of the project.

Task 2.2 Setting up the openSEEK database MESI-SEEK

The DMP will be implemented into the openSEEK instance for the MESI-STRAT project: MESI-SEEK. HITS will set up MESI-SEEK as well as a project area inside the FAIRDOM Hub. MESI-SEEK is characterized by a transparent, searchable structure, interlinking processed data to raw data, metadata and computational models according to the ISA standard (i.e., structuring as Investigations, Studies, and Assays). SOPs will be stored and linked to the data. In particular, SOPs that will be used by multiple partners, like protocols for cell cultivation and analytical methods

(metabolomics, transcriptomics, proteomics) for harmonized signaling (WP3) and metabolic (WP4) data acquisition for model parameterization, will be standardized and shared via FAIRDOMHub.

- Long-term data preservation: FAIRDOMHub offers management facilities, secure and long-term storage of up to 1.5 TB, the ability to link data with external resources and publications, and data and model curation support that are funded within this project. The data availability will be guaranteed 10 years beyond the end of the project. This is a prerequisite for making the data citable. The ownership of uploaded data and models remains with the groups that produced them and is clearly visible within openSEEK. By agreement of the MESI-STRAT partners, the uploaded data will be accessible to all partners. The PIs take the role of “gatekeepers” who decide if and when data sets are opened to the outside world, typically in conjunction with a scientific publication. DOI references to data guarantee long-term citability. Publication of data sets and models via a structured, searchable, and citable OpenSEEK database will enhance re-use of data and models.
- Linkage with public data: Next to MESI-SEEK, we will also refer to available public data and link them with data generated by MESI-STRAT to enable and facilitate their integrated processing and analysis. The following data sets are currently publicly available and will be integrated with MESI-SEEK upon project start: see tables in Section 3.1.3 of Part B.

Task 2.3. Build adaptation tools to simplify DMP adherence

Tools for DMP adherence will be based on available tools including RightField for creation of ontology-rich data templates; iPython for web-based interactive software; OpenRefine interactive tool for spreadsheet transformation. The priorities will be based on the data flow in the project and the needs of the partners.

Task 2.4 Integration of pseudonymized patient data

In collaboration with WP1 and in line with the DMP and informed consent for the respective patients and all applicable regulatory constraints concerning data security and privacy (see DMP, section 2.2.2), MESI-SEEK will use the specimen/sample support of SEEK to set up a data collection containing pseudonymized patient information relevant for the scientific analyses within MESI-STRAT in a user-friendly and extendable format.

Task 2.5 Management of unprocessed and analyzed omics data

WP2 will coordinate collection of sequencing, proteomics, and metabolomics data, molecular kinetic measurements and biomodels (WP3-5), using MIBBI compliant tables. Analyzed data will be catalogued and deposited in MESI-SEEK to make it a one-stop shop for project members that visualizes the available data and databases managing them, and enables integration of the multidimensional data types in WP5.

Raw data that presents potential issues regarding data security and privacy will be securely stored, and sharing will be restricted, according to the informed consent, the applicable legal regulations, and best practice as established by TCGA (see section 2.2.2, Table 7). Raw data that does not fall under regulatory constraints regarding patient data safety and privacy will be catalogued in MESI-SEEK. The raw data will remain stored at the host institutions generating them, and will be regularly registered with MESI-SEEK following a standardized protocol. This is particularly important upon publication following open access standards, in line with the DMP, to provide a transparent workflow and ensure long-term mining. To ensure accessibility and long term preservation our raw data will also be submitted to repositories linked to EMBL-EBI (letters included from IntAct, PRIDE and ATLAS, ENA). All these databases are member projects of ELIXIR, which guarantees wide reusability of our data. We will interact with the ELIXIR Human Genomics and Translational Data team to ensure that our methods evolve with current best practice.

Task 2.6 Provide the required input to WP5 (computational modeling and network analyses).

Model hosting. OpenSEEK includes the JWS Online tool (<http://www.jjj.bio.vu.nl/>) which hosts computational models in an interactive way allowing partners to run the models directly from OpenSEEK without needing specialized programming expertise. This improves interaction between experimentalists and modelers. JWS is SBML compliant, and the FAIRDOM team provides technical curation of the models (e.g., for standard identifiers). We will deposit ODE models and genome-scale metabolic models together with selected simulations. The modelers will document which data have been used for designing them. Model annotation will follow MIRIAM standards, and model versions will be distinguished by different names and precise annotation of updates. The project will contribute to JWS Online cost on a per-model basis.

Integrated omics platform. Once the bulk of the omics data sets are available, we will develop an integrative platform which handles transcriptomics, proteomics, and metabolomics data under a unified schema. It will then be visualized in Expression Atlas, the EMBL-EBI value-added resource for functional omics data, alongside other comparable studies.

Participation per Partner

Partner number and short name	WP2 effort
1 - UIBK	1.00
2 - PATH Biobank	1.00
3 - UKL-HD	1.00
4 - DKFZ	1.00
7 - UiB	7.00
9 - UNEW	1.00
10 - Charité	1.00
14 - HITS	18.00
Total	31.00

List of deliverables

Deliverable Number¹⁴	Deliverable Title	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
D2.1	Omics data in public resources (EMBL-EBI & others)	14 - HITS	Other	Confidential, only for members of the consortium (including the Commission Services)	57

Description of deliverables

D2.1 : Omics data in public resources (EMBL-EBI & others) [57]
 Omics data in public resources (EMBL-EBI & others)

Schedule of relevant Milestones

Milestone number¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS4	Prediction of first subgroup specific marker panels	9 - UNEW	30	Prediction of first subgroup specific marker panels: Model predictions in MESI-SEEK

Work package number ⁹	WP3	Lead beneficiary ¹⁰	10 - Charité
Work package title	Assess SIGNALLING NETWORKS for model parameterization & validation		
Start month	7	End month	57

Objectives

The overall aim of WP3 is to generate quantitative and time-resolved data for network reconstruction (WP5), focusing on the MAPK/mTOR/ER signaling network and its connections to metabolic networks (Trp, NAD, and energy metabolism, WP4). The specific objectives of WP3 are

1. time-resolved multiplex measurements of signaling components (level, activation state) in ER+BC cell lines. Protocols for signaling analyses will be harmonized with those for metabolic analyses (WP4), to provide matched signaling and metabolic data for model parameterization (WP5).
2. perturbation screens to gain information on metabolic and signaling network connectivities as a basis to establish MESI network topology for models in WP5.
3. analyses of protein levels and phosphorylation for individualized network adaptation and verification of model predictions in cell cultures, patient-derived cultures, PDX, and patient samples.
4. sequencing and proteomic analyses of selected samples representative of ER+ BC patient subgroups (cell lines, PDX + matched cultures, patient samples), if data is not available from public sources.

Description of work and role of partners

WP3 - Assess SIGNALLING NETWORKS for model parameterization & validation [Months: 7-57]

Charité, UIBK, DKFZ, VHIO, UiB, HITS

Task 3.1 Signaling data for dynamic model parameterization. Partners: CHAB (CS) with UIBK (KT).

To derive parameters required for model parameterization, perturbation studies with stimulators and inhibitors of the MAPK, mTOR, and ER networks will be performed, as described by CS (27,39) and KT/DPS (31,40,41).

Task 3.1.1. Time course data. ER+BC cell lines (defined in WP1, task 1.4) will be analyzed regarding receptor expression and activation (e.g., ER, HER2, IGF-R). Afterwards, stimulators for signaling networks in ER+BC cells will be identified by testing several activators/inhibitors of MESI networks, such as

- (a) growth factors: estradiol (E2), insulin/IGF, EGF family members;
- (b) metabolites: Trp deprivation/supplementation, nicotinamide deprivation, readdition of Trp metabolites (including L-Kyn & KA).

We will measure over time the response dynamics of the targeted signaling network components: RTK; adapters, such as Shc and IRS; mTOR and MAPK upstream regulators, incl. PTEN, Akt, and TSC1/2; mTORC1/2 itself; mTOR modulators, incl. PRAS40 or Deptor; mTOR substrates, incl. p70S6K, 4E-BP, and ULK1; MAPK pathway components, incl. CRAF, BRAF, HRAS, KRAS, NRAS, MEK, ERK, p90RSK p38 and p42/44 MAPK, JNK, MKKs; common MAPK and mTOR targets incl. MNK and eIF4E; and others).

This analysis will be performed on a short time scale (between 2 and 90 min) to determine (i) the activation kinetics of downstream messengers and (ii) a window of stable activation for later perturbation screens with the drugs listed below (step 2). Measurements of pathway activation will be performed via Bioplex assays, immunoblotting, and ELISAs for semi-quantitative analysis of kinase phosphorylation and protein levels, and (where necessary) by established MAPK and mTOR reporter assays, and proximity ligation as-says (26,42) to quantify kinase substrate interactions in situ. Absolute quantification of critical network components that define drug response will be established by targeted proteomics (28), which is a standard technology at the UIBK Institute for Biochemistry and UIBK/CCB MS core facility. Targeted proteomics measurements will also be adapted and used for the analysis of patient samples. Outcomes of this first step will be discussed and adapted in close collaboration with WP5 to determine the most informative investigations for modeling, and with WP4 to derive protocols that allow observation of signaling and metabolism kinetics on similar time scales, and/or network connections via input/output modules (see WP5). In addition to short term signaling measurements we will also record cancer-relevant phenotypic responses such as cell proliferation, survival and migration, to be integrated as endpoints into the computational models. For this purpose, we will use Incucyte technology for highly parallelized live cell imaging, established in the CS and KT labs.

Task 3.1.2. Perturbation screens will be performed with the ER+BC cell lines using combinations of pathway activators (defined in 3.1.1) and inhibitors. The latter are predicted based on simulations in WP5, and include clinically relevant compounds (singly and in combination) for

- (i) ET: Tamoxifen, Fulvestrant
- (ii) Signaling network interference: RTK inhibitors (Sunitinib, Lapatinib), mTOR inhibitors (Everolimus, Temsirolimus; dual inhibitors such as AZD8055), PI3K inhibitors (Taselisib/GDC-0032, Alpelisib/BYL719, Buparlisib/BKM120), AKT inhibitors (Afuresertib/ASB183), CDK4/6 inhibitors (Ribociclib, Palbociclib), HER2 therapies (Trastuzumab, Pertuzumab), MEK inhibitors (Trametinib, Co-bimetinib), ERK inhibitors (SCH772984), RAF inhibitors (PLX7904)
- (iii) Metabolic network interference: IDO inhibitors (Epacadostat), PARP inhibitors (Olaparib, Rucaparib), Metformin (targets energy metabolism).
- (iv) In the absence of specific inhibitors, RNA interference, CRISPR/Cas9, and fragment libraries, in place at UIBK and CHAB, will also be used to suppress network components and to have the possibility to explore networks beyond the before mentioned signaling and metabolism pathways.

Stimulators and inhibitors will be applied in a defined order, and network response will be extracted by multiplexed measurements of protein levels and phosphorylation states. Phenotypic features (proliferation, migration, survival) will be measured by automated, parallelized Incucyte live-cell-imaging screens. The observed dynamics across the network will be compared to computational simulations (WP5) and appropriate adjustments in model topology and/or generation of further data will be addressed. Altogether, this approach will provide data to derive ER+BC-specific network model topologies and dynamics in WP5.

Task 3.2 Linking signaling pathways and metabolic networks. Partners: UIBK (KT), CHAB (CS).

In parallel to the analyses outlined above, we will work closely with WP4 to determine links between signaling and metabolic networks. Optimally, we aim to apply the same experimental conditions and time-scales for signaling (WP3) and metabolic analyses in WP4 (MZ, BMB, CO). To this end, an experimental routine will be set up together by WP3 and WP4 to allow parallel and SOP-directed sample processing for signaling measurement (BioPlex, Western Blot, proteomics) and metabolic measurements (see WP4), and phenotypic analyses (proliferation, survival, migration etc., see task 3.1.1). To determine links between signaling and metabolism from both directions, we will exchange and jointly adapt protocols for perturbation experiments with signaling activators (growth factors, amino acids) and subsequent measurement of metabolic pathways, and vice versa (e.g., perturbation with metabolic intermediates and measurement of signaling responses). If it turns out that we have to work at different timescales for certain inputs and/or metabolites, we will specifically detect molecular entities that allow connecting the metabolic and signaling models via input-output modules (e.g., expression changes of enzymes in MESI networks).

Task 3.3 Data to parameterize computational models for patient-derived cultures/PDX, & individual patients. Partners: UIBK (KT), DKFZ (CO), CHAB

To enable parameterization of our computational models for patient-derived cultures, PDX, and individual patient samples (Task 5.2), we will measure the protein levels of critical MESI-network components which control signal propagation and fluxes through the MESI-networks. To allow accurate, absolute quantification of proteins within the MESI-networks from minimal amounts of sample such as from primary 3D cultures, PDX, patient tissues, and biopsies, we will apply targeted proteomics using peptide standards and single/multiple reaction monitoring (28) as routinely used by UIBK/KT. If not yet available, mutation analyses of critical network components will be analyzed by BC panel sequencing at CHAB and DKFZ (<https://dktk.dkfz.de/en/research/core-facilities/genomics>).

Task 3.4 Omics-scale characterization of selected subgroup-specific ER+ BC cell lines, patient-derived primary cultures, PDX, and patient samples. Partners: DKFZ (CO), UIBK (KT), UiB (SG) and HITS, CHAB

For selected cell lines, patient-derived cultures, PDX and patient samples, representative of ER+BC sub-groups with distinct MESI marker panels and different drug responsiveness, we will perform quantitative omics-wide RNA and protein expression analyses. We will run these analyses for up to 3 subgroups with up to 20 patients, 4 PDX models, and 4 matched cultures per subgroup.

For RNAseq, 100 ng to 1 μ g (depending on sample type) of total RNA will be used to prepare strand-specific libraries and carry out library QC according to established protocols at the DKFZ genomics facility to generate a minimum of 200 million reads of 2x 100 bases of paired end reads per sample. Basic data analysis will be carried out at DKFZ following existing and established pipelines.

Quantitative shotgun proteomics will be conducted label free or by chemical (TMT) labeling following established procedures in UIBK/KT's laboratory (31,43).

Analyzed data will be stored and curated within MESI-SEEK (see WP2) to develop an integrative platform which handles transcriptomics, proteomics, and metabolomics data under a unified scheme. It will then be visualized in Expression Atlas, the EMBL-EBI value-added resource for functional 'omics data, alongside other comparable studies, and provided to WP5 for network analyses.

Participation per Partner

Partner number and short name	WP3 effort
1 - UIBK	69.00
4 - DKFZ	4.00
5 - VHIO	3.00
7 - UiB	8.00
10 - Charité	35.00
14 - HITS	2.00
Total	121.00

List of deliverables

Deliverable Number ¹⁴	Deliverable Title	Lead beneficiary	Type ¹⁵	Dissemination level ¹⁶	Due Date (in months) ¹⁷
D3.1	Signaling time course datasets for ER+BC cell lines	10 - Charité	Report	Confidential, only for members of the consortium (including the Commission Services)	18
D3.2	Signaling marker panels for patient derived models and samples measured	10 - Charité	Report	Confidential, only for members of the consortium (including the Commission Services)	57

Description of deliverables

D3.1 : Signaling time course datasets for ER+BC cell lines [18]
 Signaling time course datasets for ER+BC cell lines

D3.2 : Signaling marker panels for patient derived models and samples measured [57]
 Signaling marker panels for patient derived models and samples measured

Schedule of relevant Milestones

Milestone number ¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS4	Prediction of first subgroup specific marker panels	9 - UNEW	30	Prediction of first subgroup specific marker panels: Model predictions in MESI-SEEK

Work package number ⁹	WP4	Lead beneficiary ¹⁰	7 - UiB
Work package title	Assess METABOLIC NETWORKS for model parameterization and validation		
Start month	7	End month	57

Objectives

The overall aim of WP4 is to identify distinct metabolic alterations in experimental models (ER+BC cell lines, patient-derived cultures, PDX) and patients' body fluids and tumor tissues. This includes characterization of various model systems regarding quantitative measurements of metabolites and metabolic fluxes, and iterative parameterization and validation for the mathematical models generated in WP5.

The specific objectives of WP4 are to:

1. Optimize and standardize reproducible procedures for metabolite extractions and analyses;
2. Establish protocols and provide quantitative metabolic data for parameterization of computational models (WP5), in close conjunction with WP3, through; comprehensive, dynamic metabolic profiling of ER+BC cell lines; identification of metabolic shifts in a signaling and metabolic intervention screens; detection of metabolic fluxes; metabolic characterization of patient-derived matched cultures and PDX models and patient samples
3. Validate models (WP5) by targeted analyses of critical pathways/metabolites
4. Based on model predictions (WP5), establish metabolic profiles (MESI marker panels) in body fluids from patient-derived models and patients, representative of ER+BC subgroups with different drug responsiveness.

Description of work and role of partners

WP4 - Assess METABOLIC NETWORKS for model parameterization and validation [Months: 7-57]

UiB, UIBK, DKFZ, Charité, Neuroimmun GmbH, UMCG

WP4 will perform metabolomics analyses of the Trp and NAD networks, and of other key metabolites identified by network analyses in WP5 as being relevant for ER+BC patient stratification. All necessary protocols are in place in the partner laboratories. In collaboration with WP3, protocols and culture conditions will be optimized to measure signaling and metabolite dynamics under the same stimulation conditions with growth factors and/or metabolic intermediates, and inhibitors of signaling and metabolism (detailed in WP3). Comprehensive profiling of intra- and extracellular Trp and NAD metabolites and abundance of key metabolic enzymes by targeted proteomics (WP3) will be performed to provide initial metabolite parameters to build the mathematical models in WP5. In addition, metabolic fluxes for the Trp and the NAD networks will be measured by stable isotope labeling (DKFZ, UiB). Depending on the outcome of network analyses (WP5) and feasibility, other relevant metabolic pathways will be analyzed, such as energy metabolism (UMCG).

Model development (WP5) for individual patients and identification of ER+BC subgroups with similar MESI marker panels and drug responsiveness will be supported by metabolic profiling of PDX and patient samples. The results of these analyses will be critical to select (WP5) MESI marker panels for validation in patient samples from observational and interventional clinical studies (WPs 6 and 7).

Task 4.1 Development and validation of standardized procedures to extract a comprehensive set of metabolites from biological samples

This task will establish validated standard protocols for the reproducible, quantitative extraction of the metabolites to be analyzed. Initially, we will consider the following metabolites:

- (i) Trp metabolism: Trp, Kyn, kynurenic acid, anthranilic acid, hydroxykynurenine, formylkynurenine, hydroxyformylkynurenine, hydroxytryptophan, serotonin, anthranilic acid, hydroxyanthranilic acid, quinolinic acid, xanthurenic acid, cinnabarinic acid, tryptamine, indole-3-pyruvate, indole-aldehyde, indole lactate, indole acetic acid, 5-hydroxyindole acetic acid;
- (ii) NAD metabolism and adenine nucleotides: nicotinamide, N1-methylnicotinamide, nicotinic acid, NAD, NADH, NADP, NADPH, nicotinamide riboside, nicotinamide mononucleotide, nicotinic acid mononucleotide, ATP, ADP, AMP. A novel multiplex method to measure Trp and its metabolites by chemical labeling with isobaric mass tags and LC-MS/MS has been developed and patented by CO, DKFZ (filed October 31 2016, Application n° PCT/EP2016/076265). This setup will be employed for the analysis of the Trp metabolome, and allows high precision and time efficiency by comparison of compounds in up to ten different samples in the same run (e.g., of time course analyses, biological replicates or multiple sample comparisons in vitro and in vivo). UiB has also recently developed measurements of NAD metabolites and the related metabolic fluxes based on isotope labeled metabolites. We will also measure other relevant metabolites identified by network analyses in WP5 to be significantly altered in different ER+BC subgroups.

For example, we are prepared to measure additional metabolites from energy metabolism: acetyl-CoA, succinyl-CoA, and glycolytic (phosphorylated sugars, pyruvate, lactate), TCA cycle (citrate, alpha-ketoglutarate, succinate, fumarate, malate), and pentose phosphate pathway intermediates; likely some of them will emerge as critical from the analyses in WP5.

Currently, different extraction procedures are used in the different partner laboratories for the before mentioned metabolites, due to different chemical instabilities. These procedures will have to be optimized and harmonized, because (i) for some of the samples (in particular patient samples) multiple extractions may not be feasible, (ii) it will be necessary to combine data sets from independent cultures or even from different laboratories.

Task 4.2 Medium-throughput metabolic profiling of ER+ BC cell lines for model parameterization

Dynamic, quantitative analyses of metabolites (detailed above) will be conducted by CO (Trp) and MZ (NAD) using established quantitative UPLC-ESI-MS/MS technology.

Further analyses are designed to quantify metabolites, enzyme concentrations and activities in a physiological range. These include

- intracellular Trp measurements using a genetically encoded Trp sensor based on the Trp-activated repressor protein, TrpR (CO, 44);
- semi-automated activity assays for selected enzymes in NAD (MZ) and Trp (CO) metabolism;
- measurements of enzyme concentrations in NAD, Trp and other metabolic pathways by quantitative, targeted proteomics with labeled standards, as detailed in WP3;
- flux measurements using stable isotopes (MZ, CO, BMB, KT): determine metabolite consumption and production by analyzing time-dependent conversions of isotope-labeled metabolites in the various pathways;
- ELISA-based measurements of Trp metabolites (KK, NIN), incl. Trp, Kyn, QA, KA, allowing analysis of a broader set of samples and translation of MESI panels to clinical applications.

The data from these measurements will be provided to WP5 for model parameterization.

Task 4.3 Linking signaling pathways and metabolic networks

To connect signaling and metabolic responses, it is critical that treatments are conducted under the exact same conditions in WP3 and WP4 (WP3 and above). In addition, the timescale of the experiments will be optimized together and a stimulation and perturbation screen (described in WP3) will be performed to reveal not only connections within signaling and metabolic pathways, but also between signaling and metabolism. If different timescales turn out to be required for some metabolic measurements, molecular connection points that can serve as hubs for input-output model connections between metabolic and signaling models will be identified (WP5) and included in our measurements.

Task 4.4 Data for model refinement and validation of model-derived subgroup-specific MESI marker panels and drug responses

The computational models (WP5) describing the MESI-networks in ER+BC cell lines will be refined by re-assessment or extension of the set of metabolites, as needed. Analyses for refinement will include, e.g., kinetic analyses of key enzymes and/or measurement of additional enzyme activities important in the respective networks. Modification of flux measurements might also be needed (e.g., use of different/additional time points).

Model-predicted ER+BC subgroup-specific MESI panels (WP5) will be validated by targeted metabolite measurements in cell lines, cultures, PDX and patient samples (WPs 1, 6, 7) with or without relapse, and treated with pharmacological modulators of signaling and metabolism (outlined in WP3).

Participation per Partner

Partner number and short name	WP4 effort
1 - UIBK	2.00
4 - DKFZ	51.00
7 - UiB	33.00
10 - Charité	1.00
12 - Neuroimmun GmbH	15.00
15 - UMCG	10.00
Total	112.00

List of deliverables

Deliverable Number¹⁴	Deliverable Title	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
D4.1	Metabolite time course datasets for ER+BC cell lines	7 - UiB	Report	Confidential, only for members of the consortium (including the Commission Services)	18

Description of deliverables

D4.1 : Metabolite time course datasets for ER+BC cell lines [18]

Metabolite time course datasets for ER+BC cell lines

Schedule of relevant Milestones

Milestone number¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS4	Prediction of first subgroup specific marker panels	9 - UNEW	30	Prediction of first subgroup specific marker panels: Model predictions in MESI-SEEK

Work package number ⁹	WP5	Lead beneficiary ¹⁰	9 - UNEW
Work package title	Integrative MESI network modeling and network analyses		
Start month	7	End month	57

Objectives

The overall aim of WP5 is to use mathematical modeling and network analysis to (i) stratify ER+BC patients into subgroups with different aberrations of metabolism and signaling, (ii) predict related differences in MESI-marker panels, (iii) predict and understand the subgroup-specific mechanisms mediating response or resistance to ET and targeted drugs, and (iv) identify alternative combinatorial treatment options.

The specific objectives are to:

1. adapt existing dynamic models of kinase signaling and metabolism for ER+BC cell lines.
2. outline the connection topology and scale the component levels for MESI networks in ER+BC cells.
3. adapt computational models to patient-specific data from PDX, primary cultures, and clinical samples.
4. predict MESI marker panels to stratify ER+BC patients into sub-groups with different therapy response and drug resistance, and monitor their drug response and arising resistance; alternative established treatments for ER+BC patients with drug resistance; and new treatments and targets for improved (combinatorial) drug targeting of MESI networks.

Description of work and role of partners

WP5 - Integrative MESI network modeling and network analyses [Months: 7-57]

UNEW, UIBK, UiB, UiT, Charité, SysBioSim B.V., HITS, UMCG

We will build predictive dynamic mathematical models of integrated MESI networks, which will be initially parameterized using ER+BC cell line derived semi-quantitative time course data (WP3, 4), and will be adapted step-wise based on quantitative measurements of protein and metabolite levels to patient derived cultures, PDX, and patient samples (WP1). Network analyses will serve to identify potential additional sub-group-specific metabolites to enrich our predictive MESI marker panels. The predictive power of our models regarding MESI-marker panels and related drug response or resistance will be validated and refined by pre-clinical and clinical trials (WP6, 7). Validated models will be customized for pharma partners. All data will be received from and models will be hosted by the MESI-SEEK data and model management platform (WP2).

Task 5.1 Describe the topologies and build and connect dynamic models of ER-mTOR-MAPK signaling and Trp-NAD metabolism. Partners: UNEW, UiT, CHAB, UIBK

First, we will build separate core dynamic models of MAPK and mTOR signaling. At the same time, we will extend and refine existing computational models of Trp and NAD metabolism. A combination of COPASI (45) and Data2Dynamics (46)/MATLAB software, designed by our IAB member A. Raue, will be used for these tasks. Using available information and expertise of MESI-STRAT partners and related consortia (GlioPATH, MAPTorNET, PROMETOV) on the network structures and dynamic properties of metabolic and signaling (MESI) models, we will work out the topologies and create dynamic models of ER-MAPK-mTOR signaling (UNEW, CHAB, UIBK) and Trp-NAD metabolism (UiT). Based on quantitative time course signaling and metabolite data from ER+BC cell lines (WP3, 4) we will parameterize and validate the MESI models. For model fitting to data, parameter identifiability will be assessed using methods such as profile likelihood (47) and estimation will use both global and local optimisation algorithms. Perturbation screens in which signaling or metabolic network components are inhibited and the effects on all parts of the MESI networks are monitored will reveal ER+BC specific network connections within and between the signaling and metabolic networks, and will serve to connect the separate network models either by merging them into one model, or by input-output schemes.

Task 5.1.1 Dynamic ER-MAPK-mTOR network models for ER+BC cells. Partners: UNEW, UIBK, CHAB

We will develop dynamic ODE-based models of signaling pathways in ER+BC cell lines (detailed in WP1), as described earlier by the partners for computational mTOR^{31,40,41} and MAPK^{27,39} models. We will incorporate information on mutational profiles if their effects on the activity of network components are known (e.g., PIK3CA or PTEN mutations activate the PI3K-Akt pathway). Experimental data for steady-state and dynamic, time-course responses of RTKs, adaptors and downstream signaling proteins (WP3), to growth factors and metabolites (WP3, 4), and inhibitor perturbation data (WP3) will be used to calibrate the models in a modular approach, as data from WP3 becomes available. Powerful model analysis techniques (e.g. global and local sensitivity analyses, systematic combinatorial perturbations simulating effects of RNA interference, inhibitors and drugs) will enable us to determine critical nodes and dissect the network response dynamics. Robust global estimation methods such as adaptive simulated annealing will return large

ensembles of permissible fitting parameters, which will allow characterizing the uncertainty of the model predictions. The predictive value of the dynamic models will be validated by comparing model simulations to drug perturbation data (detailed in WP3) that has not been used for model parametrization.

Task 5.1.2 Computational models of Trp and NAD metabolism for ER+BC cells. Partners: UiT, UIBK, UMCG

We will refine and extend existing models of Trp- and NAD-metabolism, using available information on the network topology and interface components with signaling models (17,30,48). Experimental data obtained for ER+BC cell lines under steady state and dynamic conditions in WP4 will be used to calibrate the models based on measured expression levels of components (expression data, protein concentrations, Vmax) and fit-tting the models to metabolic fluxes and metabolite time courses. Where possible primary biochemical data, such as affinity constants for substrates, products, inhibitors and activators, will be used. Initial validation of the predictive value of the models will essentially be conducted as in 5.1.1, e.g., by predicting the effects of metabolic interventions (e.g., IDO inhibitors, Olaparib/Rucaparib), on the concentration of Trp or NAD metabolites (detailed in WP4).

Task 5.1.3 Link signaling and metabolic network models. Partners: UNEW, CHAB, UIBK, UiT

Once separate models for signaling and metabolism have been built, parameterized, and validated, they will be connected. To facilitate the integration of our metabolic and signaling models, the signaling data (WP3) and the metabolic data (WP4) will be measured under identical conditions. Initial information on integration of mTOR-MAPK signalling with Trp-NAD metabolism networks will come from literature and collaborating consortia (GlioPATH, MAPTor-NET, PROMETOV), and be communicated to WP3 and 4 to be included in experimental analyses. Perturbation screens with drugs targeting signaling or metabolism (detailed in WP3) and RNAi or Crispr-Cas9 libraries, and measurement of signaling components (detailed in WP3) and metabolites (detailed in WP4) will deliver information on ER+BC specific connectivities within and between ER-mTOR-MAPK signaling and Trp-NAD metabolic networks. Iterative rounds of modeling, experimental testing and model refinement will be needed to identify potential missing connections and mutual influences of the pathways. For fully integrated MESI models, model complexity might have to be reduced to ensure identifiability of the model parts that are critical for predictions of drug response and associated MESI marker panels. Time-scale separation between signal transduction and metabolic adaptation may be an issue impeding the setup of fully integrated dynamic MESI models. Therefore, an alternative approach will be to use an input-output coupling to combine metabolic and signaling models. For this, the metabolic models will be tuned for different metabolic conditions (such as high and low Trp due to different IDO levels), and the related metabolite levels will be predicted. These metabolite levels will be used as inputs to the signaling models to define the activity of the metabolite-sensitive signaling network components, determined by the perturbation screens (WP3, 4). Likewise, the metabolic models can be tuned to different signaling conditions (e.g., high versus low ER, PI3K or mTOR activity) and the effects on MESI marker panels and their response to drug interventions can be predicted. Once the models are linked we will also include quantitative phenotypic data from WP3 (cell proliferation, survival, migration etc.) to integrate cancer-relevant phenotypic modeling endpoints. To achieve this, we will consider the phenotypic processes as additional nodes in the networks and infer the specific connections and their relative importance by applying model selection strategies as we have carried out with molecular component31,41. Confidence in putative connections will be enhanced with gene ontology analysis of omic data from Task 5.5.

An initial quality check will be performed by analysing model predictions for our observations (see section 1, preliminary data, Fig. 2) that ET induces IDO and reduces Trp levels, and that an mTOR inhibitor phenocopies this effect. To pass the quality check, the models have to correctly predict these observations. For further validation, data from experiments (WP3, 4) in which metabolism will be monitored upon interventions in signaling and vice versa (see WP3 for detailed lists of metabolic and signaling inputs and perturbations) will be compared to model simulations. Based on the resulting data from WP3 and 4, and their fit with model simulations, we will suggest model improvements and initiate a next round of experimental testing.

Next, we will perform sensitivity analyses of our MESI models to identify components whose lev-els/activity alter responses to ER+BC drugs (listed in WP3) for modeling endpoints including oncogene activity (e.g., Akt, PI3K, mTOR, MEK/ERK and phenotypic features (proliferation, survival, migration). The resulting list of critical network components (proteins/metabolites) will be provided to WPs 3 and 4 for measurement in PDX and patient samples to enable individualized model parametrization in Task 5.2.

Task 5.2 Adapt dynamic models to patient derived cultures and PDX. Partners: UIBK, UiT, UNEW, CHAB

A critical step will be the adaptation of our models from ER+BC cell lines to patient samples from which dynamic time course data can usually not be obtained. Our approach is based on the idea that enzyme activities per se are the same in all systems (cell lines, PDX, patient tumor tissues), and are modulated by differences in enzyme abundance and mutations in individual systems or patients. This means that dynamic mod-els, parametrized based on time course data from cell lines, can be parametrized for other samples in which time course data are not easily measureable, by altering protein levels and accounting for mutations in central network components. This concept is frequently used in

metabolic studies and recently shown to be applicable²⁵ to signaling networks. Thus we will adapt the models based on ER+BC cell lines (task 5.1) to patient derived cell cultures and PDX based on differences in protein levels, measured by targeted proteomics (WP3), and mutations with known effects on signaling and metabolic networks analysed here. We will validate that the dynamic simulations properly reflect signaling and metabolic dynamics and perturbation responses in patient-derived systems. For this we will measure basal levels of signaling proteins and metabolites in four PDX and matched 3D cultures, of which always two show similar drug responses as determined by the VS lab (VHIO). For model validation, the MESI network response dynamics to perturbations with growth factors, metabolites, and drugs (detailed in WPs 3+4) will be simulated and compared to measured time course data (cultures) and drug responses (PDX).

Task 5.3 Pharmacogenomics I: derive patient-specific models, and predict ER+BC subgroups with distinct drug response mechanisms and different MESI marker panels. Partners: UNEW, UIBK, UiT, CHAB

Next we will parametrize the models based on protein (WP3) and metabolite (WP4) levels and mutation analyses for individual patient samples. To do this, we will analyse our models parametrized for ER+BC cell lines, patient cultures and PDX and predict signaling proteins and metabolites that critically alter metabolite marker panels or drug responses. Model parametrization based on these protein & metabolite panels will be validated and refined by measurements in up to three matched PDX and 3D cultures. The same refined pan-els will then be measured in patient tissues and body fluids for subsequent model parametrization. Based on the dynamic simulations of growth factor/metabolite stimulation and drug response dynamics for individual patients, we will group the patients into subgroups with common drug response mechanisms and MESI pan-els.

Based on this we will predict:

- o patient subgroups with common therapy response/resistance mechanisms to ET and targeted drugs (listed in WP3), and MESI marker panels to distinguish between these subgroups
- o optimized treatments for combinatorial targeting of signaling and metabolism with established drugs
- o new targets for improved (combinatorial) drug targeting

For example, for our Relapse Prediction Trial (WP6, trial 6.3) metabolite panels or signaling network components (detailed in WPs 3+4, and narrowed down as described above) will be measured in the exploratory co-hort. Based on model parametrization with the measured protein levels, we will predict metabolite panels that distinguish stable disease from future relapse, and we will validate these predicted markers by comparison to our metabolite measurements in the exploration and validation cohorts. Next we will computationally analyse the mechanistic differences in signaling networks that potentially lead to ET resistance. By simulating drug perturbations, we can propose combinatorial targeted drug interventions which sensitize patients with different ET resistance mechanisms for ET.

Similar schemes will be run for model-based analyses of the Risk and Relapse Detection (trials 6.1 and 6.2) as well as the WOO and ET Termination Trials (trials 7.2 and 7.3) to predict and validate MESI-marker pan-els to detect progression risk at the start of ET (6.1), ET response at the start of ET (7.2, WOO), and relapse during ET (6.2) and after ET (7.3); and to predict suitable alternative targeted therapies for high risk patients and ET resistance at all these stages.

Task 5.4 Pharmacogenomics 2: guide experiments to validate ER+BC subgroups with distinct drug response mechanisms and different MESI marker panels in preclinical trials and clinical cohorts

Partners: UIBK, UiT, UNEW, CHAB. We will validate MESI marker panels predicted to correlate with different ET resistance mechanisms and related different responses to targeted therapies in our Intervention Validation Trial (WP7, trial 7.4). For example, if our models, based on data from the the Relapse Prediction Trial (6.3), suggest that a given MESI marker panel predicts at ET start a later relapse (i.e., ET resistance) we will measure this panel in samples from the PRAEGNANT study and analyse correlation with time of re-lapse. If the MESI model, parametrized based on the MESI panel, predicts sensitization of the tumor to ET by a given targeted treatment, e.g., CDK4/6 inhibitors or mTOR inhibitors, the panel will be tested in the respective cohorts (mTOR: Exemestane/Everolimus study; CDK4/6: Parsifal, Ribecca). Based on the validated MESI marker signatures, we will assign our ER+BC PDX models to the different patient subgroups (Pre-clinical Model - Subgroup Assignment, WP6, trial 6.5). In the subgroup-matched PDX models we can run prospective preclinical trials to test if the drug responsiveness of the PDX models corresponds to the responsiveness predicted by the computational models (WP7, trial 7.1, Preclinical Intervention Trials). Ultimately, prospective clinical IIT will need to be designed and initiated, and the panels and related therapies may be also included in umbrella trials to be designed and applied for in WP7 (task 7.5).

Task 5.5 Network analyses to identify MESI-ancillary networks and broaden MESI marker catchment for ER+BC patient subgroups. Partners: UIBK, UiT, UNEW, CHAB, UiB/SG, HITS

It could be that not only the signaling (ER-mTOR-MAPK) and metabolic (Trp-NAD) networks tested here, but also other networks differ between the patient subgroups. To identify such differences and refine our MESI-marker panels and computational models predictive of the drug responses, network analyses of omics wide expression data at RNA and protein level for cell cultures, PDX models and patient samples representative of the previously identified ER+BC subgroups will be conducted.

We will examine public resources of ER+BC expression data, e.g., from TCGA and METABRIC, but based on earlier reports (49), we expect that although useful to identify tumour-specific pathways, the datasets are too complex to identify patient subgroups without further information. We will tackle this issue by searching our ER+BC subgroup-specific patterns of differently expressed MESI network components in RNA expression data, and use this information to stratify the public datasets into our subgroups to identify additional candidates.

Of note, proteomic data is very scarce in public resources. Therefore, our own analyses will mainly focus on protein expression (WP3) which we will analyse in conjunction with RNAseq (expression) and panel seq (mutation) data to identify expression differences at protein level between the subgroups and correlate proteomic information (KT43) with RNA expression, splicing (SG, 50,51) and mutation information (RF, 52) (proteogenomics). RNAseq data will be mapped to the GrCh38 release and tools such as TopHat2 (53) and cufflinks (54) will be used on our high depth sequencing data to identify potential differentially regulated isoforms that could be matched to our proteomics data. Further normalization and gene differential expression will be carried out using different tools limma (Voom, 55,56), DESeq2 (57) and edgeR (58), applying univariate and multivariate analyses. We will also collaborate with EMBL-EBI (see letters) in using integrative network analysis of RNAseq and proteomics data to identify genes interacting with the MESI network (via IntAct), as well as whose expression profiles are kinetically correlated. This will involve integration of the data sets at multiple levels for systematic identification of cross-talk among key MESI pathways by using random walk on protein interaction networks to identify ancillary MESI network regulator genes bridging these cross-talking pathways.

Additional lists of candidates with subgroup-specific expression patterns will be followed using a step-wise bioinformatic network analysis pipeline entailing supervised and unsupervised data driven methods. To group candidates into pathways, we will use a combination of both GSEA and GSA on the MSigDB (59) gene sets, especially C2 (KEGG & REACTOME), C5 (GO) and C7 (Immune signatures). Additional unsupervised consensus clustering will be applied to refine unique features of our previously defined subgroups. To overlay different dataset types (mainly RNA expression and mutation profiles), eQTL analyses will be performed. Methods such as Bayesian network analysis and tools such as Cytoscape (60) and Ingenuity Pathway Analysis and MetaCore will be used for robust network mapping and reconstruction with the multi-omics datasets overlay. Subgroup-specific additional, ancillary MESI networks can be analysed by genome scale modelling where, in the absence of detailed kinetic data, methods such as constraint-based modelling and flux balance analysis can be used to predict related differences in the abundance of secreted metabolites between the subgroups, as described by BMB (61). This can be validated experimentally (WP4) by measuring the newly predicted metabolites in cultures, PDX models, and patient samples representative of the different subgroups. Alternatively, if the size of the ancillary networks allows it (max. 20 components) we will directly integrate them into our dynamic ODE-based subgroup specific MESI-models. For some pathways frequently altered in cancer, such as energy metabolism, we already have detailed dynamic models for glycolysis (32) and fatty acid oxidation (62) (BMB) that can be integrated into our dynamic MESI models. For others we may need to develop new models. As this is a considerable effort, we will limit the number to maximum of three newly identified networks which encompass subgroup-specific drug targets and MESI markers. For these, dynamic data from cell lines and protein and metabolite levels in PDX models and patient samples will be acquired to integrate these networks into the sub-group specific models predictive of drug response and specific MESI marker panels. The widened MESI models and marker panels will have the advantage that more MESI metabolites can be measured in patient samples, enhancing the level of confidence for the predictive value of the marker panels.

Task 5.6 Model Customization for pharma clients. Partners: SBS, UIBK, UNEW, UiT

SBS will contact potential clients to introduce the MESI-STRAT models and their potential use, discuss clients' strategies for the development of new BC therapies and identify parallels between the capabilities of the models and client's needs. Frequent interaction will be made, e.g., with Novartis and Merrimack (both on our IAB) and with the pharma companies involved in our linked trials (see 1.3.a) for feedback on model development and prioritization of therapeutics to be considered for model development. Together with the pharma stakeholders, SBS will identify the interactions between the drug candidate of the client (pharma) company and pathway elements such as elements of mTOR pathway in MESI-STRAT models to analyse the potential effect, efficacy and mode of action of the drug candidate. The customization is done in a step-wise approach where SBS performs data mining on the drug candidate and its potential interaction within the cell, literature search, data integration, model writing, model integration and simulation runs. In case a cross talk with other relevant pathways is observed during the data mining and literature search steps, SBS will integrate the models of the additional pathways to MESI-STRAT models within its capabilities and capacity. SBS adopts hybrid modelling strategy utilizing logical and kinetic modeling of signaling and metabolic pathways at intracellular level (including flux balance analysis, rule-constraint based approaches and alike). Parametrization of the models will be done based on the data from WP1, publicly available resources, as well as from clients' proprietary data if available. Based on the developed models and simulations, SBS analysis produces outputs such as predictions about the dosage, drug efficacy, drug efficiency, mode of action and advice towards downstream

research such as animal and clinical studies, which can be done in a more cost and time efficient based on results from simulations.

Participation per Partner

Partner number and short name	WP5 effort
1 - UIBK	48.00
7 - UiB	20.00
8 - UiT	35.00
9 - UNEW	42.00
10 - Charité	6.00
13 - SysBioSim B.V.	12.00
14 - HITS	1.00
15 - UMCG	8.00
Total	172.00

List of deliverables

Deliverable Number¹⁴	Deliverable Title	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
D5.1	Computational signaling and metabolic models for ER+BC cell lines	9 - UNEW	Other	Confidential, only for members of the consortium (including the Commission Services)	18
D5.2	First MESI model parametrized for patient samples	9 - UNEW	Other	Confidential, only for members of the consortium (including the Commission Services)	27
D5.3	First customized model for pharma	13 - SysBioSim B.V.	Other	Confidential, only for members of the consortium (including the Commission Services)	36

Description of deliverables

D5.1 : Computational signaling and metabolic models for ER+BC cell lines [18]

Computational signaling and metabolic models for ER+BC cell lines

D5.2 : First MESI model parametrized for patient samples [27]

First MESI model parametrized for patient samples

D5.3 : First customized model for pharma [36]

First customized model for pharma

Schedule of relevant Milestones

Milestone number¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS4	Prediction of first subgroup specific marker panels	9 - UNEW	30	Prediction of first subgroup specific marker panels: Model predictions in MESI-SEEK

Work package number ⁹	WP6	Lead beneficiary ¹⁰	4 - DKFZ
Work package title	Preclinical and clinical trials without drug treatments in ER+BC patient-derived models and the longitudinal PATH cohort		
Start month	1	End month	57

Objectives

The main aim of WP6 is to derive MESI marker panels that identify clinically relevant ER+BC patient sub-groups and to find preclinical models (matched primary cells and PDX models) representative for the distinct ER+BC subgroups. Our specific objectives are

1. Identification and validation of MESI marker panels to discriminate high risk versus low risk ER+ BC patient subgroups; detect ER+BC patient subgroups with relapse; and predict at diagnosis patient subgroups with future relapse
=> Identification of ER+BC patient subgroups with different resistance mechanisms
2. Identification of preclinical models representative for different ER+BC patient subgroups

Description of work and role of partners

WP6 - Preclinical and clinical trials without drug treatments in ER+BC patient-derived models and the longitudinal PATH cohort [Months: 1-57]

DKFZ, UIBK, PATH Biobank, UKL-HD, VHIO, DDI

Task/Trial 6.1 Risk Detection Trial: Identification and validation of MESI marker panels discriminating high risk versus low risk ER+ BC patient subgroups. Partner: PATH

Analysis of 66 sera collected at diagnosis from women with high and low risk ER+ BC, respectively, (for high/low risk criteria see WP1) for signalling pathways (WP3) and metabolites (WP4) will allow identification of MESI marker panels (WP5) detecting high/low risk in ER+BC patients. To validate if the identified markers indeed discriminate between high and low risk patients, 66 sera of women with high and low risk ER+BC, respectively, will be analysed in a blinded fashion and assigned to high and low risk groups according to their MESI marker panels. Comparison with the known clinical characteristics will allow validation of the discriminatory power of the identified MESI markers (see Figure 5A). In addition, selected tumor tissues representative for specific MESI markers signatures will be analysed in detail regarding their signaling and metabolic networks to gain a better understanding of the molecular mechanisms underlying the MESI mark-er panels discriminating high and low risk patients.

Task/Trial 6.2 Relapse Detection Trial: Identification and validation of MESI marker panels detecting ER+BC patient subgroups with relapse. Partners: PATH, UKL-HD, UIBK, VHIO

60 prospectively collected sera of stable patients from the PATH cohort matched to 60 sera collected from ER+BC patients at relapse/distant metastasis in the frame of studies (appropriate baseline samples from the PRAEGNANT, IMPACT or Everolimus/Exemestane studies) will be employed. Analysis of signalling pathways (WP3) and metabolites (WP4) in these sera will allow identification of MESI marker panels (WP5) detecting relapse in ER+BC patients. To validate if the identified markers indeed detect relapse, 60 sera of matched stable or relapsed women, respectively, will be analysed in a blinded fashion (WP3&4) and assigned (WP5) to relapsed vs. stable groups according to their MESI marker panels. Comparison with the known clinical characteristics of the patients will allow validation of the discriminatory power of the identified ME-SI marker panels to distinguish between stable and relapsed patients (see Figure 5B).

Task/Trial 6.3 Relapse Prediction Trial: Retrospective identification and validation of MESI marker panels at diagnosis predicting patient subgroups with future relapse or stable disease. Partner: PATH

Analysis of 50 sera obtained at diagnosis from patients that developed relapse/distant metastasis during follow-up compared to 100 sera from patients that remained stable for > 5 years for signalling pathways (WP3) and metabolites (WP4) may allow identification of MESI marker panels (WP5) predictive for future re-lapse/distant metastasis. To validate if the identified markers indeed are able to predict future relapse/distant metastasis, 75 sera will be analysed in a blinded fashion (WPs 3-5) and assigned to deriving either from stable or relapsed patients according to their MESI marker panels. Comparison with the known clinical characteristics of the patients will allow validation of the predictive power of the identified MESI marker panels for future relapse. Comparison with the markers identified in Task 6.1 and 6.2 will determine whether the markers for high risk ER+BC at diagnosis and acute relapse overlap with those for developing future relapse (see Figure 5C). In addition, selected tumor tissues representative for MESI markers panels of patients that remained stable or relapsed during follow-up will be analysed in detail regarding their signaling and

metabolic networks (WPs 3&4) to investigate the molecular mechanisms underlying the MESI markers predictive for future relapse.

Task/Trial 6.4 Tissues for Preclinical Trials: Screening and collection of ER+BC tissues with subgroup-specific MESI marker panels for preclinical models (PDX, bioreactor). Partners: VHIO, UKL-HD

Fresh human ER+BC tissue for cultivation in perfusion-based bioreactors or the generation of PDX-models (in case a preclinical model for a relevant, newly defined ER+ BC subgroup is missing) will be collected in ongoing clinical studies at VHIO and UKL-HD.

Task 6.5 Preclinical Model - Subgroup Assignment: Identification of primary cell and PDX models representing ER+BC subtypes defined by differential MESI marker expression. Partners: VHIO, DKFZ, DDI

Comparison of the MESI networks and the expression of MESI marker panels (WPs 3-5) in our 9 matched primary cell and PDX models (including at least one immunocompetent model) with the MESI-marker de-fined ER+BC subgroups to identify which models best represent specific subgroups of patients for preclinical analyses. If a preclinical model for a relevant, newly defined ER+ BC subgroup is missing, available models from EurOPDX will be analysed or up to two novel PDX models will be established at VHIO.

Participation per Partner

Partner number and short name	WP6 effort
1 - UIBK	2.00
2 - PATH Biobank	8.00
3 - UKL-HD	8.00
4 - DKFZ	35.00
5 - VHIO	3.50
6 - DDI	2.00
Total	58.50

List of deliverables

Deliverable Number ¹⁴	Deliverable Title	Lead beneficiary	Type ¹⁵	Dissemination level ¹⁶	Due Date (in months) ¹⁷
D6.1	Preclinical Model-Subgroup Assignment	4 - DKFZ	Report	Confidential, only for members of the consortium (including the Commission Services)	36

Description of deliverables

D6.1 : Preclinical Model-Subgroup Assignment [36]
Preclinical Model-Subgroup Assignment

Schedule of relevant Milestones

Milestone number¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS4	Prediction of first subgroup specific marker panels	9 - UNEW	30	Prediction of first subgroup specific marker panels: Model predictions in MESI-SEEK

Work package number ⁹	WP7	Lead beneficiary ¹⁰	3 - UKL-HD
Work package title	Preclinical and clinical trials with drug treatments: preclinical drug tests, WOO, ET Termination and Intervention Validation Trials		
Start month	1	End month	57

Objectives

The overall aim of WP7 is to validate the predictive power of the MESI models and marker panels derived from WPs 5+6 for stratification of ER+BC patient subgroups for drug interventions.

Clinical studies in ER+BC present several challenges including the long time to relapse, the low percent-age of relapsing patients, and the risk for relapse remaining constant over two decades. Hence, trials with endpoints such as progression free survival are long-term efforts that cannot be carried out within the typical budget and duration of a H2020 project. MESI-STRAT overcomes this limitation by taking advantage of existing cohorts and trials, by conducting own trials where needed, and by collaborating with pharma companies for IIT and umbrella trials to be designed based on the MESI-STRAT outcomes.

The specific objectives of WP7 are to

- 1) Validate predictive MESI marker panels in primary cell cultures, cultured primary tissues and preclinical interventional trials in PDX models. (Task 7.1)
- 2) Identify the alterations in MESI marker panels through ET and their association with therapy response to enable stratification for ET. (Tasks 7.2 & 7.3)
- 3) Validate MESI-models and marker panels in clinical trials performed by partners and collaborators and test if the identified MESI marker panels also apply to male ER+BC (Task 7.4)
- 4) Design own IIT and umbrella trials, in which ER+BC patients will be stratified to different therapies by MESI marker panels. (Task 7.5)

Description of work and role of partners

WP7 - Preclinical and clinical trials with drug treatments: preclinical drug tests, WOO, ET Termination and Intervention Validation Trials [Months: 1-57]

UKL-HD, UIBK, PATH Biobank, DKFZ, VHIO, DDI

Task 7.1 Preclinical Intervention Trials: Validation of predictive MESI marker panels in primary cultures, cultured primary tissues and preclinical interventional trials in PDX models.

Partners: VHIO, DDI, DKFZ, UIBK. The therapy schemes predicted by our computational MESI-STRAT models will initially be validated in vitro using primary cell cultures and primary human ER+BC tissues cultured in perfusion-based bioreactors. As the primary cell cultures are matched to our PDX models, results obtained in cell culture can swiftly be translated to the PDX models.

However, using primary cell cultures the effects of the tumor microenvironment on therapy responses can-not be assessed. In addition, some ER+BC subgroups may not grow as primary cell cultures and have very poor take rates in mice. Therefore, freshly excised ER+BC tissue will be cultured in perfusion-based bioreactors developed for tissue engineering purposes, which successfully maintain viable tumor, immune and stromal cells in ER+BC tissues for up to 21 days. This platform will be used in addition to primary BC cells to test the targeted therapies predicted (WP5) for specific ER+BC subgroups (WP6).

We will investigate at least 8 interventions relevant for the MESI network (tamoxifen, fulvestrant, trastuzumab, mTOR inhibitors, PI3K inhibitors, CDK4/6 inhibitors, MEK inhibitors, PARP inhibitors and IDO1 inhibitors) and combinations thereof in appropriate primary cultures or cultured tissues. The most promising therapies for specific subgroups identified by this approach (up to 4 per PDX) will be validated in up to 6 PDX models representative for different subgroups. In the case of validation of therapies requiring the immune system, e.g., IDO1 inhibitors, up to 4 immunocompetent PDX models will be established. If no PDX model exists for a subgroup of interest, we will try to establish it in the course of the project, by screening patients for the respective MESI marker panels before surgery and trying to derive primary cultures, cultured tissues and PDX from the fresh tissue. If the tumor cells do not grow as primary cultures and PDX we at least will be able to study their drug response in primary tissue cultured in perfusion-based bioreactors.

Treatment schemes for PDX mice, representing clinical cancer therapy schemes, are regularly conducted at VHIO. Samples for several interventions (P13K, CDK4/6 inhibitors and combination thereof) are already available for analysis; other relevant regimens, based on MESI model predictions will be easily implemented.

Samples for several interventions are already available for analysis (see table below); other relevant regimens, based on MESI model predictions will be easily implemented. While some tumors will recapitulate the model-predicted therapy responses, others are expected to escape immediately, or therapy resistance will arise with time in the initial responders. We will take advantage of this phenomenon to elucidate the differences between the responding tumors versus immediate and emerging resistant tumors. PDX tissues will be taken to molecular characterization of the response differences by panel sequencing and RNASeq (WP3) as well as metabolic measurements (WP4) of therapy-resistant versus responsive PDX. We will establish kinetic MESI networks and their response to drug perturbation in different ER+BC PDX-derived genetic back-grounds as a novel means of ER+BC phenotyping. We expect that MESI-models will display a higher predictive power regarding individual ER+BC therapy response, as compared to established histology or expression-based tumor-phenotyping. The knowledge gained by this approach will again feed into analyses of patient material to enable an iterative optimization of MESI marker panels for prediction of therapy response.

Task/Trial 7.2 WOO Trial: Prospective Window Of Opportunity Trial: 2 weeks neoadjuvant Anastrozole in Postmenopausal Women with ER+BC. Partner: UKL-HD

The WOO Trial will allow us to study the patients' response to ET, by comparing BC tissue, serum and urine from patients at diagnosis without and with ET (for details see Study No.5 in the Clinical Annex)

The following primary endpoint will be assessed:

- association of MESI networks & MESI marker panels with biological/pathological responses.

The following secondary endpoints will be assessed:

- percent change in Ki67 expression from baseline to the core biopsy 2 weeks after the start of treatment;
- pCR defined as absence of invasive cancer in the breast and sampled regional lymph nodes;
- clinical response of the breast tumor to therapy as assessed by histopathology;
- radiologic response of the breast tumor as assessed by radiologic or ultrasound assessment.

Study design: We will perform an investigator-initiated monocenter, open label, prospective non-randomized neoadjuvant trial investigating the biological effects of 2 weeks of Anastrozole monotherapy in tumor tissue, serum, plasma and urine in 70 postmenopausal women with ER+ breast cancer. After routine biopsy post-menopausal patients predicted to receive an Aromatase inhibitor after surgery will receive Anastrozole therapy for 2 weeks prior to surgery. The primary objective of the trial is to investigate the biological effects of Anastrozole monotherapy in serum, urine and tumor tissue of ER+ BC patients by assessing the percentage of change from the baseline value in Ki67 expression after 2 weeks of therapy and analyzing gene expression, protein expression and metabolites in the tumor tissue (before and after Anastrozole treatment) as well as analyzing MESI marker panels in the sera and urine of the patients. The clinical research organization (CRO) KKS will support SS and AS in conducting this clinical trial (see budget included in UKL-HD and letter of support).

Diagnosis and Main Criteria for Inclusion and Exclusion: The study will enroll 70 postmenopausal women with early-stage ER+ breast cancer. Study participants will be required to have breast cancers with a tumor size >1 cm. Patients enrolled shall not have received prior therapy for their BC and will not have inflammatory cancers.

Test Product, Dosage, and Mode of Administration: The trial medication Anastrozole will be supplied as tablets administered orally, 1 mg daily (for details on neoadjuvant Anastrozole see Study No.5 in the Clinical Annex).

Criteria for Evaluation: Efficacy: • percent change in Ki67 expression from baseline to the core biopsy 2 weeks after the start of treatment • pCR defined as absence of invasive cancer in the breast and sampled regional lymph nodes • clinical response of the breast tumor to therapy as assessed by histopathology • radio-logic response of the breast tumor as assessed by radiologic or ultrasound assessment.

Safety: • adverse events Health Outcomes: • EORTC QLQ-C30. Biomarkers: • Plasma, serum, urine and fresh frozen tissue samples will be tested for MESI markers

Task/Trial 7.3 ET Termination Trial: Analysis of longitudinally collected serum and urine from ER+ BC patients before and after termination of ET. Partner: PATH

PATH will coordinate the collection of longitudinal sera and urine from PATH cohort patients (for details see Study No. 6 in the Clinical Annex). ER+ PATH patients in the last year of endocrine treatment as well as in the following years without endocrine therapy will be invited to donate serum and urine every year. This will allow us to obtain serum and urine in the presence and absence of ET. Analysis of serum/urine from patients before and after termination of ET and comparison to clinical follow-up may allow identification of MESI marker alterations predictive of recurrence after termination of ET. Patients with these markers might benefit from prolonged treatment beyond the current standard of 5 years.

Task/Trial 7.4 Intervention Validation Trial: Clinically validate predictive MESI-models and marker panels for targeted drug interventions. Partners: UKL-HD, PATH, UMCG, VHIIO, UIBK

Due to the long time to relapse, the low percentage of relapsing patients, and the risk for relapse remaining constant over two decades, trials with endpoints such as progression free survival are long-term efforts that cannot be carried out

within the typical budget and duration of a H2020 project. MESI-STRAT overcomes this limitation by taking advantage of existing trials to analyze MESI-models and marker panels in patients receiving targeted drug interventions. MESI-STRAT will investigate the effects of targeted drug interventions on MESI marker panels and their association with drug response in human ER+ BC patients in appropriate clinical studies performed by partners and collaborators (for details see Study No. 7 in the Clinical Annex). If enough patients of a MESI-marker defined ER+BC subgroup predicted to respond to the investigated drug intervention are available in a clinical trial, the predictive power of the MESI marker panel to stratify patients for the targeted drug intervention will be validated by analyzing if the patients of this sub-group respond better to this drug than the rest of the study population. Furthermore, by analyzing three male BC cohorts it will be investigated whether the MESI markers identified for female ER+BC also apply to male ER+BC.

Task 7.5 IIT/Umbrella Trial Design: Design own IIT and umbrella trials, in which ER+BC patients will be stratified to different therapies by MESI marker panels. Partners: UKL-HD, UMCG, VHIO

Our clinical partners (UKL-HD, UMCG, VHIO) will design IIT and umbrella trials to prospectively validate the identified MESI marker panels, predicting response or resistance to (combinatorial) targeted therapies. We will seek support from public funding agencies and our collaborating pharmaceutical companies (see 1.3.a, consortium description). Links with pharma partners are in place to apply for dry substance and funding following established pipelines which involve step-wise review of trial design, required budget, and the study protocol (see, e.g., letter of support by Novartis); public funding will be applied for with National and European funding bodies, e.g., the DFG, NWO, KWF, and EC.

Participation per Partner

Partner number and short name	WP7 effort
1 - UIBK	21.00
2 - PATH Biobank	3.00
3 - UKL-HD	25.00
4 - DKFZ	23.00
5 - VHIO	12.00
6 - DDI	20.00
Total	104.00

List of deliverables

Deliverable Number ¹⁴	Deliverable Title	Lead beneficiary	Type ¹⁵	Dissemination level ¹⁶	Due Date (in months) ¹⁷
D7.1	WOO trial: First study subject approvals package	3 - UKL-HD	Report	Confidential, only for members of the consortium (including the Commission Services)	6
D7.2	ET termination trial: First study subject approvals package	2 - PATH Biobank	Report	Confidential, only for members of the consortium (including the Commission Services)	6
D7.3	WOO trial: Midterm recruitment report	3 - UKL-HD	Report	Confidential, only for members of the consortium (including	24

List of deliverables

Deliverable Number¹⁴	Deliverable Title	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
				the Commission Services)	
D7.4	ET termination trial: Midterm recruitment report	2 - PATH Biobank	Report	Confidential, only for members of the consortium (including the Commission Services)	30
D7.5	WOO trial: Report on status of posting results	3 - UKL-HD	Report	Public	57
D7.6	ET termination trial: Report on status of posting re-sults	2 - PATH Biobank	Report	Public	57

Description of deliverables

D7.1 : WOO trial: First study subject approvals package [6]
 WOO trial: First study subject approvals package
 D7.2 : ET termination trial: First study subject approvals package [6]
 ET termination trial: First study subject approvals package
 D7.3 : WOO trial: Midterm recruitment report [24]
 WOO trial: Midterm recruitment report
 D7.4 : ET termination trial: Midterm recruitment report [30]
 ET termination trial: Midterm recruitment report
 D7.5 : WOO trial: Report on status of posting results [57]
 WOO trial: Report on status of posting results
 D7.6 : ET termination trial: Report on status of posting re-sults [57]
 ET termination trial: Report on status of posting re-sults

Schedule of relevant Milestones

Milestone number¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS1	WOO Trial First Patient, First Visit (FPFV)	3 - UKL-HD	12	WOO Trial First Patient, First Visit (FPFV):Informed consent signed
MS2	ET Termination Trial First Patient, First Visit (FPFV)	2 - PATH Biobank	18	ET Termination Trial First Patient, First Visit (FPFV): Informed consent signed
MS4	Prediction of first subgroup specific marker panels	9 - UNEW	30	Prediction of first subgroup specific marker panels: Model predictions in MESI-SEEK

Schedule of relevant Milestones

Milestone number¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS5	ET Termination Trial Last Patient First Visit (LPFV)	2 - PATH Biobank	45	ET Termination Trial Last Patient First Visit (LPFV): Informed consent signed
MS6	WOO Trial Last Patient First Visit (LPFV)	3 - UKL-HD	51	WOO Trial Last Patient First Visit (LPFV): Informed consent signed
MS7	WOO Trial Last Patient Last Visit (LPLV)	3 - UKL-HD	54	WOO Trial Last Patient Last Visit (LPLV): Samples in NCT tissue bank (UHH)
MS8	WOO Trial End of Study	3 - UKL-HD	57	WOO Trial End of Study : Data analysis complete
MS9	ET Termination Trial Last Patient Last Visit (LPLV)	2 - PATH Biobank	57	ET Termination Trial Last Patient Last Visit (LPLV): Samples in PATH biobank
MS10	ET Termination Trial End of Study	2 - PATH Biobank	57	ET Termination Trial End of Study: Data analysis complete

Work package number⁹	WP8	Lead beneficiary¹⁰	1 - UIBK
Work package title	Project coordination: management and communication		
Start month	1	End month	57

Objectives

The overall aim of WP8 is the implementation of the management plan to coordinate all MESI-STRAT actions. Iterative procedures are inherent to systems bio-medicine. The MESI-STRAT management will adhere to this iterative principle throughout to achieve continuous improvement of its processes.

The specific objectives for WP8 are the

1. administrative and financial coordination, and communication with and reporting to the EC
2. coordination of the MESI-STRAT workflow, risk and gender issues.
3. coordination of knowledge exchange between the MESI-STRAT partners.
4. IPR management plan: Innovation and intellectual property (IP) management and protection.

Description of work and role of partners

WP8 - Project coordination: management and communication [Months: 1-57]

UIBK, PATH Biobank, UKL-HD, DKFZ, UiB, UNEW, Charité, SysBioSim B.V., HITS, UMCG

WP8 is dedicated to MESI-STRAT management and organization, and will be led by the project coordinator (UIBK/KT) and the co-coordinator (PATH/TA), supported by a project manager and by the facilities of the coordinating host institution (UIBK). The tasks are outlined here, details can be found in section 3.2.

Task 8.1 Management plan, administrative/ financial coordination, and communication / reporting to the EC Based on the management plan (drafted in 3.2), a project management manual will be put in place and continuously adapted where necessary, to guide all further implementation, incl. the decision-making processes, interfaces management, progress assessment, cost and risk management and reporting, organization of sub-contracted work, and monitoring of quality indicators throughout the project. The coordinator (UIBK/KT, f) will be responsible for achieving the objectives of the project in line with the Grant Agreement. She will be the dedicated contact person liaising with the European Commission (EC) on behalf of MESI-STRAT, transferring the reports and informing the EC of any major issues/modifications of the work plan. As de-tailed in section 3.2.1., strategic management will be carried out by the strategic board (SB), and day-to-day management will be supported by an experienced EU project manager (PM).

Task 8.2 Coordination of the workflow

As coordinator, UIBK/KT will oversee the interfaces between the various WPs as well as the preparation and dissemination of the project reports using information provided by partners. As the chairperson of the SB, KT will ensure optimal coherence between decision-making bodies to minimize constraints. Any risk issues will be addressed as detailed below in section 3.2.3.

The SB will set the annual scientific objectives, policy and strategic orientations of the project in accordance with the project program, our Consortium Agreement and the rules of the Grant Agreement. It will coordinate the workflow and exchange of materials. A prime task of the SB is to ensure, jointly with the WP9 leaders PATH and SBS, the implementation of the plans for dissemination and exploitation, and for communication (Section 2.2 and WP9). In these tasks the SB will be supported by the international advisory board (IAB), the dissemination and exploitation committee (DEC), and the Gender Committee (GC) (detailed in section 3.2.1, management).

The PM will collect information at least every 6 months to monitor the progress of the project to-wards its objectives, deliverables and milestones. The PM and KT will ensure compliance of the project with the technical annex and, if necessary, propose modifications to the SB. Accordingly, KT and the PM will prepare the agendas of SB meetings, propose decisions, and will be responsible for the proper execution and implementation of the decisions of the SB.

Task 8.3 Coordination of knowledge exchange between the partners, and meeting schedule.

Information that can influence the project implementation will be communicated and implemented by a communication and meeting structure that relies on iterative management strategies that have proven successful in previous and ongoing collaborations. Specifically, the partners work in interdisciplinary MESI-STRAT expert teams of modelers/informaticians and experimentalists/clinicians, who specialize in different aspects of cancer signaling, metabolism, computational modeling/network analysis and data handling (see Section 3.3). The expert teams will be the smallest internal communication units who develop their joint research foci and report to their mutual WP groups. MESI-STRAT expert teams will come together in bi-weekly individual online and on-site meetings. A dedicated meeting schedule,

detailed in 3.2.1, will ensure smooth information flow at all levels of our consortium and the speedy identification and resolution of any risks arising.

Task 8.4 Innovation and intellectual property (IP) management and protection.

This MESI-STRAT innovation management (detailed in Section 3.2.2) follows well-established iterative practice in systems approaches and implements the guiding principle of continuous improvement through iterative development within all WPs and their interactions. This gives MESI-STRAT the possibility for self-correction, enabling it to respond to an external or internal opportunity. The understanding of other market and technical problems is ensured by the open communication between the SMEs, and scientific and clinical partners in our consortium.

The management of knowledge and IP will be monitored by the Coordinator subject to the decision of the SB, advice by the DEC, and the Consortium Agreement. Based on the ownership of MESI-STRAT Results (i.e., Foreground), and evaluation by the DEC and the coordinator, foreground with potential for commercial exploitation shall be protected in an adequate and effective manner as laid out in section 2.2.3.

The decision on whether to publish open access documents must come after the more general decision on whether to go for a publication directly or to first seek protection using IPR, as it is crucial to maintain the option to exploit research results commercially, e.g., through patenting. Following our consortium agreement, MESI-STRAT will implement the IPR management plan (outlined in section 2.2.3) through the grant agreement. The academic partner institutions have dedicated TTOs that ensure proper handling and protection of IP. The TTO of UMCG has been actively involved in the MESI-STRAT proposal preparation to shape the measures of the IPR management plan, which will be taken over by UIBK.

WP8 will work in synergy with each individual WP and partner to facilitate each WP's own dissemination of specific technical activities, innovations, and findings, with due recognition of the IP management and ownership. At the critical times of (1) patenting, (2) licensing, or (3) own industrial initiatives, the contributions of all involved consortium members up to this point will be documented and frozen to define what the object of the patent/license will be. The efforts of the leading institutions for patenting, licensing, feasibility analyses for establishing a possible a spin-off will be continuously documented, to reward continuing investment.

Participation per Partner

Partner number and short name	WP8 effort
1 - UIBK	22.00
2 - PATH Biobank	1.00
3 - UKL-HD	1.00
4 - DKFZ	1.00
7 - UiB	2.00
9 - UNEW	1.00
10 - Charité	1.00
13 - SysBioSim B.V.	1.00
14 - HITS	1.00
15 - UMCG	7.00
Total	38.00

List of deliverables

Deliverable Number¹⁴	Deliverable Title	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
D8.1	Management plan	1 - UIBK	Report	Confidential, only for members of the consortium (including the Commission Services)	3

Description of deliverables

D8.1 : Management plan [3]

Management plan

Schedule of relevant Milestones

Milestone number¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification

Work package number ⁹	WP9	Lead beneficiary ¹⁰	13 - SysBioSim B.V.
Work package title	Dissemination, exploitation, and communication		
Start month	1	End month	57

Objectives

The overall aims of WP9 are to (i) achieve a significant and durable impact on EU citizens' health, in particular BC patients and their families, by promoting the use MESI-STRAT's new models for ER+BC patient stratification to inform clinical decision making, (ii) accelerate the translation of the biomedical and clinical research results of MESI-STRAT to medical use, (iii) promote the use of MESI-STRAT's models and marker panels by health care professionals and the industry on the basis of increased cost-effectiveness in comparison to current practice, (iv) increase research and innovation opportunities, particularly for SMEs active in system medicine. Specific objectives: WP9 coordinates measures to maximize impact, by implementing the (1) Dissemination and exploitation plan, (2) Plan for open access and open data, and (3) Communication plan.

Description of work and role of partners

WP9 - Dissemination, exploitation, and communication [Months: 1-57]

SysBioSim B.V., UIBK, PATH Biobank, UKL-HD, DKFZ, VHIO, DDI, UiB, UiT, UNEW, Charité, Neuroimmun GmbH, HITS, UMCG

WP9 is dedicated to the dissemination, exploitation and communication of the MESI-STRAT results. The SME SBS (BA) and PATH (DS, patient expert) will jointly lead WP9 to ensure optimal scientific and commercial dissemination, recognition and implementation of opportunities for exploitation, and communication of the MESI-STRAT programme and its results to all stakeholders. SBS and PATH will be supported by the MESI-STRAT management team (UIBK), the Cancer Information Service KID & its European partners, and the IAB.

Task 9.1 Dissemination and exploitation plan, and implementation

As detailed in Section 2.2.1, this plan ensures the promotion of MESI-STRAT's scientific and clinical results as well as commercial outcomes and opportunities to all stakeholders. WP9 will work closely with WP8 (co-ordination) in liaison with all WP leaders to ensure that all key interim and final results are disseminated appropriately – with a balance between dissemination of results by WP leaders and expert teams, and IP protection as outlined in WP8 and section 2.2.3. Scientific dissemination will be through conference presentations, workshops, peer-reviewed journal publications, and own workshops and symposia. Effective commercial exploitation of new MESI models and MESI marker panels will be achieved with (i) MESI-STRAT's SMEs providing systems medicine services (SBS, HITS) or developing diagnostic tools (NIN, QuantuMDX, CELLEC BIOTEK); (ii) collaborating pharmaceutical industry (see 1.3.a); and (iii) TTOs of the academic partners to evaluate the potential for an own industrial engagement.

Task 9.2 Open access and open data

MESI-STRAT will adhere to the goals set by the EC for open science feeding into the policy for RRI, by actively pursuing open access publishing and participating in the Open Research Data Pilot, in line with restrictions imposed by patient confidentiality and IPR protection. As detailed in section 2.2.3, measures to provide open access and open data ensure accessibility of MESI-STRAT results by the entire scientific community, commercial entities and the public. Exploiting the opportunities of upcoming EU legislation for publicly funded research, MESI-STRAT papers will be made accessible from 2018 on (when the according legislation becomes effective) 6 months after their publication in scientific journals via open repositories of the partner institutions (green open access), and linked to the MESI-STRAT website. Publication costs for gold open access will be either covered by institutional or university funds, or will be applied for at National funding agencies. For cases where none of these options exist, there is a budget reserved to be allocated to MESI-STRAT partners in need. For participation in the Open Research Data Pilot, MESI-STRAT will deposit research data in repositories to enable third parties to access, mine, exploit, reproduce and disseminate these data (2.2.2). EMBL-EBI will support deposition and accessibility of MESI-STRAT raw and curated data in EMBL-EBI-hosted repositories.

Task 9.3 Communication plan and implementation

MESI-STRAT seeks to promote its results to a broader group of stakeholders in order to have a significant impact on future health-related societal challenges. The comprehensive MESI-STRAT communication plan, detailed in section 2.2.4, is core to WP9 and complements our dissemination and exploitation strategy. Next to scientific, commercial,

and societal stakeholders including patients and their families, our communication plan also addresses clinical opinion leaders involved in deciding future health policies, and the public.

As detailed in section 2.2.4, MESI-STRAT will promote its results and receive feedback at own patient days, by a European telephone survey, and by participating in local and national patient days, and presentations at events and initiatives aimed at patients' literacy, integration, and involvement in the process of medicines research and setting research priorities. Materials on the website will be important, as will be electronic newsletters, podcasts, YouTube films and social media, and publications in lay journals.

WP9 will work by initially commissioning the design and delivery of a common web portal, then it will link with other WP leaders and other project partners to set the pattern of the initial formative communication programme. Feedback and coordination by the partnering patient organization PATH during internal meetings, and feedback systematically collected by questionnaires and electronic polls, will help to direct the MESI-STRAT strategy based on the medical needs of patients to improve quality of life as well as survival. Awareness about new standards in the implementation of systems medicine approaches will be raised by educational training for medical professionals and basic scientists and students, offered by the partnering experts, and for the public (e.g., Medical Public Academy, Studium generale at partnering institutions and the European patient academy EUPATI). Joint press releases, reviews, and interviews in lay language, and a lay accessible public version of MESI-STRAT's final report, distributed via the project portal and linkage to other key websites, will complete our communication plan, which will be topped off by a large audience conference at the conclusion of the project to promote MESI-STRAT's findings on systems medicine of metabolic signalling networks to treat ER+BC, and derive future implications thereof for other cancer diseases.

Participation per Partner

Partner number and short name	WP9 effort
1 - UIBK	8.00
2 - PATH Biobank	2.00
3 - UKL-HD	1.00
4 - DKFZ	1.00
5 - VHIO	1.00
6 - DDI	1.00
7 - UiB	2.00
8 - UiT	1.00
9 - UNEW	1.00
10 - Charité	1.00
12 - Neuroimmun GmbH	1.00
13 - SysBioSim B.V.	5.00
14 - HITS	1.50
15 - UMCG	4.00
Total	30.50

List of deliverables

Deliverable Number ¹⁴	Deliverable Title	Lead beneficiary	Type ¹⁵	Dissemination level ¹⁶	Due Date (in months) ¹⁷
D9.1	Dissemination & exploitation plan	13 - SysBioSim B.V.	Report	Confidential, only for members of the	3

List of deliverables

Deliverable Number¹⁴	Deliverable Title	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
				consortium (including the Commission Services)	
D9.2	Communication plan	2 - PATH Biobank	Report	Confidential, only for members of the consortium (including the Commission Services)	3
D9.3	MESI-STRAT website with continuous updates	1 - UIBK	Websites, patents filling, etc.	Public	6

Description of deliverables

D9.1 : Dissemination & exploitation plan [3]
 Dissemination & exploitation plan

D9.2 : Communication plan [3]
 Communication plan

D9.3 : MESI-STRAT website with continuous updates [6]
 MESI-STRAT website

Schedule of relevant Milestones

Milestone number¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS3	MESI-STRAT patient days	2 - PATH Biobank	18	MESI-STRAT patient days: First patient day held

Work package number⁹	WP10	Lead beneficiary¹⁰	1 - UIBK
Work package title	Ethics requirements		
Start month	1	End month	57

Objectives

The objective is to ensure compliance with the 'ethics requirements' set out in this work package.

Description of work and role of partners

WP10 - Ethics requirements [Months: 1-57]

UIBK

This work package sets out the 'ethics requirements' that the project must comply with.

List of deliverables

Deliverable Number¹⁴	Deliverable Title	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
D10.1	NEC - Requirement No. 1	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D10.2	POPD - Requirement No. 2	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D10.3	H - Requirement No. 3	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D10.4	HCT - Requirement No. 4	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D10.5	A - Requirement No. 5	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	6
D10.6	GEN - Requirement No. 7	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	3

List of deliverables

Deliverable Number¹⁴	Deliverable Title	Lead beneficiary	Type¹⁵	Dissemination level¹⁶	Due Date (in months)¹⁷
D10.7	H - Requirement No. 8	1 - UIBK	Ethics	Confidential, only for members of the consortium (including the Commission Services)	3

Description of deliverables

The 'ethics requirements' that the project must comply with are included as deliverables in this work package.

D10.1 : NEC - Requirement No. 1 [12]

1. The applicant must confirm that the ethics standards and guidelines of Horizon2020 will be rigorously applied, regardless of the country in which the research is carried out. 2. The applicant must provide details on the material which will be imported/to/exported from EU and provide the adequate authorisations.

D10.2 : POPD - Requirement No. 2 [6]

1. The applicants must devise a data management plan including detailed information on the procedures that will be implemented for data collection, storage, protection, retention, reuse and/or destruction. Compliance confirmation with current national and EU legislation must be included. 2. The applicants must also include in the plan a policy making sure that the collected data is harvested on strict "need to know" and "need to use" basis. As such, but non-limitedly, the applicants must also include in the plan a privacy impact assessment. 3. Copies of current legal "paper trail evidence" by the competent Data Protection Authority/ "one stop shop" as applicable, must be collected and provided to the Commission, upon request, to ensure continuing compliance with ongoing legislation. 4. If the position of a Data Protection Officer is established, their opinion/confirmation that all data collection and processing will be carried according to current EU and national legislation should be collected and submitted to the Commission upon request, as well as all administrative documents and permissions in relation to data import and export. 5. Applicants should provide detailed information on privacy/confidentiality and the procedures that will be implemented for data collection, storage, access, sharing policies especially when third party countries are concerned, protection, retention and destruction. Confirmation that they comply with national and EU legislation. 6. Templates of the informed consent forms and information sheet for data collection and processing must be submitted.

D10.3 : H - Requirement No. 3 [6]

1. Details on incidental findings must be provided. The applicants must detail the three management pathways (right "not to know", "transmission of the collected information to the GP" and "direct information disclosure"). A policy must be devised and implemented. 2. Details on the procedures and criteria that will be used to identify/recruit research participants must be provided. 3. Templates of the informed consent forms and information sheet must be submitted on request. 4. Copies of ethics approvals for the research with humans must be submitted for each of the studies listed in table 2, page 45 part B2. 5. Detailed information must be provided on the informed consent procedures studies that will be or have been implemented for the participation of humans, i.e. each of the studies listed in table 2, page 45 part B2. For Info, Specifically: Participants must have the right: - To know that participation is voluntary - To ask questions and receive understandable answers before making a decision - To know the degree of risk and burden involved in participation - To know who will benefit from participation - To know the procedures that will be implemented in the case of incidental findings - To receive assurances that appropriate insurance cover is in place - To know how their data will be collected, protected during the project and either destroyed or reused at the end of the research, if plans to reuse the data exist, participants should be duly informed, and consented also for this further usage, - To withdraw themselves and their data and samples from the project at any time - To know of any potential commercial exploitation of the research.

D10.4 : HCT - Requirement No. 4 [6]

1. In case of use of human cells/tissues available commercially, details on cells/tissues type and provider must be submitted. 2. In case human cells/tissues are obtained within the project, details on cells/tissues type and ethics approval must be provided. 3. In case human cells/tissues are obtained within another project, details on cells/tissues type and authorisation by primary owner of data (including references to ethics approval) must be provided 4. In case of human cells/tissues stored in a biobank, details on cells/tissues type must be provided, as well as details on the

biobank and access to it. 5. Clarification is required as to whether informed consent is in place for the use and re-use, i.e. the propagation, of patient derived human breast cancer tissues in the 6. PDX mouse models. Informed consent forms and information sheets must be provided. 7. Regarding liquid biopsies at DKFZ and UHH, Heidelberg, the informed consent information sheet and the clinical study protocol must be revised to allow withdrawal of both data and samples from the biobank and from the study.

D10.5 : A - Requirement No. 5 [6]

1. In case research protocols are not defined, general information must be kept by the beneficiary in the project files on the nature of the experiments, the procedures to ensure the welfare of the animals, and how the Principle of the Three Rs will be applied. This information must be provided upon request. 2. When submitting the application for scrutiny to the competent local/national ethics boards/bodies for authorization, detailed information should be provided on why living animals have to be used and why that species has been chosen. In addition, information should be given on the numbers of animals to be used in experiments, the nature of the experiments, the procedures that will be carried out and their anticipated impact (e.g. potential for pain, suffering, stress) and how that has been minimised. Furthermore, details should be provided on what procedures have been implemented to ensure the welfare of the animals during their lives (e.g. husbandry, minimising harms, criteria for humane endpoints, inspection protocols). The applicant should provide evidence of awareness of relevant European legislation and regulations covering animal experimentation and that the Principle of the Three Rs will be rigorously applied. 3. Copies of relevant authorisations (for breeders, suppliers, users, and facilities) for animal experiments must be submitted. These must cover the work with genetically modified animals where applicable. 4. Copies of ethical approvals by the competent local/national ethical/legal bodies, together with copies of relevant authorizations for animal experiments must be forwarded to the European Commission prior to the commencement of the research. These must cover the work with genetically modified animals where applicable. 5. Copies of training certificates/personal licenses of the staff involved in animal experiments must be provided.

D10.6 : GEN - Requirement No. 7 [3]

1. Due to the severity of the ethics issues raised by the proposed research work, it is required that an independent Ethics Advisor is appointed to oversee the implementation the ethical concerns involved in this research. A report by the ethics Advisor must be submitted to the Agency/Commission/ERC with the financial reports.

D10.7 : H - Requirement No. 8 [3]

6. The applicant must clarify whether adults unable to give informed consent will be involved and, if so, justification for their participation must be provided. 7. The applicant must clarify how consent/assent will be ensured in case adults unable to give informed consent are involved. 8. The applicant must clarify whether vulnerable individuals/groups will be involved. Details must be provided about the measures taken to prevent the risk of enhancing vulnerability/stigmatisation of individuals/groups, e.g. in the case of male breast cancer.

Schedule of relevant Milestones

Milestone number ¹⁸	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification

1.3.4. WT4 List of milestones

Milestone number ¹⁸	Milestone title	WP number ⁹	Lead beneficiary	Due Date (in months) ¹⁷	Means of verification
MS1	WOO Trial First Patient, First Visit (FPFV)	WP7	3 - UKL-HD	12	WOO Trial First Patient, First Visit (FPFV): Informed consent signed
MS2	ET Termination Trial First Patient, First Visit (FPFV)	WP7	2 - PATH Biobank	18	ET Termination Trial First Patient, First Visit (FPFV): Informed consent signed
MS3	MESI-STRAT patient days	WP9	2 - PATH Biobank	18	MESI-STRAT patient days: First patient day held
MS4	Prediction of first subgroup specific marker panels	WP2, WP3, WP4, WP5, WP6, WP7	9 - UNEW	30	Prediction of first subgroup specific marker panels: Model predictions in MESI-SEEK
MS5	ET Termination Trial Last Patient First Visit (LPFV)	WP7	2 - PATH Biobank	45	ET Termination Trial Last Patient First Visit (LPFV): Informed consent signed
MS6	WOO Trial Last Patient First Visit (LPFV)	WP7	3 - UKL-HD	51	WOO Trial Last Patient First Visit (LPFV): Informed consent signed
MS7	WOO Trial Last Patient Last Visit (LPLV)	WP7	3 - UKL-HD	54	WOO Trial Last Patient Last Visit (LPLV): Samples in NCT tissue bank (UHH)
MS8	WOO Trial End of Study	WP7	3 - UKL-HD	57	WOO Trial End of Study : Data analysis complete
MS9	ET Termination Trial Last Patient Last Visit (LPLV)	WP7	2 - PATH Biobank	57	ET Termination Trial Last Patient Last Visit (LPLV): Samples in PATH biobank
MS10	ET Termination Trial End of Study	WP7	2 - PATH Biobank	57	ET Termination Trial End of Study: Data analysis complete

1.3.5. WT5 Critical Implementation risks and mitigation actions

Risk number	Description of risk	WP Number	Proposed risk-mitigation measures
1	Delayed start up due to resource or communication problems (medium)	WP8	Early kick-off to check appropriateness of allocated manpower and communication structure. Enable corrective actions if needed
2	Shortage of resources and financial changes (medium)	WP8	Partner will have to continue the work with the available resources, and seek to supplement with internal resources. If necessary tasks will be adjusted.
3	Lack of communication between the consortium partners (medium)	WP8	Virtual meetings and on-site meetings at different partner sites will regularly take place, to maintain contact and enhance collaboration.
4	Delays on reporting/deliverables (high)	WP8	The Project Coordinator is responsible for solving any procedural problems that will appear. Conflict resolution mechanisms in place.
5	Illness of WP leader (high)	WP8	A system of co-leaders and deputies is already in place.
6	Data sharing restricted due to legal restrictions arising during the project (medium)	WP2	Wide range of algorithmic possibilities, tools & techniques for creating aggregated, sharable, pseudonymized data
7	Too rigid database design might limit data exploitation as research questions evolve (low)	WP2	Choice of database strategy supporting expansion, and regular consultation with coordinators to anticipate required additions.
8	Insufficient adoption of MESI-SEEK platform (medium)	WP2	Teaching and training of partners by HITS and UiB high quality easy-to-use software
9	Insufficient data quality (medium)	WP2	Curation support, training, & software that helps creating high quality data; Strong support by coordinator for such measures.
10	Issues with time scale differences in metabolic and signaling responses to perturbations (medium)	WP3	Adaptation of time-series measurements; change of time points; adaption of measured biological level (e.g., RNA in addition to protein); measurements taken under steady-state conditions
11	Insufficient tumor material in samples for molecular characterization (medium)	WP3	Collect additional samples; repeat the analysis and optimize them for lower amounts of proteins or metabolites
12	Unexpected network interactions discovered by network interference studies (WP3, 4) not covered by the models (WP5) (high)	WP3	Meet the network specialists (WPs3, 4, 5) and discuss potential adaptation of the model
13	Design of experimental approaches (WP3, 4) not optimal for perturbation studies (WP5), as initially selected time points may be	WP3	Run small experimental tests to quickly re-design the experimental approaches, to adapt time points, extraction protocols or perturbation regimens

Risk number	Description of risk	WP Number	Proposed risk-mitigation measures
	unsuitable or inhibitors too unspecific (high)		
14	Setup of standardized metabolite extraction protocols delayed, as some metabolites might be unstable or LC-MS may not be accurate enough for their quantification (low/medium)	WP4	Use metabolite-specific extraction protocols or biochemical kits (rather than, for example, LC-MS-based methods) for measurements of key metabolites
15	Calibration and validation issues with computational models of MESI networks (medium).	WP5	Structural and practical identifiability analyses will ensure that model parameters can be estimated from data. Arising issues will be addressed by additional data or by model reduction. Problems of model validation (i.e., differences in model predictions and experimental testing) will be addressed with modifications in topology, i.e., model reduction, or model enrichment and additional data.
16	The initial models covering ER-mTOR-MAPK and Trp-NAD networks may not cover sufficient components to distinguish between different patient subgroups (low).	WP5	Omics and network analyses will be expanded to identify RNAs/ proteins whose differential expression correlates with MESI networks to strengthen their predictive power.
17	The available ER+BC PDX models of VS are not representative of critical subgroups identified by MESI-STRAT (medium)	WP6	Agreements via EurOPDX are in place to share available ER+BC PDX models among consortium partners. VS can generate additional models for critical subgroups for which no PDX is available.
18	Poor engraftment rate of ER+BC PDX in immunocompetent models (medium)	WP6, WP7	Collection of additional patient material; adaptation of xeno-transplantation protocols
19	Poor recruitment or high dropout for WOO Trial (Study 5) (low)	WP1, WP7	Our estimates on recruitment rates are low and already entail 20 possible dropouts. We will provide high quality training and information about the MESI-STRAT studies to support the recruiting physicians. In case recruitment rates are not met, (1) the recruitment period will be extended by 6 months, (2) and recruitment will be expanded to other sites.
20	Poor recruitment or high dropout for ET Termination Trials (Study 6) (low)	WP1, WP7	Enhance measures to promote awareness and motivation by information, e.g., at patient days, via letters, networking with patient organization and patient information platforms etc. (see impact, 2.2.4). In case recruitment rates are not met, (1) the recruitment period will be extended by 6 months, (2) and recruitment will be expanded to other sites.

Risk number	Description of risk	WP Number	Proposed risk-mitigation measures
21	Insufficient stakeholder engagement (low)	WP9	Improve workflow with other WPs and the efficiency of the process.
22	Lack of stakeholder availability at annual meetings and workshops (medium).	WP9	Early planning, early availability assessment, and early notification of potential workshop dates.

1.3.6. WT6 Summary of project effort in person-months

	WP1	WP2	WP3	WP4	WP5	WP6	WP7	WP8	WP9	WP10	Total Person/Months per Participant
1 - UIBK	1	1	69	2	48	2	21	22	8		174
2 - PATH Biobank	9	1	0	0	0	8	3	1	2		24
3 - UKL-HD	10	1	0	0	0	8	25	1	1		46
4 - DKFZ	1	1	4	51	0	35	23	1	1		117
5 - VHHIO	3	0	3	0	0	3.50	12	0	1		22.50
6 - DDI	1	0	0	0	0	2	20	0	1		24
7 - UiB	0	7	8	33	20	0	0	2	2		72
8 - UiT	0	0	0	0	35	0	0	0	1		36
9 - UNEW	0	1	0	0	42	0	0	1	1		45
10 - Charité	0	1	35	1	6	0	0	1	1		45
11 - UDUR	0	0	0	0	0	0	0	0	0		0
12 - Neuroimmun GmbH	0	0	0	15	0	0	0	0	1		16
13 - SysBioSim B.V.	0	0	0	0	12	0	0	1	5		18
14 - HITS	2	18	2	0	1	0	0	1	1.50		25.50
15 - UMCG	0	0	0	10	8	0	0	7	4		29
Total Person/Months	27	31	121	112	172	58.50	104	38	30.50		694

1.3.7. WT7 Tentative schedule of project reviews

No project reviews indicated

1. Project number

The project number has been assigned by the Commission as the unique identifier for your project. It cannot be changed. The project number **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

2. Project acronym

Use the project acronym as given in the submitted proposal. It can generally not be changed. The same acronym **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

3. Project title

Use the title (preferably no longer than 200 characters) as indicated in the submitted proposal. Minor corrections are possible if agreed during the preparation of the grant agreement.

4. Starting date

Unless a specific (fixed) starting date is duly justified and agreed upon during the preparation of the Grant Agreement, the project will start on the first day of the month following the entry into force of the Grant Agreement (NB : entry into force = signature by the Commission). Please note that if a fixed starting date is used, you will be required to provide a written justification.

5. Duration

Insert the duration of the project in full months.

6. Call (part) identifier

The Call (part) identifier is the reference number given in the call or part of the call you were addressing, as indicated in the publication of the call in the Official Journal of the European Union. You have to use the identifier given by the Commission in the letter inviting to prepare the grant agreement.

7. Abstract

8. Project Entry Month

The month at which the participant joined the consortium, month 1 marking the start date of the project, and all other start dates being relative to this start date.

9. Work Package number

Work package number: WP1, WP2, WP3, ..., WPn

10. Lead beneficiary

This must be one of the beneficiaries in the grant (not a third party) - Number of the beneficiary leading the work in this work package

11. Person-months per work package

The total number of person-months allocated to each work package.

12. Start month

Relative start date for the work in the specific work packages, month 1 marking the start date of the project, and all other start dates being relative to this start date.

13. End month

Relative end date, month 1 marking the start date of the project, and all end dates being relative to this start date.

14. Deliverable number

Deliverable numbers: D1 - Dn

15. Type

Please indicate the type of the deliverable using one of the following codes:

- R Document, report
- DEM Demonstrator, pilot, prototype
- DEC Websites, patent filings, videos, etc.
- OTHER
- ETHICS Ethics requirement
- ORDP Open Research Data Pilot

16. Dissemination level

Please indicate the dissemination level using one of the following codes:

- PU Public
- CO Confidential, only for members of the consortium (including the Commission Services)
- EU-RES Classified Information: RESTREINT UE (Commission Decision 2005/444/EC)
- EU-CON Classified Information: CONFIDENTIEL UE (Commission Decision 2005/444/EC)
- EU-SEC Classified Information: SECRET UE (Commission Decision 2005/444/EC)

17. Delivery date for Deliverable

Month in which the deliverables will be available, month 1 marking the start date of the project, and all delivery dates being relative to this start date.

18. Milestone number

Milestone number: MS1, MS2, ..., MSn

19. Review number

Review number: RV1, RV2, ..., RVn

20. Installation Number

Number progressively the installations of a same infrastructure. An installation is a part of an infrastructure that could be used independently from the rest.

21. Installation country

Code of the country where the installation is located or IO if the access provider (the beneficiary or linked third party) is an international organization, an ERIC or a similar legal entity.

22. Type of access

- VA if virtual access,
- TA-uc if trans-national access with access costs declared on the basis of unit cost,
- TA-ac if trans-national access with access costs declared as actual costs, and
- TA-cb if trans-national access with access costs declared as a combination of actual costs and costs on the basis of unit cost.

23. Access costs

Cost of the access provided under the project. For virtual access fill only the second column. For trans-national access fill one of the two columns or both according to the way access costs are declared. Trans-national access costs on the basis of unit cost will result from the unit cost by the quantity of access to be provided.

Systems Medicine of Metabolic-Signaling Networks – A New Concept for Breast Cancer Patient Stratification



History of changes

Date	Change	Reason
22-09-17	Section B4, table under paragraph 4.2 for participant 2 (PATH): amount for subcontracting, indicated in brackets, was changed to comply with the budget table for participant 2.	The change was introduced to resolve the financial/administrative issues pointed out by financial officer Massimo Sibona on 09-08-2107.
22-09-17	Table 3.4b: Estimated costs for the obtaining of the Certificates on the Financial Statements (CFS) were added for partners 1 and 4.	The change was introduced to resolve the financial/administrative issues pointed out by financial officer Massimo Sibona on 09-08-2107.
22-09-17	Milestones and deliverables reduced and condensed.	Request of our PO Adoracion Navarro-Torne as of September 08 2017
22-09-17	Milestones and deliverables listed in the annex “Essential Information (...) for (...) Clinical Trials” were changed to match the amended milestones and deliverables (see previous line).	Request of our PO Adoracion Navarro-Torne as of September 08 2017
22-09-17	A confirmation and a list of documents that we have collected to meet all requirements signalled by the Ethics reviewers as pre-grant requirements was added to section B5.	Request of our PO Adoracion Navarro-Torne as of September 08 2017
22-09-17	A paragraph in which we explain point-by-point how we will comply with the post-grant requirements, as listed in the ethics report, has been added to section B5.	Request of our PO Adoracion Navarro-Torne as of September 08 2017
22-09-17	A list of the ethics deliverables, including the amended delivery dates, text amendments and comments has been added to section B5.	Request of our PO Adoracion Navarro-Torne as of September 08 2017
22-09-17	A confirmation that partners from third countries, including UK partners in the future, will perform all data management, curation and protection according to EU regulation has been added to the post grant ethics requirements in section B5 (protection of personal data, point 5)	Request of our PO A. Navarro-Torne and M. Sibona as of Sep. 12 2017
22-09-17	In part B1 the title “Linked national or international research and innovation actions...” has been changed to “Possible/Potential....” We added a note to the same paragraph that the PO will be notified if one the mentioned projects shares data or samples with MESI-STRAT, and IPR will be regulated beforehand.	Request of our PO A. Navarro-Torne and M. Sibona as of Sep. 12 2017
22-09-17	Tables 3.1b, and 3.1c removed from section 3.1.	EC instructions for preparation of part B for GA.
22-09-17	Note that tables 3.1a remained in part B.	The complex text, formatting, tables and figures of the WP descriptions cannot be pasted into the online forms for part A in the participant portal.
22-09-17	Tables 3.2a and 3.2b removed from section 3.2.	EC instructions for preparation of part B for GA.
22-09-17	Table 3.4a removed from section 3.4.	EC instructions for preparation of part B for GA.
22-09-17	The following information was added at the bottom of each page “[Proposal number] [Proposal acronym] – Part B – [Page number (starting at 1 for Part B)]”	EC instructions for preparation of part B for GA.
29-09-17	Section 4.2: “No third parties involved” replaced by “see page 78”	Request of our PO A. Navarro-Torne and M. Sibona as of Sep. 26 2017
29-09-17	“The subcontracting will be carried out ensuring the best value for money and avoiding any conflict of interests.” added on p. 78.	Request of our PO A. Navarro-Torne and M. Sibona as of Sep. 26 2017
29-09-17	p. 9: heading changed to “National or international research and innovation activities”	Request of our PO A. Navarro-Torne and M. Sibona as of Sep. 26 2017
29-09-17	p. 132: paragraph “In agreement with (...) beneficiary institutions.” deleted	Compliance with comments of our PO A. Navarro-Torne and M. Sibona as of Sep. 26 2017
06-10-17	Timelines in Section 3 modified	Comments of M. Sibona as of 05-10-17
06-10-17	p. 8 paragraph "Novartis (...) trial design." deleted	Comments of M. Sibona as of 05-10-17
06-10-17	p. 34 paragraph “Prof. E. (...) see letter)” deleted	Comments of M. Sibona as of 05-10-17
06-10-17	Clinical Study No. 2, 2.2.1: “The samples will be provided by MESI-STRAT partners.” was added.	Comments of M. Sibona as of 05-10-17
06-10-17	paragraph 3.7.7: “samples (...) VUMC)” deleted.	Comments of M. Sibona as of 05-10-17
06-10-17	Tab. 3.4.b, CHAB: “Furthermore (...) apply.” deleted.	Comments of M. Sibona as of 05-10-17
06-10-17	Text under 2.9, 3.9, 4.9, 7.9, 8.9 replaced by “Not applicable.”	Comments of M. Sibona as of 05-10-17
06-10-17	The section 4.2 was included after 4.1, on page 110.	Comments of M. Sibona as of 05-10-17
27-10-17	p. 35, Task 1.3: “E. Boven, G. Wulf” deleted	Request of M. Sibona as of 25-10-17
27-10-17	p. 50, Task/Trial 6.2: “, collaborator: E. Boven” deleted	Request of M. Sibona as of 25-10-17

09-11-17	Omitted MS1 (kick-off meeting) from Part A.	Request of M. Sibona as of 09-11-17
19-12-18	Numeration and due dates of milestones in the annex "Essential Information (...) for (...) Clinical Trials", Sections 6.7.1 and 7.7.1 were changed to match the omission of MS1 in Part A. Gantt and PERT charts in part B were updated accordingly.	Request of our PO L. Quiros as of 11-12-18
19-12-18	The date for submission of D5.1 was changed to M18 in the Gantt chart to align Part A and B.	Request of our PO L. Quiros as of 11-12-18
19-12-18	Due to change of relevant staff (Sushma Grellscheid, SG) from UDUR to UiB, all tasks formerly allocated to UDUR were reallocated to UiB. Details are given in the amendment request letter. Information in Part A and B was changed accordingly.	Change of partners as of voting by General Assembly, taking effects as of February 01 2019 As of request of our PO L. Quiros, UDUR remained in B4 (partner descriptions). The date of termination was added to this entry.
19-12-18	Due to change of relevant staff (Kathrin Thedieck, KT) from UMCG to UIBK, UIBK was newly added as a partner and coordinator. UMCG remains a partner with BMB as main PI. Details are given in the amendment request letter. Part A and B were changed as detailed in the amendment request letter.	Change of partners and coordination as of voting by General Assembly, taking effects as of February 01 2019 Amendment request letter phrased in consultation with our PO L. Quiros as of 18-12-18 (phone call).
19-12-18	Ethics related documents for UIBK were added to 5.3.1 Pre-Grant Requirements (list of copies of facilities authorisations)	Request of our PO L. Quiros during phone conversation on 18-12-18
19-12-18	In Part A, responsibilities for all milestones related to the ET Termination Trial (MS2, MS5, MS9 and MS10) were changed to PATH, as they had been erroneously assigned to UKL-HD during the GA preparation, when information was transferred from Part B to Part A.	The change was introduced to reconcile Part A with Part B. We informed our PO L. Quiros as of 27-11-18.
19-12-18	In Part A and in B1 (Work package overview), leadership role of WP9 was corrected to be SBS/BA to align the information with the work package description in Part B3.	The change was introduced to reconcile Part A with Part B. We informed our PO L. Quiros as of 27-11-18.
19-12-18	The numeration of the objectives in the description of WP3 was corrected.	Request of our PO L. Quiros as of 11-12-18
19-12-18	In section 3.2.1 and description of WP8, the entity (UIBK) was indicated as project coordinator instead of KT.	Request of our PO L. Quiros as of 11-12-18
19-12-18	In section 3.2.1, "Grant Agreement" was replaced by "Consortium Agreement".	Request of our PO L. Quiros as of 11-12-18
19-12-18	Inconsistencies of the DoA with part B3 were removed by aligning all text with the information given in B3. Therefore, - due dates of D7.5 and 7.6 in the "Essential Information (...) for (...) Clinical Trials", Sections 6.7.1 and 7.7.1 were changed to month 57. - Partners listed in table 2 "MESI-STRAT clinical and preclinical trials" in part B1, B5 and "Essential Information (...) for (...) Clinical Trials" were aligned with B3/WP6+7. - preclinical studies were assigned throughout to VHHIO, DDI, DKFZ and UIBK to align with B3/WP7.	In consultation with our PO L. Quiros as of 18-12-18 (phone call), the changes were introduced to resolve inconsistencies,
19-12-18	Description of implementation of the work contained in table 3.1.3 was migrated to Part A. Figures and tables which could not be entered in A were left in Part B, with a precise reference to which WP/tasks in Part A they refer.	Request of our PO L. Quiros as of 14-12-18

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Definitions:

MESI models. Combined computational models of metabolic and signaling (MESI) networks that govern drug response in ER+BC.

MESI marker panels. Panels of metabolites and signaling proteins which in conjunction with MESI computational models predict drug response in distinct patient subgroups. Initially, proteins and metabolites will be measured in tumor tissue and body fluids. Ultimately, we aim to develop MESI marker panels measurable solely in body fluids to stratify ER+BC patients to targeted drug therapies, and continuously monitor drug response without the need for tumor tissue.

Abbreviations

BC	breast cancer	L-Kyn	kynurenine
CDK4	cyclin dependent kinase 4	MAPK	mitogen activated protein kinases (MEK-ERK pathway)
DEC	dissemination and exploitation committee	MBC	metastatic breast cancer
DMP	data management plan	MESI	metabolic signaling
EC	European Commission	MP	management plan
ER	estrogen receptor alpha	mTOR	mammalian target of rapamycin (targeted by Everolimus)
ER+	ER-positive	ODE	ordinary differential equations
ET	endocrine therapy	PDX	patient derived xenograft
GC	gender committee	PI3K	PI3 kinase
GSEA	gene set enrichment analysis	RTK	receptor tyrosine kinase
HER2	human EGF receptor 2	SB	strategic board
IAB	international advisory board	SOC	standard of care
IDO1	Indoleamine-2,3-dioxygenase	SOP	standard operating procedure
IIT	investigator initiated trial	Trp	tryptophan
KA	kynurenic acid	TTO	technology transfer office
KID	German Cancer Information Service (CIS) / Krebsinformationsdienst	WOO	window of opportunity

1. Excellence

Summary. Breast cancer (BC) is a complex disease with high prevalence in the EU. 75% of the tumors are estrogen receptor-positive (ER+), and are treated with endocrine therapies (ET). The MESI-STRAT consortium will develop new models for knowledge-based stratification of patients into subgroups with different ET resistance mechanisms. We will establish predictive pipelines for (1) patient stratification prior and during ET; (2) recurrence risk assessment when ending ET; (3) marker panels to guide established targeted therapies for ET-resistant patients; (4) novel ET resistance mechanism-based therapy design.

The unique collection of matched BC tissue, serum, and >10 years follow-up from the patient organization PATH is essential for the longitudinal analysis of ET resistance and relapse. Our team of oncologists, modelers, bioinformaticians and experimentalists will develop new computational models in combination with network analyses and pharmacogenomics, to integrate multi-omics data and explore **metabolic and signaling (MESI)** networks driving ET resistance. Metabolite marker panels measured in biological fluids will enable patient stratification, resistance monitoring and clinical decision-making. This is a new concept as BC metabolism is poorly explored for diagnostics and therapy. Upon successful validation in preclinical models, the predictive marker panels and related treatments will be jointly investigated by our clinical and industrial partners in clinical studies.

1.1 Objectives

Background. BC claims the lives of 92,000 European women per year¹ (33.4/100,000 inhabitants) and accounts for the highest costs of all cancer-related healthcare (€6.73 billion; 13%)². Each year 332,000 new cases are registered (incidence 62.8/100,000)³ with 75–80% of them being ER+. ET, which block ER-related tumor growth show high efficacy⁴. Yet, even though most early-stage ER+ patients receive ET, approximately 30% will eventually relapse with metastatic BC (MBC). 5–10% of patients present with MBC at diagnosis⁵, of which only one-fifth will survive 5 years³. More than 40% of MBC patients do not respond to first-line ET (intrinsic resistance), and a significant percentage experience relapse, despite initial response (acquired resistance)⁴. ER+BC is unique in that recurrence rates remain almost constant for up to 20 years⁶ and this long follow-up is critical to understand relapse. But most cancer registries do not capture relapses and most trials do not follow the patients long enough, leading to a lack of accurate data on ET resistance and recurrence⁵. Mechanisms contributing to ET resistance include loss or mutations of ER, as well as changes in the expression of ER coregulators⁴. As ER is a signaling molecule, research and clinical trials on ET resistance focus on the crosstalk of ER with other oncogenic signaling networks⁴. Among them, the mammalian target of rapamycin (mTOR) and the mitogen-activated protein kinase (MAPK) pathways are major drivers of BC escape from ET⁴. Both pathways control ER phosphorylation and expression, and can endogenously activate the ER (Fig. 1). The mTOR inhibitor Everolimus (Novartis) has been

approved for targeted combinatorial ET with aromatase inhibitors – yet with limited success as the number of non-responders is high⁷. One reason for this limitation may be that Everolimus enhances MAPK activity⁸. The contribution of MAPK to ET resistance is currently not therapeutically exploited although genetic alterations of HER2 (13%) and PIK3CA (36%) are frequent in BC. Both drive activity of PI3 kinase (PI3K) and AKT, activators of mTOR and MAPK, which are currently explored as clinical targets in BC (Roche, Novartis & others). Cyclin dependent kinase 4 (CDK4) has recently emerged as another promising clinical BC target (Novartis, Pfizer & others). Importantly, CDK4 not only drives cell cycle progression and ER signaling but also mTOR activity, by inhibiting the mTOR suppressor tuberous sclerosis complex (TSC1/2)⁹. As PI3K and CDK4 concomitantly activate mTOR via TSC1/2,

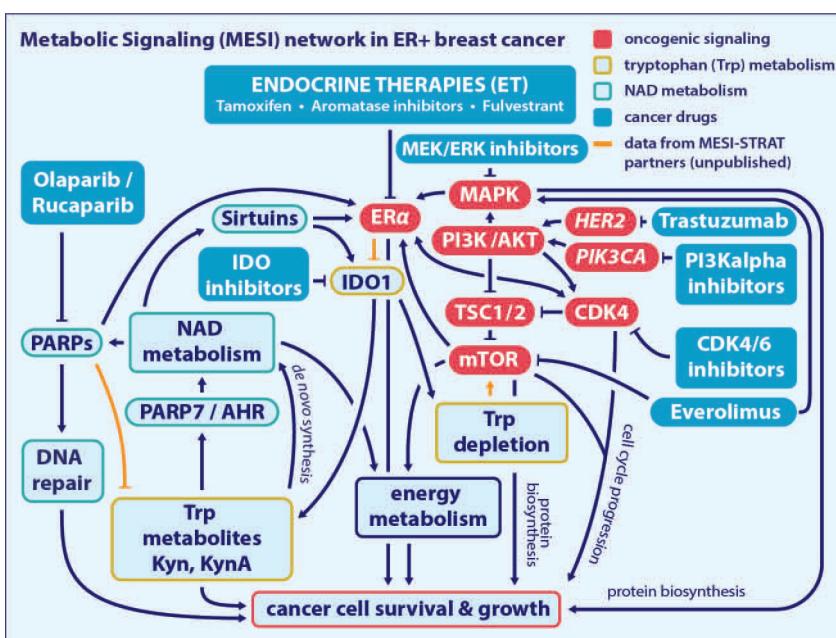


Figure 1. Metabolic Signaling (MESI) network in ER+ breast cancer (BC). The estrogen receptor (ER α) is central BC driver which is inhibited by endocrine (hormonal) therapies (ET). Central oncogenic signaling (red) and metabolic (light blue) routes are closely intertwined, suggesting that tumor metabolism contributes to endocrine resistance. We propose to exploit this to derive new concepts for patient stratification to endocrine therapies and other targeted cancer drugs (dark blue). See "background" section for details.

CDK4/6 inhibitors sensitize PIK3CA-mutant BC for PI3K inhibitors¹⁰, and raise hope for combinatorial use with ET^{5,11}. Although ER levels and oncogenic mutations are markers in BC therapy, their predictive power regarding targeted therapy response remains limited. In recent years, intense sequencing efforts, such as the METABRIC study¹², provided new insights, but did not improve therapy response.

Therefore, **new concepts for decision-making** are urgently required at several stages during ET.

(i) **At therapy onset:** overtreatment with additional chemotherapy is a concern, as it offers only ca. 4% absolute gain in survival¹³, has short- and long-term side effects and a considerable socioeconomic burden. Multigene prognostic tests¹⁴ can identify good-prognosis patients who might safely omit chemotherapy, but are limited to intrinsic ET resistance and unable to identify alternative targeted therapies. We propose MESI marker panels to stratify patients based on their individual ET-resistance mechanism(s), which would significantly improve this.

(ii) **During endocrine therapy:** it is currently impossible to predict the time-point of acquired resistance and, if it occurs, no markers are available to identify which ET resistance mechanism(s) are active, in order to determine which of the available targeted therapies would be superior to chemotherapy.

(iii) **When ending the therapy:** no method is available to predict which patients will relapse and might profit from prolonged treatment beyond the current standard of 5 years. Tumor material is typically only available at therapy onset and cannot be used to monitor acquired resistance and recurrent disease.

Furthermore, marker panels measured in body fluids would represent primary and metastatic tissues throughout the body. MESI-STRAT will develop such marker panels, measurable in body fluids, to assess the mechanism(s) of ET resistance and guide the stratification of patients with ET resistance for targeted (combinatorial) therapies. The combinatorial inhibition of ER and mTOR and/or MAPK appears promising but the limited success of combinatorial aromatase inhibitor/Everolimus therapies suggests that we are missing important aspects of BC biology. One reason is certainly that mTOR and MAPK are embedded in a highly dynamic kinase signaling network with complex wiring by multiple feedback mechanisms (**Fig. 1**). Moreover, the dynamics of these networks differ in a tumor- and patient-specific manner. Given this enormous complexity, the outcome of drugs targeting the oncogenic signaling network cannot be intuitively predicted. Rather, dynamic modeling techniques are required, to quantitatively capture the context- and patient-specific network tuning and predict therapy outcome. Such predictive models hold great promise for patient stratification at all stages of ET.

Given the tremendous efforts to identify new therapeutic targets and reliable markers for therapy monitoring in BC, it is surprising that tumor metabolism is only rarely considered. PI3K, MAPK and mTOR are all critical regulators of central metabolic pathways. Two key metabolic molecules, tryptophan (Trp) and NAD, have recently emerged as major tumor-promoting players^{15,16}. The enzyme indoleamine-2,3-dioxygenase 1 (IDO1) catalyzes the degradation of Trp to kynureneine (Kyn) (**Fig. 1**), an onco-metabolite which enhances cancer aggressiveness by suppressing anti-tumor immunity and enhancing cancer cell motility¹⁵. The CO laboratory recently showed that the ER status determines IDO1 levels in BC¹⁷, and that ET enhances IDO1 expression in ER+BC cells (unpublished, **Fig. 2 A-C**; similar observations with Fulvestrant, not shown due to space constraints). Hence, IDO1 derepression may contribute to ET resistance. Indeed, we observe elevated Kyn levels in the serum, and increased *IDO1* levels in tumor tissue of ER+BC patients on ET (**Fig. 2D, E, CO**, unpublished), suggesting that Trp metabolites can serve as markers to monitor developing ET resistance. In keeping with this, high *IDO1* levels correlate with worse outcome in ER+BC patients on ET (**Fig. 2F, CO**, unpublished), suggesting that IDO1 contributes to ET resistance. Enhanced IDO1 activity deprives cells of Trp. Trp deprivation in ER+BC cells enhances mTOR activity, as assessed by phosphorylation of the mTOR substrate 4E-BP (**Fig. 2G, KT**, unpublished), and mTOR inhibition increases IDO1 levels (**Fig. 2H, CO** unpublished), suggesting multiple feedback regulations between them. Of note, mTOR is known to activate the ER¹⁸ (**Fig. 1**), indicating that the effects of mTOR inhibitors on IDO1 are mediated in part by the ER. Of note, we also find that ERK kinase is required for IDO1 suppression by the ER agonist estradiol (E2, **Fig. 2I, CO**, unpublished), suggesting that the MAPK pathway mediates ER effects on *IDO1*. For all these reasons, we propose that Trp metabolism is a hitherto neglected mediator of ET resistance in ER+BC. Hence, Trp metabolites could serve as diagnostic markers (explored by the partnering SME NIN), and IDO1 inhibitors are currently being developed and investigated for cancer therapies by the BE laboratory and his pharma partners.

Trp and NAD metabolism are closely linked (**Fig. 1**), as NAD is synthesized *de novo* from Trp, and Trp metabolites activate NAD metabolism via the aryl hydrocarbon receptor (AHR, **Fig. 1**)¹⁵, which is counteracted by poly (ADP ribose) polymerase 7 (PARP7)¹⁹. NAD-dependent enzymes including PARPs and sirtuins (protein deacetylases) affect ER signaling^{20,21} and are promising drug targets for ER+BC therapy. PARP inhibitors, such as Olaparib, are used to induce synthetic lethality in tumors with mutations in the DNA repair protein BRCA1/2 (occurring in 5–10% of all ER+ and ER- BC cases²²). We find that the Trp metabolite kynurenic acid (KA) is reduced in Olaparib-treated BC cells (**Fig. 2J**, unpublished, GW, Harvard), indicating that PARPs influence Trp metabolism, possibly via the NAD pathway, and that Trp metabolites can serve to monitor therapy response to PARP inhibitors. 36% of

BRCA1/2 mutated patients are ER⁺²³; even though they are rare, studying them will provide general insights into the interplay of NAD and Trp metabolism in ER+BC patients. NAD metabolism is closely linked with glycolysis and mitochondrial activity, which are central to energy metabolism and are closely intertwined with the mTOR pathway²⁴. Indeed, we find alterations in TCA cycle metabolites in serum of Everolimus-treated BC xenograft models (BMB and HJ, unpublished), suggesting that energy metabolism is affected as well.

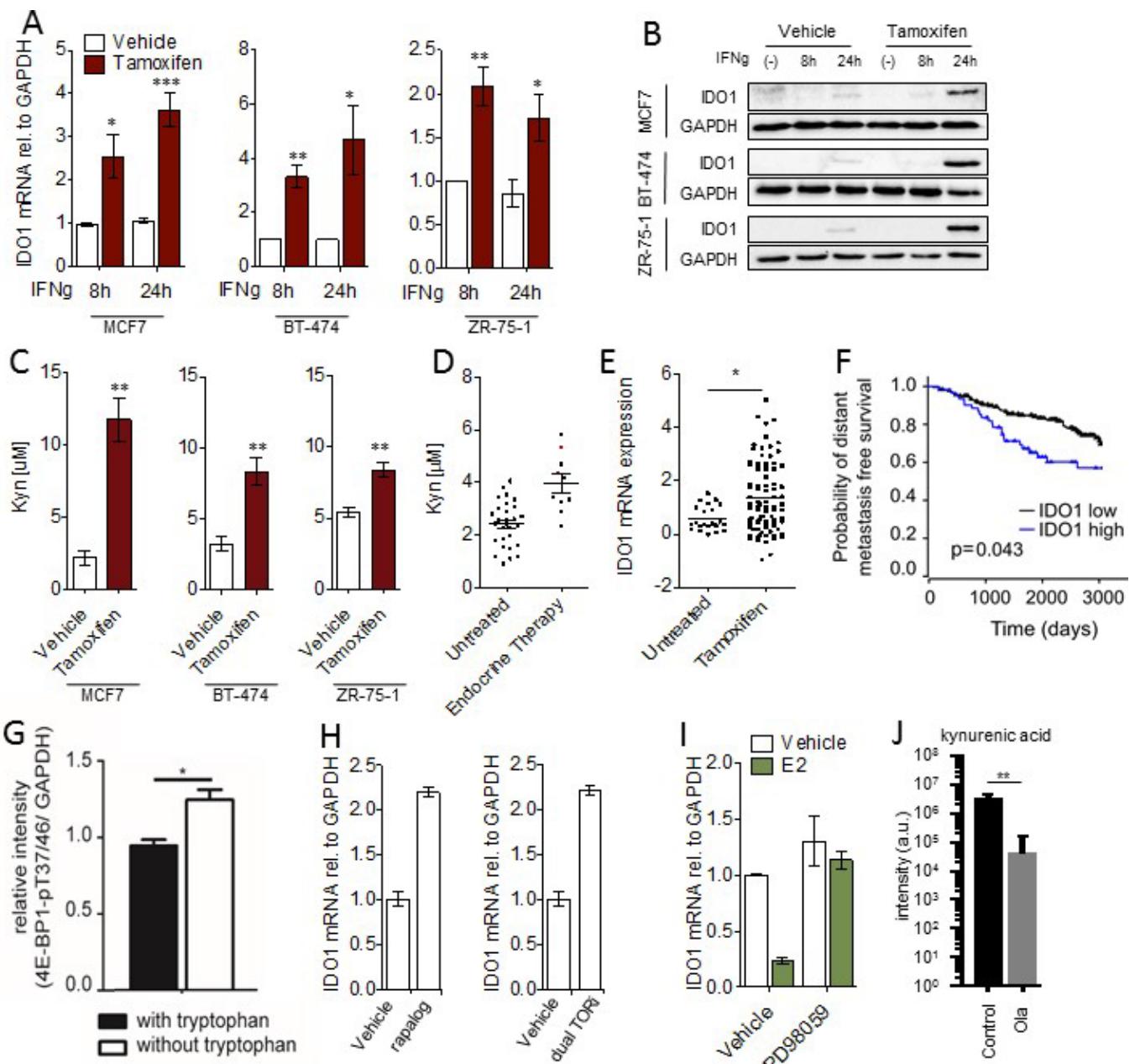


Figure 2. Preliminary data of the MESI-STRAT consortium. (A-F) Endocrine Therapy (ET) enhances Trp degradation by IDO1 in ER+BC cells and patients. (A) 48 h Tamoxifen (100 nM) + IFNγ (1000 U/mL, 8 or 24 h) increases IDO1 mRNA (qRT-PCR, n = 3–4); (B) IDO1 protein (immunoblot, n = 3); (C) and kynurenine (Kyn) release (HPLC, n = 3). Similar results observed with Fulvestrant (not shown). (D) 3 weeks neoadjuvant ET with Tamoxifen (n = 8) or Letrozole (n = 2) increases Kyn (ELISA) in sera of ER+ BC patients (control: 30 untreated ER+ BC patients). (E) IDO1 mRNA (microarray) is increased in Tamoxifen-treated (n = 87) ER+ BC patients with an inflammatory tumor microenvironment (upper quartile of IFNγ expression) (control: untreated ER+BC patients, n = 22, Mann-Whitney U test). (F) High IDO1 mRNA expression (upper quartile of tamoxifen-treated ER+ BC cohort, n = 258) reduces the probability of distant metastasis-free survival (microarray, GEO datasets GSE9195, GSE6532). (G-H) Low Trp enhances mTOR activity, and mTOR inhibitors induce IDO1 in MCF-7 ER+BC cells. (G) 24 h Trp starvation enhances mTOR substrate 4E-BP1-pT37/46 (quantified immunoblot signal, n = 3). (H) 48 h rapamycin (20 nM) or dual mTOR inhibitor Torin1 (250 nM) enhances IDO1 mRNA (qRT-PCR). (I-J) MAPK and PARP inhibitors alter Trp metabolism. (I) 48 h MEK inhibitor PD98059 (20 μM) prevents suppression of IDO1 expression (qRT-PCR) by estradiol (E2, 10 nM). (J) 3 h Olaparib (Ola) reduces kynurenic acid secretion (mass spectrometry analysis). Results are expressed as means, error bars indicate s.e.m. Statistical significance was determined by Student's t-tests; *p < 0.05, **p < 0.01, *p < 0.001.**

Objectives. The main MESI-STRAT aim is to develop new models for the disease-mechanism-informed stratification of ER+BC patients into ET responsive or resistant subgroups, based on their clinical/molecular phenotypes. Using advanced mathematical modeling approaches, we will include not only qualitative but also *quantitative* changes of network parameters to establish predictive pipelines for (i) patient stratification prior to ET; (ii) assessment of resistance development during ET; (iii) recurrence risk assessment when ending ET; and (iv) personalized (combinatorial) therapy approaches for patients with intrinsic or acquired ET resistance.

The clear, realistic and measurable MESI-STRAT objectives are:

- MESI-REPOSITORY - a searchable database of matched fresh frozen tissue, serum, and pseudonymized patient data (treatment and follow-up) of BC patients from clinical cohorts (PATH, UKL-HD, UMCG, VHO, and collaborators), and patient-derived model systems (matched cultures & patient-derived xenograft (PDX) models, VHO + EurOPDX). – WP1
- A MESI-SEEK data management platform for integration of experimental, preclinical and clinical data with computational models, network analyses, and pharmacogenomics. – WP2
- Datasets covering ER+ BC signaling and metabolism for model parameterization, including MESI marker panels specific for ER+BC subgroups with different drug response mechanisms. – WP3 and WP4
- Mathematical small-scale dynamic models of integrated metabolic signaling (MESI) networks parameterized for ER+ BC, and modified for individual patients and patient subgroups; network analyses and genome scale models to identify metabolic alterations beyond Trp and NAD in ER+BC subgroups; model-based prediction of targeted (combinatorial) therapies for patient subgroups with different drug response mechanisms that can be stratified by MESI marker panels. – WP5
- Clinical trials without drug treatments to determine MESI marker panels that detect at diagnosis high- versus low-risk patients, during ET stable disease versus relapse, and at diagnosis stable disease versus future relapse; and model predictions on improved targeted drug therapies for all these situations. These trials rely on existing BC patient cohorts at clinical partner centers, and a longitudinal sample collection of blood and urine of patients from the PATH Biobank for up to 10 years after diagnosis. – WP6
- Trials with drug treatments including preclinical trials in subgroup-matched patient-derived cultures, tissues, and PDX models, as well as clinical trials: a Window Of Opportunity (WOO) Trial and an ET Termination Trial in the PATH cohort, to identify and validate MESI marker panels which stratify patients into subgroups with different resistance mechanisms, and predict improved targeted drug therapies. Links with 21 ongoing clinical trials including 3 male cohorts to conduct Intervention Validation Trials to clinically test the predictive value of MESI marker panels for subgroup specific drug responses. Design of investigator initiated (IIT) and umbrella trials to assess individualized (combinatorial) therapies and novel therapeutic targets. – WP7

1.2 Relation to the work programme

Table 1. Relation of MESI-STRAT to the challenge and scope in the SCI-PM-02 work programme. Note: The relation with the expected impact is addressed at the beginning of section 2.1 (Impact).

SC1-PM-02 Challenge & scope	Relation with MESI-STRAT activities and objectives
Patient stratification: more effective therapeutic interventions tailored to (groups of) individuals with common molecular phenotypes	Stratification of ER+ BC patients into subgroups with common, better defined metabolic and signaling (MESI) phenotypes enables selection of ET-resistant patients for targeted therapies, based on their individual ET resistance mechanisms. This will allow the timely identification of ET resistance and stratification of patients to established targeted therapies. MESI-STRAT will also develop novel concepts to target metabolic vulnerabilities in ER+BC.
Novel concepts for disease-mechanism based patient stratification	Metabolic changes are closely linked to known signaling alterations in BC (Fig. 1) but are currently neglected as BC biomarkers. Model-informed approaches for BC patient stratification are not available. MESI-STRAT implements both aspects to address the need for novel concepts for patient stratification to targeted therapeutic interventions in BC.
Integrate multidimensional and longitudinal data	The data integrated by MESI-STRAT spans multiple dimensions including the genome, transcriptome, proteome, metabolome, and clinical cancer phenotypes in model systems and patients. Our longitudinal clinical cohorts allow long term studies that are so crucial to understand ET resistance and relapse in ER+BC. The integration of this multidimensional and longitudinal data is achieved by computational model and network analysis (WP5) and our MESI-SEEK data management platform (WP2, Fig. 4).
Harness the power of omics, including pharmacogenomics, systems biomedicine approaches, network analysis and of computational modelling.	Our comprehensive systems bio-medicine approach entails the following steps: computational dynamic MESI network models will predict MESI marker panels correlating with ET response in distinct ER+BC patient subgroups. For MESI marker panels predictive of ET resistance, targeted therapies (depicted in Fig. 1 & other relevant drugs) will be explored in silico. Network analyses will widen the marker panels, by mapping them onto subgroup-specific genome, transcriptome, and proteome data to identify correlating alterations in ancillary metabolic networks. As a result, we derive comprehensive MESI marker panels (measurable in blood/urine) and matched computational models, which predict ET and targeted drug response in distinct patient subgroups (pharmacogenomics).
Validate in pre-clinical and clinical studies	Predictive MESI marker panels will be measured in samples from the longitudinally collected PATH cohort, and our WOO and ETTermination Trials (WPs 6 + 7) to validate their predictive value for intrinsic and acquired ET resistance, and relapse after ending ET. MESI marker panels and predicted targeted therapies will be preclinically and clinically validated in patient-derived cultures, tissues, and PDX

Table 1 (continued)

	models, and in Intervention Validation Trials for which MESI-STRAT links with 21 ongoing clinical ER+ BC trials. MESI marker panels validated in these clinical trials and novel therapy concepts successful in preclinical tests will be taken further by initiating IIT and umbrella trials (WP7).
Take into account sex and gender differences	While BC accounts for 25% of all cancers in women, male breast cancer is rare (less than 1% of all BCs). The majority of male BC is ER+ and despite the fact that some differences have been detected between the molecular phenotype of female and male BC, we expect that some of the MESI-STRAT results will also be applicable to male BC. The 21 ER+ BC trials linked with MESI-STRAT include 3 male cohorts which will be a precious resource to test whether the MESI marker panels with strong predictive value in female ER+ BC also apply to male ER+BC.
Actively involve patient associations	The patient organization PATH co-coordinates MESI-STRAT (leader WP 1 + co-leader WP 9). PATH harbors a unique BC collection of over 9,200 matched blood/serum, tumor, and adjacent normal tissue samples, and follow-up data. Clinicians and patient experts at PATH support patient recruitment for clinical trials (WP7), communicate the MESI-STRAT mission and results to the BC patients, promote the continuous investigation and implementation of BC patients' interests into the MESI-STRAT strategy and actions, and promote the implementation of successful new stratification concepts (WP9).
Consider regulatory aspects of clinical practice and commercialisation opportunities	Three SMEs will be active at different levels of our value-creation chain (diagnostics, computational models for the pharma sector, data/model management). The partnering clinical centers and PATH have longstanding experience with clinical practice and trials for BC patients. The SMEs and clinical partners will continuously guide the adherence to regulatory aspects for the clinics and commercialization.
Focus on complex diseases having high prevalence and high economic impact	ER+ BC is a highly complex disease consisting of diverse, yet incompletely understood molecular subtypes which define the response to ET. BC has a 5-year prevalence of 1,814,572 in the EU, 75% of which are ER+. BC accounts for the highest healthcare costs (€6.73 billion; 13%) of all cancer-related healthcare in the EU.

1.3 Concept and methodology

(a) Concept

The MESI-STRAT consortium (**Fig. 3**) is organized around the **central idea** that patient-individualized, quantitative model-based simulations of the metabolic and signaling (MESI) networks converging on ER will allow us to predict the individual response to ET and further targeted drugs. This will enable:

- continuous response monitoring by measuring ET resistance-mechanism-specific MESI panels in body fluids;
- stratification for existing therapies, targeting signaling molecules which mediate ET resistance (**Fig. 1**);
- new concepts for combinatorial targeting of metabolic and signaling (MESI) networks.

Our modeling strategy (outlined in **Fig. 4**) is a hypothesis-driven bottom-up approach, which relies on the **basic concept** that differences in the molecular networks, which are directly targeted by cancer drugs, define the drug response. We directly reconstruct the networks that are targeted by ER+BC drugs, including ET, mTOR, CDK4/6, PI3K, and HER2 inhibitors, and include signaling networks often altered in ER+BC such as MAPK. Markers currently considered for drug response prediction are mostly direct components of these signaling networks but they can only be measured in tumor tissue, which is not available for monitoring purposes. Molecules measurable in body fluids, such as metabolites of the Trp and NAD pathways, would be much better suited for patient stratification. They can be expected to represent tumor signaling network tuning because tumor metabolic and signaling networks are multiply intertwined. However, due to the complex cross-regulation within and between them, it is not possible to intuitively deduce signaling network behavior and related drug response from metabolite panels. To deal with this complexity and to account for the highly dynamic and nonlinear response behaviors of signaling and metabolic networks, we will apply dynamic computational modeling in iterative cycles of model calibration and experimental verification. Using ordinary differential equations (ODEs) calibrated with experimental and clinical data, our models will provide a quantitative framework for systematic analysis of network components whose properties (levels, activity) govern MESI marker panels and associated drug responses in different ER+BC subgroups. To complement our hypothesis-driven strategy, we will also take advantage of top-down approaches by applying network analyses of omics wide data and genome-scale modeling to identify and cover additional networks, such as energy metabolism, that potentially harbor additional features that distinguish our MESI subgroups. This combination enables a comprehensive pharmacogenomic approach, which allows us to (*i*) predict drug responses based on expression levels and activities of tumor proteins that form part of the targeted signaling networks, and (*ii*) detect the tuning of the tumor networks and related drug response based on secreted metabolite marker panels measurable in body fluids.

The MESI-STRAT consortium: interdisciplinary and stakeholder focused

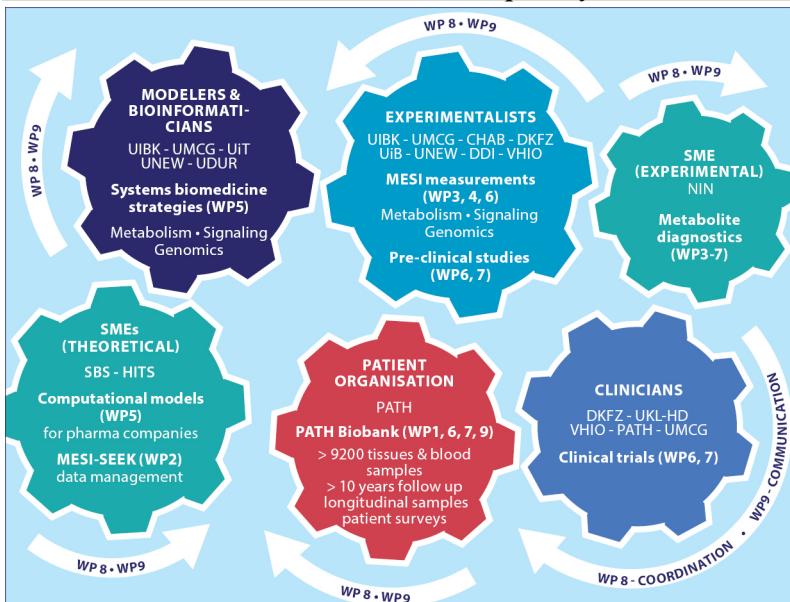


Figure 3: The MESI-STRAT consortium. Roles and expertises of MESI-STRAT partners.

combine modeling and experimental expertise in signaling (KT, CS, NC, DPS, BA/SBS) and metabolism (CO, MZ, EV, IH, BMB). The **MESI-SEEK platform** (WM, HITS) will enable **omics wide data integration** by network analysis (RF, UMCG & SG, UiB) and small- and genome-scale modeling (DPS, BMB, IH, BA). **Three SMEs** play pivotal roles in MESI-STRAT and ascertain timely implementation of commercialization opportunities: HITS (WM) implements the MESI-SEEK platform; SBS (BA) guides the development of MESI-STRAT models to ensure high commercial value, and commercializes the end product; NIN (KK) develops and commercializes diagnostic assays for metabolite markers;

Positioning of the project (innovation stage)

MESI-STRAT is situated early in the spectrum of “idea to application”. Data, samples, and cell models (WP1) are available to start WPs 1-7. Thus, analysis and construction of computational MESI-STRAT models are already within reach. The output of our objectives would categorize WPs 2-5 within **TRL 2** (basic technology research), and WPs 6-7 within **TRL3-4** (research to prove feasibility). Commercial systems biology and diagnostics services by the partnering SMEs SBS, HITS, and NIN are on the market, which will enable MESI-STRAT to recognize and implement the commercialization potential of newly developed models and metabolite marker panels for patient stratification. Section 2.2.1.2 (commercial exploitation) details the specific measures with all three SME partners that will lead to commercialization of MESI-STRAT results, including a **pipeline for computational MESI model development and customization** for the pharma market.

Our experience with patent protection of relevant computational models, target molecules, and diagnostics provides substantial background IP and will ensure timely patenting of MESI-STRAT results, thus improving the European innovation potential for systems medicine. MESI-STRAT consortium partners have patented (1) dynamic mTOR models and applications thereof for patient stratification in clinical studies and personalized medicine (KT+DPS, WO2012163440); (2) novel clinical targets modulating mTOR in cancer (KT, WO2014108532); (3) diagnostic Kyn assays (SME NIN, EP11797208.3 and 10 2015 104 088.3) – a multiplex method to measure Trp and its metabolites by chemical labeling with isobaric mass tags and LC-MS/MS (CO, PCT/EP2016/076265) – and PARP-based cyto- & histochemical detection kits (MZ, US 20100196909, A1/EP2214020). In addition, our experience in conducting clinical trials, our close ties with pharma companies (see 1.3.a, consortium description), and the support by our local tech transfer offices (TTOs, see letters) will enable rapid translation of our results into clinical practice.

The **MESI-STRAT** coordination team combines **systems biology** (KT) and **clinical BC expertise** (TA) with the perspective of a **patient organization** (PATH), which runs the only BC biobank led by an executive board of three BC survivors. Hence, we develop our systems medicine strategy with a special focus on patient and societal involvement. **Clinicians** (TA, CSC, HJ, LV, SS, AS, CSA, MP, MO, MB) from the **PATH Biobank**, **three European clinical BC centers** (UKL-HD, UMCG, VHI-O), and **clinical collaborators** (EB, GW) provide access to patients’ data, samples, biobanks, and clinical follow-up; and enable transfer of findings to clinical trials. **Preclinical testing** is done by VHI-O (VS) and DDI (BE) in ER+BC PDX, and by DKFZ (CO) and UIBK (KT) in cultures and tissues. **Expert teams**

National or international research and innovation activities

Leading European systems medicine centers in Germany (**DKFZ & CHAB**), UK (**CISBAN, UNEW**), and the Netherlands (**SBC-EMA, UMCG**) partner MESI-STRAT. DKFZ and **EMBL-EBI** are members of Infrastructure for Systems Biology Europe (**ISBE**), providing access to collaborations and resources for infrastructure, data management and modeling such as **Elixir Human Data management, Biomodels, ENA, and IntAct**. BC PDX models will be shared via the **EurOPDX** consortium, with SJ as board member and VS as member. Our data will be integrated with existing large-scale omics data, e.g., from **TCGA** invasive BC, **METABRIC**, and **DKTK** (German Cancer Consortium). Coordinators of two German systems medicine consortia (CHAB, MAPTorNET; DKFZ, GlioPATH) and an ERA-NET TRANSCAN-2 consortium (DKFZ; PROMETOV) partner MESI-STRAT. These three projects build resources connecting oncogenic signaling to metabolism in different cancers and will be highly complementary with the MESI-STRAT focus on BC: **PROMETOV** analyses ovarian cancer heterogeneity with a focus on Trp metabolism; **MAPTorNET** connects mTOR and MAPK signaling networks in neuroendocrine tumors (NET); **GlioPATH** connects NAD, Trp, and mTOR models to derive novel treatment paradigms in glioma. The coordinators of the **EPIPREDICT** consortium are on the IAB and provide links to European systems research into epigenetic changes in ER+BC. Also, the **European Working group of Breast Cancer Research** and the EU-funded **BASIS** project (breast cancer somatic genetic study), that is part of the **ICGC (International Cancer Genome Consortium)** and linked to **METABRIC**, are represented by our IAB (see 3.2.1).

Note that the above listed projects are currently not linked with MESI-STRAT. In case one of the mentioned project should share data or samples with MESI-STRAT in the future, the PO will be notified and IPR will be regulated beforehand.

(b) Methodology

The MESI-STRAT patient cohorts, and patient-derived model systems

With PATH as co-coordinator, the MESI-STRAT consortium (Fig. 3) has the outstanding opportunity to exploit a unique collection of fresh frozen tumor tissues, matching normal adjacent tissues and sera, as well as longitudinal therapeutic and follow-up datasets from **>9,200 BC patients** (out of which **>7,400 ER+**), processed and stored according to strict SOPs. For metabolite and phosphoprotein measurements, immediate freezing and storage at ultralow temperatures are essential, making this extremely high-quality repository central to our project. The PATH cohort is complemented by the WOO and ET Termination Trials, and linkage of MESI-STRAT with 20 ongoing clinical ER+BC trials by partners and collaborators investigating ET and targeted drugs including PI3K, mTOR, CDK4/6, HER2, and PARP inhibitors. The trials are detailed below (p.12, ff), in WPs 1,6-7, clinical annex.

Patient samples will be matched with a wide range of **experimental BC model systems** (cultures, PDX, tissues). VHHIO (VS) has 9 ER+BC PDX models with matched cultures (detailed in WP1) and currently develops further models. The 9 models are available at project onset to immediately start WPs 3-4. 35 additional ER+BC models can be accessed via the EurOPDX consortium (partnered by VHHIO and UMCG). If specific subtypes, identified by MESI-STRAT, are not represented by the available PDX models, they can be generated by VS (VHHIO) from selected patients. BE (DDI) has developed mice with a humanized immune system into which selected PDX representative of different MESI subtypes will be transferred. This will enable preclinical testing of anti-tumor immune responses. The PDX models will be complemented by tissue bioreactor experiments (DKFZ, CO; UIBK, KT; and the collaborating SME CELLEC BIOTEK, Basel, CH) in which drug interventions can be tested for up to three weeks in freshly cultured ER+BC patient tissues, enabling analysis of the drug effects not only on the tumor cells but also on tumor-infiltrating immune and stromal cells.

Approach and project phasing

In a stepwise, iterative approach (Fig. 4), we will match biochemical, phenotypic, and omics analyses of BC model systems and patient samples with existing large-scale sequencing data (TCGA, METABRIC) to establish a set of predictive MESI markers for disease monitoring and patient stratification for targeted therapies (pharmacogenomics). Our staggered phased plan ensures that the MESI-STRAT goals are reached within 51 months.

Phase I – Data and samples from clinical cohorts, patient-derived cell and PDX models will be compiled and longitudinal samples will be collected (WP1). The WOO and ET Termination Trials (WP7) will be initiated. MESI-SEEK data and model management platform will be set up (WP2). Small-scale metabolic and signal transduction models (WP5) will be integrated, parameterized and validated stepwise, based on experimental time course measurements and cancer-relevant phenotypic data (proliferation, migration, survival) (WPs 3,4) in ER+BC cell lines. **Deliverables:** data, samples, cell/PDX models distributed; MESI-SEEK platform; theoretical models addressing cross talks and parameterized for cell lines.

Phase II – Model setup and validation for patient-derived cultures & supernatants, and PDX models & sera/urine (WPs 3-7). Iterative cycles of experiment-model refinement using metabolic and signaling data. A critical step

will be validating that models parameterized on protein and metabolite levels – as measurable in patient samples – accurately simulate individual dynamics of signaling and metabolism in cultures and PDX (WP5, task 5.2). Our preliminary (KT) and published²⁵ data indicate feasibility. If not, patient-specific models will be parameterized based on dynamic time course data from patient-derived cultures and PDX. To define the minimal datasets necessary for model parameterization, sensitivity analyses in our MESI models will determine critical proteins and metabolites whose changes lead to different drug response and MESI marker panels. These components will be measured from patient tissues & biological fluids, and used for individual model parameterization, subsequent identification of patient subgroups with similar drug response mechanisms, and related marker panels differing between the subgroups. RNA-seq, panel-seq & discovery proteomics (expression) of patient samples representative of MESI subgroups with different ET response will be performed (WP3). **Deliverables: pharmacogenomics I:** identify subgroups with different MESI-signatures (component levels) in patient cohorts & correlate with ET response (ER and oncogene activity, onco-metabolites, clinical outcome); predict intervention strategies involving signaling and metabolism for non-responders.

Phase III – Preclinical testing and validation of marker panels and related therapies in subgroup-matched patient-derived cultures/PDX and samples (WPs 6, 7). PDX models representative for subgroup-specific MESI signatures will be established in immune-competent animals to test anti-tumor immune responses. If necessary, new representative PDX models and matched cell cultures will be obtained from EuroPDX or established from selected patients (WP1). Predictive MESI signatures will be mapped onto RNA-seq and proteome expression and panel mutation data from different MESI subgroups; these analyses will be extended to RNA-seq data in TCGA and from the METABRIC¹² study. Network analyses entailing Gene set enrichment (GSEA) and Bayesian network analyses will overlay mutations, expressed transcript isoform balance and protein sets in the multilevel omics data, and identify major altered metabolic pathways and their network structure. For up to three of them, ET-resistant-subgroup specific genome-scale and/or small-scale dynamic models at isoform resolution will be setup to predict specific metabolic alterations leading to characteristic secreted metabolite signatures, to enrich our subgroup-specific MESI marker panels (WP5). **Deliverables: pharmacogenomics II** – preclinical testing and validation of subgroup-specific drug responses and related secreted metabolite marker panels.

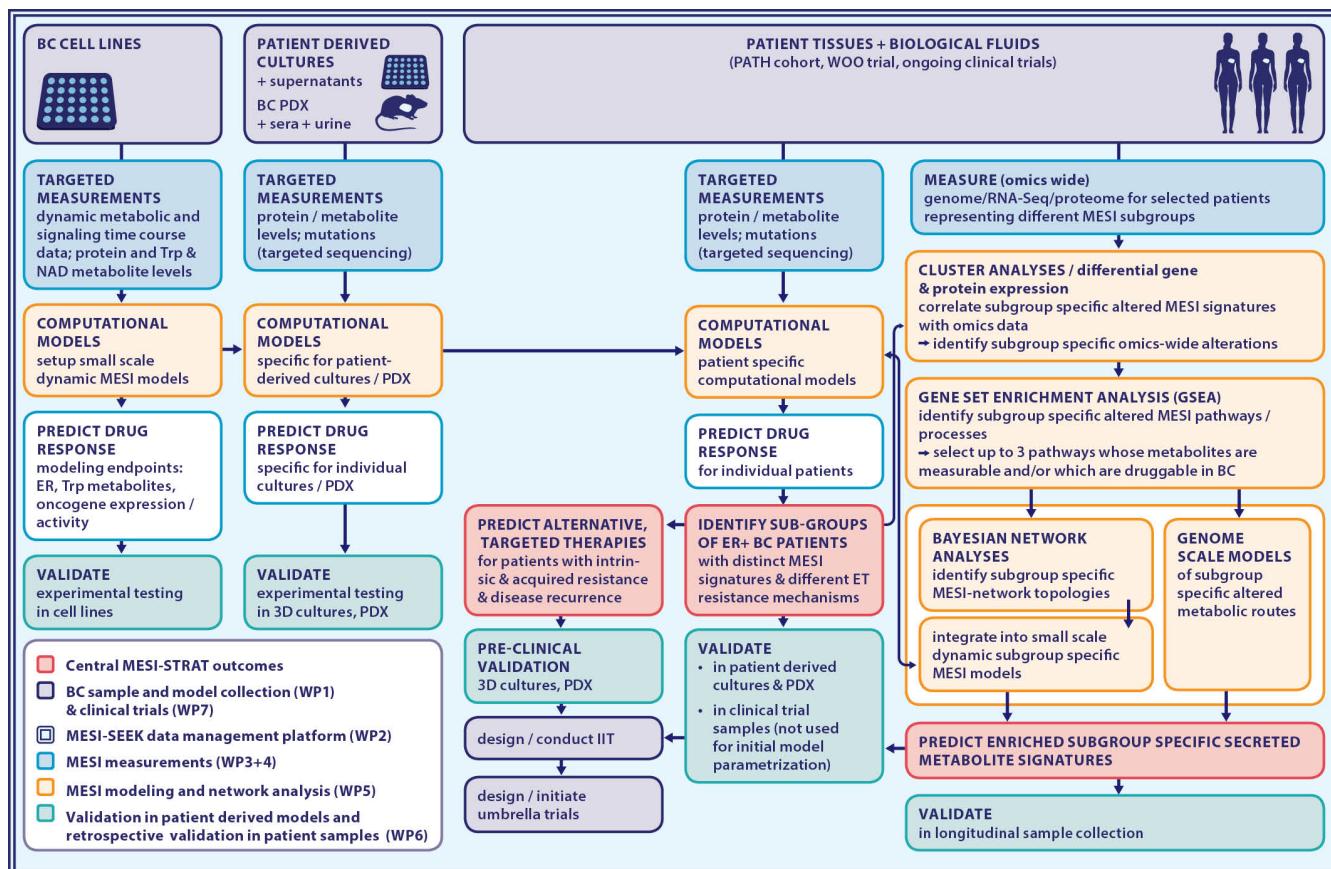


Figure 4 – The MESI-STRAT strategy.

Phase IV – Validation of predictive MESI signatures in patient body fluids and tissues: in the longitudinal PATH cohort (WP6), WOO, ET Termination, and Intervention Validation Trials (WP7). Design and initiation of IIT and

umbrella trials (WP7). The clinical trial strategy is detailed in **Table 2**, in WPs 6-7, and the clinical annex. **Deliverables:** validation in clinical trials; patent applications for predictive biomarkers and models.

Work package (WP) Overview

The clinical WPs (1, 6, 7) will be led by clinicians; the systems WPs (2-5) will be led by modelers, experimentalists and data management experts; and the coordination and impact WPs (8, 9) are led by the coordinator UIBK, the co-coordinating patient organization PATH, and the SME SBS. A short overview is given here, and the detailed descriptions are provided in section 3 (implementation).

WP1 Data survey of existing patient samples and materials (Leader PATH, TA)

MESI-REGISTRY: pseudonymized clinical and follow-up data, protocols, patient materials (PATH and other sources); patient-derived models; continuous integration of clinical data on newly collected samples (WPs 6, 7).

WP2 Setup and maintenance of MESI-SEEK data and model management platform (Leader HITS, WM)

MESI-SEEK: computational models; signaling, metabolic, omics, and phenotypic data generated by WPs 3&4, data from external sources (TCGA, METABRIC, others), scientifically relevant pseudonymized clinical data.

WP3 Assess SIGNALING NETWORKS for model parameterization & validation (Leader CHAB, CS)

Measurements of ER, mTOR²⁶ and MAPK²⁷ network components in cultures, PDX, and patient samples (tissues, body fluids): Biplex assays, targeted proteomics, reporter assays, and proximity ligation assays. Phenotypic readouts include cell cycle distribution, apoptosis sensitivity, clonogenicity, and proliferation.

- Monitor signaling dynamics and conduct intervention screens by combining metabolite & growth factor stimuli (e.g., Trp, IGF, EGF) with drugs targeting signaling and metabolism (Fig. 1; drug panels and signaling molecules to be measured detailed in WP3).
- Quantitative measurement (targeted proteomics²⁸) of signaling proteins that determine subgroup-specific drug responses in patient samples, predicted by WP5
- Quantitative omics analyses: discovery proteomics (expression), deep RNA-seq + panel-seq to complete existing omics data for selected cell & PDX models and patients, representative of predicted MESI subgroups (WP5).
- Analysis of patient-derived ER+BC models and samples, treated with model-predicted drug combinations.

WP4 Assess METABOLIC NETWORKS for model parameterization and validation (Leader UiB, MZ)

Analyze Trp, NAD, and energy metabolites, pathway component expression and function. Samples and perturbations of metabolic networks as in WP3, to assure identical conditions required for modeling.

- Quantitation of enzyme concentrations & activities by targeted proteomics²⁸ & semi-automated activity assays.
- Quantitative measurements of intracellular and extracellular metabolites (ESI-MS/MS, ELISA).
- Metabolic flux analyses: metabolite consumption, production; stable isotopes incorporation²⁹.

WP5 Integrative MESI network modeling and network analyses (Leader UNEW, DPS)

- Build integrated MESI models by connecting existing and newly developed ODE-based dynamic network models of Trp³⁰ and NAD metabolism with mTOR³¹ and MAPK²⁷ models. Integrate other metabolic pathways (e.g., energy metabolism³²) depending on network analysis (see below).
- Parameterize integrated models using detailed molecular & biochemical time course and cellular & high-throughput data (WPs 3, 4).
- Incorporate biological and clinical data (patient samples, outcome) into computational models using the MESI-SEEK platform (WP2), employing model reduction techniques for sparse data as necessary.
- Global and local sensitivity analyses and systematic combinatorial perturbations with inhibitors to dissect network dynamics, characteristic metabolite profiles, and minimal parameterization data sets (WPs 3,4,6,7) for patient subgroup specific models.
- Guide validation of predictive MESI markers in cells, PDX and patient samples (WPs 6,7) and selection of models and patient samples representative for distinct MESI subgroups for in depth omics analyses (WP3).
- Network analyses to predict and guide validation of extended metabolite panels characteristic of different MESI subgroups measurable in body fluids (WPs 4,6,7).
- Predict targeted (combinatorial) therapies for ET resistant subgroups and guide validation in preclinical and clinical studies, and IIT and umbrella trial design (WP7).

WP6 Preclinical and clinical trials without drug treatments in ER+BC patient-derived models and the longitudinal PATH cohort (Leader DKFZ, CO)

- Longitudinal PATH collection of biological fluids for the MESI-STRAT Risk Detection, Relapse Detection, and

Relapse Prediction Trials (detailed in Table 2, WP6, and clinical annex).

- Validation of computationally predicted MESI-signatures (a) in preclinical models (cultures and PDX) with known therapy outcome; (b) in patient samples and correlation with risk and relapse; identify patient subgroups with different ET resistance mechanisms, different drug responses, and distinctive MESI marker panels.

WP7 Preclinical and clinical trials with drug treatments: preclinical drug tests, WOO, ET Termination and Intervention Validation Trials (Leader UKL-HD, SS)

- Preclinical testing of predicted therapies (WP5) in cultures and PDX models; analysis of immune effects of promising therapies in immunocompetent PDX models (established by BE) and tissue bioreactors.
- WOO, ET Termination, and Intervention Validation Trials to identify and validate MESI marker panels predictive of intrinsic ET resistance and response to targeted therapies; details in **Table 2**, WP7, and clinical annex.
- To comprehensively test the predictive power of the identified MESI marker panels for patient stratification for targeted therapies, and for fundamentally new treatment avenues, IIT and umbrella trials will be planned with academic and industrial partners (Novartis and others, see consortium description 1.3.a and letter).

WP8 Project coordination: management and communication (Leader UIBK, KT)

The MESI-STRAT strategic board, supported by the project manager, ensures day-to-day management.

- Coordination of the workflow and exchange of materials within the MESI-STRAT consortium.
- Coordination of knowledge exchange and in depth training among the partners in regular consortium meetings and visits, channeling feedback and ideas.
- Administrative and financial coordination, communication with and reporting to the EC.
- Intellectual property (IP) management plan.
- An international advisory board of patient organizations and external experts (oncology, signaling, metabolism systems medicine, see 3.2.1) will attend the meetings, receive progress reports, and advise MESI-STRAT on the project research, strategic orientations, and project progression.

WP9 Dissemination, exploitation, and communication (Leader SBS, BA; Co-Leader PATH, TA)

- Dissemination & exploitation plan: measures and pipelines to implement MESI-STRAT scientific and clinical results into scientific, clinical, regulatory, and commercial practice and to enhance patient literacy.
- Communication plan: communicates the MESI-STRAT results to and receives input from a broad group of stakeholders including scientists, healthcare professionals & managers and commercial stakeholders plus societal stakeholders such as patients and their families, policy makers, EU citizens.

Sex/gender-related aspects

The CCI of gender is consequently implemented at the **consortium level** as 50% of the PIs are female, (p. 1).

The annual death rate for BC is 33.4 and 0.5 per 100,000 inhabitants for women and men, respectively. Hence BC in men is rare. ET are used for over 70% of all female BC. Since the majority of male BC is ER+, we expect that some of the MESI-STRAT results will also be applicable to male BC. Thus, developing improved stratification and targeted therapy concepts for ER+BC addresses the largest proportion of BC patients in the EU, and is potentially relevant for both female and male patients.

A **gender committee (GC)** will focus on the consequent consideration and implementation of gender issues at all project levels. This concerns in particular the translation of results from female ER+BC to male ER+ BC. SS (UKL-HD) and CSC (UMCG) both have a strong focus on male BC and access to large male BC sample collections (see clinical annex, Study 7). MESI-STRAT has access to these male BC cohorts, which encompass collections of FFPE tissues, fresh frozen tissues, and body fluids. The male BC sample collections are very precious as male BC is rare. Hence, the GC will evaluate and decide on the validation of strongly predictive MESI marker panels from female ER+BC subgroups in the male cohorts. Furthermore, the GC will constantly evaluate MESI-STRAT actions and results regarding the proper consideration of gender issues.

Clinical trial strategy

Our multilevel clinical trial strategy is designed to account for the biological and clinical traits of ER+BC, which presents several challenges including the long time to relapse, the low percentage of relapsing patients, and the risk for relapse remaining constant over two decades. Consequently, trials with endpoints such as progression-free survival are long-term efforts that cannot be realized within the typical budget and duration of an H2020 project. MESI-STRAT overcomes these limitations by taking advantage of existing cohorts and trials, by conducting own trials where needed, and by collaborating with pharma and academic partners for IIT and umbrella trials, designed based on the MESI-STRAT outcomes. Table 2 provides an overview of all preclinical and clinical MESI-STRAT

studies. Studies No 1–6 are essential, unique and innovative approaches to develop new predictive MESI models and marker panels for stratification of ER+BC into subgroups and to inform clinical decision-making. Study 7 and the prospective design of IIT and umbrella trials (7.5) accelerate the translation of our biomedical and clinical results to medical use by pioneering the application of new MESI models and marker panels for ER+BC therapy monitoring and design.

Table 2. MESI-STRAT clinical and preclinical trials. Trials without any drug treatments are grouped into WP6, and trials with drug treatments into WP7. *The clinical study number corresponds to the numbers in the Clinical Annex, where all study details are provided, incl. a list of all trials in Study No 7. Trial numbers correspond to the task numbers in WPs 6 and 7.

Study category	Study type	Clinical Study No & Trial #*	Short name	Study title	Study design
Trials without drug treatments: WP6	clinical	Study No 1 WP6: Trial 6.1	Risk Detection Trial	Identification and validation of MESI marker panels discriminating high-risk vs. low-risk ER+BC patient subgroups	Samples and clinical data from PATH biobank
		Study No 2 WP6: Trial 6.2	Relapse Detection Trial	Identification and validation of MESI marker panels detecting ER+BC patient subgroups with relapse	Samples and clinical data from PATH biobank and clinical trials associated with MESI-STRAT
		Study No 3 WP6: Trial 6.3	Relapse Prediction Trial	Retrospective identification and validation of MESI marker panels at diagnosis predicting patient subgroups with future relapse or stable disease	Samples and clinical data from PATH biobank
		Study No 4 WP6: Trial 6.4	Tissues for Preclinical Trials	Screening and collection of ER+BC tissues with subgroup-specific MESI marker panels for preclinical models (PDX, bioreactor)	Samples obtained in the frame of ongoing clinical studies at VHIO and UKL-HD
	preclinical	WP6: Task 6.5	Preclinical Model-Subgroup Assignment	Identification of primary cell and PDX models representing novel ER+BC subgroups defined by differential MESI marker expression	Samples and data from preclinical trials at VHIO, DKFZ and DDI
		WP7: Task 7.1	Preclinical Intervention Trials	Validation of predictive MESI marker panels in primary cell cultures, cultured primary tissues, and preclinical interventional trials in PDX models	Samples and data from preclinical trials at VHIO, DDI, DKFZ and UIBK
Trials with drug treatments: WP7	clinical	Study No 5 WP7: Trial 7.2	WOO Trial	Prospective window of opportunity trial: two weeks neoadjuvant Anastrozole in postmenopausal women with ER+BC	Interventional clinical trial performed at UKL-HD
		Study No 6 WP7: Trial 7.3	ET Termination Trial	Analysis of longitudinally collected serum and urine from ER+BC patients before and after termination of ET	Prospective clinical trial by PATH, collecting samples/ clinical data from patients on and off ET
		Study No 7 WP7: Trial 7.4	Intervention Validation Trials	Clinically validate predictive MESI models and marker panels for targeted drug interventions	21 clinical trials by partners and collaborators; incl. 3 male cohorts
		WP7: Task 7.5	IIT/Umbrella Trial Design	Design own IIT and umbrella trials, in which ER+ BC patients will be stratified to different therapies by MESI-marker panels	For future impact, UKL-HD, UMCG, VHIO will design and initiate IIT & umbrella trials

The longitudinal PATH cohort, initiated and driven by BC patients, is unique because of the timeline (>10 years follow-up) and case numbers (over 9,200 cases), which is not offered by any other existing clinical BC cohort or registry, and which would be impossible to realize within the time and budget of the present H2020 project. Hence, PATH offers us the unprecedented opportunity to design a comprehensive study throughout ET in which we will

- detect at diagnosis: high- versus low-risk patients (**Fig. 5A, Risk Detection Trial**, Study No1);
- detect at relapse: stable disease versus relapse (distant metastasis); this cohort will be enriched with samples from other cohorts, such as the PRAEGNANT cohort (UKL-HD) (**Fig. 5B, Relapse Detection Trial**, Study No 2);
- predict at diagnosis: patients with future relapse or stable disease under ET (**Fig. 5C, Relapse Prediction Trial**, Study No 3);
- predict at the end of ET: relapse and prevention strategies by targeted drugs (**Fig. 6, ET Termination Trial**, Study No 6).

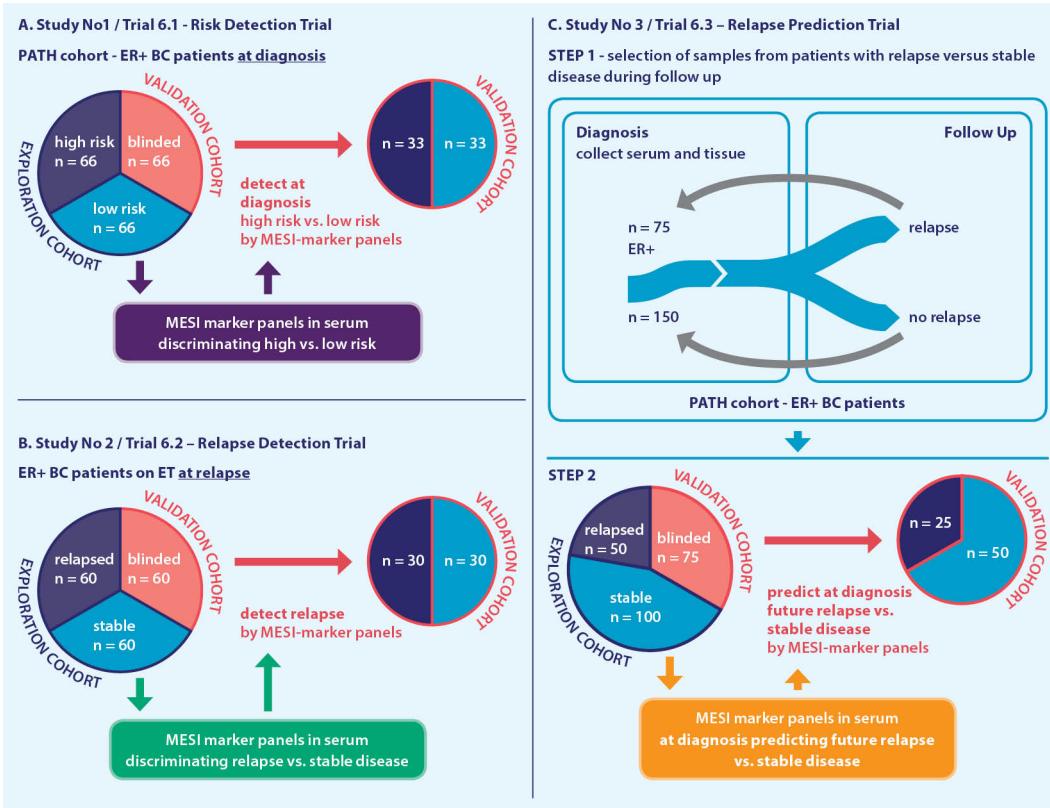


Figure 5. Clinical Studies 1-3 are enabled by the longitudinal PATH cohort.
(A) Risk Detection Trial.
(B) Relapse Detection Trial.
(C) Relapse Prediction Trial

The **WOO Trial** (study No 5, Trial 7.2 **Fig. 6**) complements the ET Termination Trial, as we compare longitudinal samples from the same patients at diagnosis before and on ET. This is novel as typically only tissues from patients without ET are used to guide initial therapy decisions, and matched patient samples without and with ET are not available. This is a serious limitation for ER+BC research, as ET itself triggers processes that alter therapy responses. Due to the lack of matched samples without and with ET, ET-inherent effects on MESI networks and the implications for the response to combined targeted therapies are currently neglected. For example, immunomodulatory therapies such as IDO inhibitors are so far not clinically tested in ER+BC as basal immune infiltration is low. However, several studies³³⁻³⁵ and our own data (**Fig. 2**) suggest that ET itself triggers tumor immune infiltration and changes in immunosuppressive Trp metabolites, and that this is associated with ET resistance. Therefore, we need to study the MESI networks and their drug response in preclinical models and in patients under ET. Our WOO trial follows a timely strategy, which will allow us to study ET-induced MESI panels. The combination of our WOO trial with the PATH cohort trials (Studies No 1-3 and 5-6) will be essential to reach our central aim of developing computational models and define MESI marker panels that can stratify ER+BC patients into subgroups with different ET resistance mechanisms, and guide decisions for combinatorial treatment schemes of ET with targeted drugs.

Figure 6. Clinical trials to predict ET response and relapse

(i) **when ending ET** (ET Termination Trial, Study 6) and (ii) **when starting ET** (WOO, windows of opportunity) Trial, Study No 5).

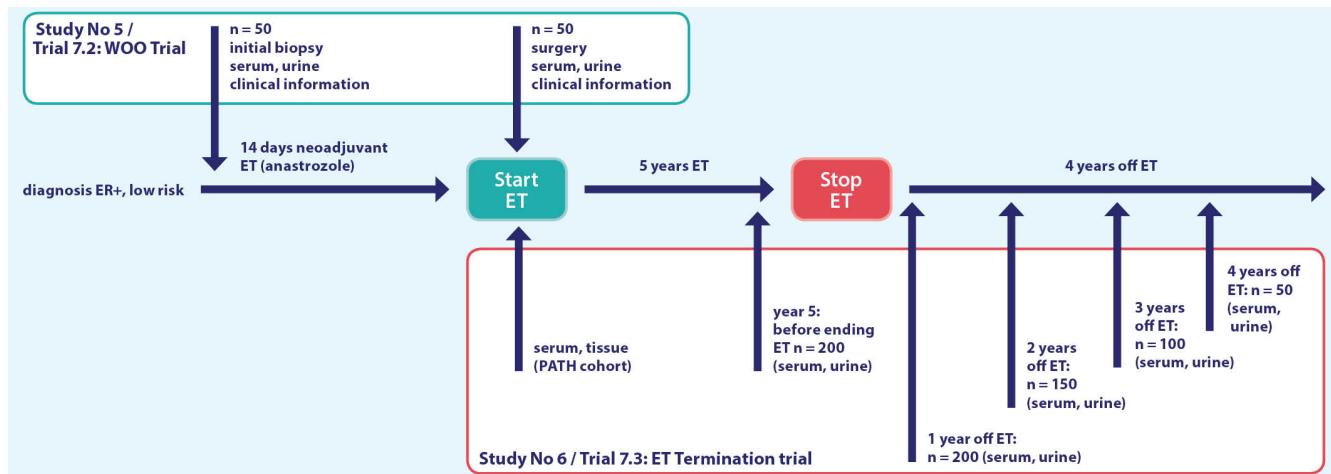
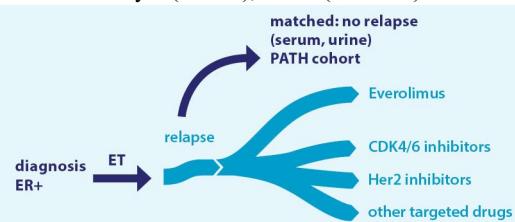


Figure 7. Intervention Validation Trials

Clinical Study 7 (Annex), WP 7 (Trial 7.4).



marker panels also apply to male ER+BC. **This will directly address the criterion of gender-sex analysis.**

To pioneer the application of new MESI marker panels for ER+BC patient stratification, MESI-STRAT will conduct **preclinical tests** in patient-derived cultures, tissues, and PDX models (WP6, 6.4 and 6.5; WP7, 7.1). Furthermore, we will **design own interventional IIT and umbrella trials** (Fig. 8; WP7, 7.5) with academic (UKL-HD, UMCG, VHO and further European centers) and pharma partners (e.g., Novartis, Celgene, Pfizer, and others; see 1.3.a). Due to their long duration exceeding the typical timeline of EU projects, and the necessary funding volume exceeding the MESI-STRAT budget, these trials cannot be conducted as a part of MESI-STRAT, but they will be a direct result from our project. The necessary links with pharma companies who can partner and fund these trials are in place, and initial trial planning has been setup with Novartis (see attached letter) to apply for dry substance and funding following an established pipeline. Furthermore, we will apply for public funding with National and European funding bodies.

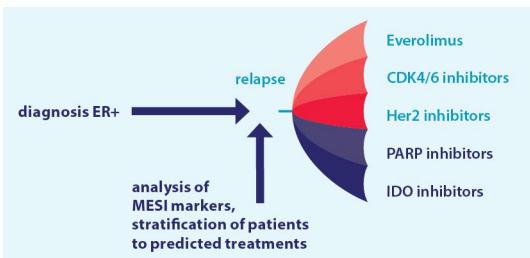


Figure 8. Umbrella trial design. See WP7 for details.

1.4 Ambition

- **Advance beyond the state of the art.** MESI-STRAT is poised for groundbreaking discoveries of subgroup- and patient-specific vulnerabilities. Our findings will identify patients at risk for relapse, and enable evidence-based therapy. Avoiding ineffective treatments by informed ET resistance mechanism-based clinical decisions on targeted therapies will improve overall survival and quality of life of ER+BC patients. Drugs targeting PI3K, mTOR, and MAPK networks are in clinical use for many cancers. And, alterations in MESI networks, including Trp, NAD, and energy metabolism, are major hallmarks in nearly all tumors. Thus, the metabolic and signaling alterations predisposing ER+BC to individual therapy responses may also contribute to specific therapy responses in other cancers, enabling translation of predictive MESI marker panels to other cancer types.

- **Innovation potential.** The PATH cohort is a unique chance to correlate ER+BC therapy responses and relapse in individual patients with input-output maps of detailed dynamic and genome-scale MESI models. This will allow us to identify patient subgroups with distinct MESI marker panels and ET response. MESI-STRAT will develop MESI marker panels measurable in body fluids and matched MESI models that predict the risk of progression, AND stratify patients for targeted therapies.

No prognostic test predicting response to targeted therapies is available for BC. Current multigene prognostic tests (e.g., Mammaprint, OncoDX) predict the risk of ET resistance only at ET onset, as they require tumor tissue. Patients classified by these tests as medium/high risk undergo chemotherapy with considerable costs for therapy and treatment of short- and long-term adverse effects. In contrast, subgroup-specific MESI marker panels do not only predict the risk of ET resistance, but they allow ET resistance mechanism-based stratification of patients at risk for targeted therapies with fewer adverse effects. Furthermore, no tumor tissue is required for MESI marker panels, which are therefore detectable at any stage of the disease and throughout ET.

Current efforts to identify circulating markers focus almost exclusively on circulating tumor DNA (e.g., by the supporting pharma company Novartis) which have been correlated with the risk of disease progression. However, they are not used in conjunction with computational models predictive of disease and resistance mechanisms. Therefore, our MESI marker panels will reach beyond these efforts: in combination with our MESI models, the MESI marker panels will allow to determine individual ET resistance mechanisms, and to simulate and predict responses to multiple alternative drug interventions.

New marker panels and related MESI models will be patented, building the basis of effective development of MESI-STRAT outcomes for the market. At project start patent landscaping and freedom to operate analyses will be provided by the partner TTOs at UIBK and DKFZ. According to our own patent search there are currently no competing patents in our field (MESI models for patient stratification). Relevant patents for diagnostics, targets and computational models for patient stratification are held, and models (services, SysBioSim) and diagnostics

To clinically test in **Intervention Validation Trials** the predictive value of MESI marker panels for subgroup-specific responses, MESI-STRAT made links with 20 ongoing clinical trials with ET and targeted drugs (Everolimus, CDK4/6, HER2, PI3K inhibitors, others; WP7, Trial 7.4, Clinical Annex/Clinical Study No 7) (Fig. 7). SS (UKL-HD) and CSC (UMCG) have access to 3 trials with over 1,100 male BC samples (WP1, Clinical Annex/ Study No 7) which will be a precious resource to test which predictive MESI

marker panels also apply to male ER+BC. **This will directly address the criterion of gender/sex analysis.**

To pioneer the application of new MESI marker panels for ER+BC patient stratification, MESI-STRAT will conduct **preclinical tests** in patient-derived cultures, tissues, and PDX models (WP6, 6.4 and 6.5; WP7, 7.1). Furthermore, we will **design own interventional IIT and umbrella trials** (Fig. 8; WP7, 7.5) with academic (UKL-HD, UMCG, VHO and further European centers) and pharma partners (e.g., Novartis, Celgene, Pfizer, and others; see 1.3.a). Due to their long duration exceeding the typical timeline of EU projects, and the necessary funding volume exceeding the MESI-STRAT budget, these trials cannot be conducted as a part of MESI-STRAT, but they will be a direct result from our project. The necessary links with pharma companies who can partner and fund these trials are in place, and initial trial planning has been setup with Novartis (see attached letter) to apply for dry substance and funding following an established pipeline. Furthermore, we will apply for public funding with National and European funding bodies.

Figure 8. Umbrella trial design. See WP7 for details.

(products, NIN) are marketed by MESI-STRAT partners (see “Positioning of the project”).

2. Impact

2.1 Expected impacts

2.1.1 MESI-STRAT impact

a) Expected impacts set out in the work programme

Table 3. Expected MESI-STRAT impacts in relation to the work programme.

Expected impact	Relation with MESI-STRAT activities and objectives
1. New models for patient stratification to inform clinical decision making	MESI-STRAT will deliver new computational models that enable individualized assessment of body fluids and/or tumor tissue, to stratify patients for ET and/or targeted treatments based on the individual ET resistance mechanism(s). Therapy response throughout ET and the risk of recurrence when ending ET can be assessed. This enables model-based clinical decisions during ET and timely switching to established or new targeted therapies. The concept of considering circulating metabolites for computational-model-informed therapy decisions is innovative, as current BC marker research focuses mainly on tumor and circulating DNA. Hence, MESI-STRAT will reach beyond other efforts in academia (e.g., TCGA, METABRIC) and pharma (e.g., Novartis) and will deliver new concepts and models for patient stratification.
2. Accelerate the translation of biomedical and clinical research results to medical use	Preclinical and clinical trials run by MESI-STRAT partners and collaborators, and IIT and umbrella trials designed by MESI-STRAT will validate (1) MESI marker panels for patient stratification, and (2) individualized, new therapy concepts for ET resistant patients. These trials will place the MESI-STRAT results at the threshold of clinical and commercial implementation by our SME partners and the pharma industry (see 4 below).
3. Increased cost-effectiveness of the novel concepts in comparison to already established practices	MESI model-based stratification concepts will increase cost-effectiveness in three principal ways: (1) The lack of markers for stratification of ER+BC patients to targeted therapies results in high rates of non-responders. Ineffective therapies cause high costs (i) as the medications themselves are expensive, (ii) due to the management of potential adverse events, and (iii) due to increased risk of progression to severe metastatic disease with high health care and socioeconomic costs (e.g., hospitalization, inability to work, etc.). MESI-model-informed stratification to treatments efficacious for specific subgroups, will reduce these costs by avoiding ineffective treatments. (2) The use of metabolite marker panels, measureable in body fluids which are readily accessible without surgical intervention, will significantly reduce diagnostic costs. (3) In conjunction with informative MESI markers, our disease-mechanism-based models will allow response prediction for compounds targeting the MESI networks. Hence, our models can be used for clinical trial design, to stratify cohorts, based on MESI marker panels, into predicted responders and non-responders. Inclusion of only predicted responders into the trials increases the expected response rate. This enhances cost-effectiveness by reducing the numbers of participants and the related costs for the trials.
4. Increased research and innovation opportunities in this innovative industries-driven field, particularly small or medium-sized enterprises (SMEs)	Our 3 SME partners will closely co-develop and conduct the MESI-STRAT research, and directly exploit our results in the sectors of diagnostics (NIN), computational modeling services for efficient and fast drug development catering to the pharma sector (SBS), and systems medicine data and model management (HITS). To maximise innovation opportunities, we implement dedicated pipelines with our partnering SMEs to develop MESI-STRAT results toward industrial application (section 2.2.1.2). Several SMEs and pharma companies collaborate with MESI-STRAT for diagnostics and compound development, services to pharma industry, and clinical trials (see consortium description in 1.3.a, and letters of support). The partnering and collaborating companies are main commercial MESI-STRAT stakeholders and will guide our efforts in annual meetings and workshops toward the development of stratification and therapy concepts with high clinical & commercial potential.

b) Improving innovation capacity

In a pan-European effort, MESI-STRAT will - for the first time - computationally link kinase signaling and Trp/NAD metabolic networks in ER+BC (WPs 3-7). MESI-STRAT will explore the clinical feasibility of systems-driven biomarker and therapy design by validation in preclinical PDX and tissue models, in longitudinal patient cohorts (WP6), in preclinical and clinical interventional trials (WP7), and by designing and initiating IIT and umbrella trials for prospective validation (WP7). Specifically, MESI-STRAT will enhance:

- Scientific innovation capacity**

of its academic and clinical partners and of the systems medicine field in general by developing a new bottom-up systems biomedicine concept for marker panel development: new MESI models for ER+BC patient stratification will inform clinical decision making for ET and targeted therapies.

- We will develop and connect dynamic computational models of metabolism and signalling in ER+BC across longitudinal time scales, and use network analyses to integrate multidimensional omics data types (genome, transcriptome, signalling/ proteome, metabolome). This is innovative as signalling and metabolism have hitherto only been analysed separately by systems approaches.
 - We will enable stratification of ER+BC patient subgroups based on their metabolic makeup and related marker panels in biological fluids, which is innovative, as so far BC metabolism has been poorly explored and metabolite marker panels have not been considered for BC patient stratification.
 - Because our strategy is broadly applicable to any cell type or organism, MESI-STRAT will pioneer a modeling-enhanced integrated understanding of how changes in signalling networks influence metabolic phenotypes, and vice versa.
- Scientific innovation will be measureable by invited conference presentations, the number of scientific papers, their impact in terms of citations, and the standing of the journals in which they are published.
- ***Clinical innovation capacity***
 - of our clinical partners and clinical research by accelerating the translation of our biomedical and clinical research results to medical use.
 - We will implement clinical trials at all levels; observational and longitudinal cohorts and trials, an interventional WOO trial, participation in numerous trials with targeted drug interventions, and the design of IIT and umbrella trials to prospectively test the predictive power of our MESI marker panels for patient stratification for targeted therapies. MESI-STRAT also has access to male BC cohorts for testing predictive marker panels, addressing the cross-cutting priority of gender. Clinical testing under strict implementation of regulatory aspects (see 2.1.2) ensures the quality and medical usability of the MESI marker panels and aids swift implementation in the clinic.
 - We will develop new, modeling-enhanced concepts for clinical trial design and management. MESI models can be used to stratify patients for novel drugs that target the networks covered by the MESI models, in addition to stratification for existing therapies. For instance, IDO inhibitors are currently in clinical trials, and PARP inhibitors may have uses beyond BRCA mutated patients as they affect NAD metabolism, which is closely intertwined with Trp, ER, mTOR and MAPK networks. Our MESI models can be used to individually stratify patients by their MESI markers. This increases the response rate and improves the statistics, thereby decreasing the necessary cohort size for clinical trials, accelerating patient inclusion into clinical trials and decreasing trial costs, as compared to current practise.
 - We introduce a novel concept for disease-mechanism-based tumor characterization by MESI model-derived metabolite marker panels in body fluids, which complements classical histology and tumor marker based phenotyping in BC. This will allow for the first time to predict tumor progression, monitor therapy response and relapse, and enable optimal therapy design without the need for tumor tissue; therefore, ER+BC patients can be closely monitored over years in a non-invasive and cost efficient manner, thus improving their outcome by earlier detection of progression to metastatic disease, and marker-guided therapy decisions for targeted drugs and ET prolongation. This is innovative, as currently no markers exist for this purpose in ER+BC.
 - Initially developed here for ER+ BC, the MESI-STRAT bottom-up approach is broadly applicable to most cancers and thus has the potential to not only innovate BC therapy but also cancer therapy as such.
- Clinical innovation will be measureable by the predictive strength of the MESI marker panels, as assessed in our clinical trials, and by the number of trials, which will be designed for prospective marker testing.

- ***Commercial innovation capacity***

Increased research and research and innovation opportunities in the innovative industries-driven field of systems medicine will be created particularly for our partner SMEs by

- implementing an innovation pipeline with SBS (detailed in 2.2.1.2) to educate young scientists for MESI model development at our academic sites, who will subsequently customize our models at SBS for the pharma industry (e.g., Novartis). The innovation potential is dual: SBS wins highly educated employees with the tailor-made profile fitting SBS' requirements; and there is a clear development strategy for the MESI-STRAT models from earliest setup to customization and use by the pharma industry. All entities involved in this value creation chain are partners or collaborators of MESI-STRAT.

- deriving metabolite marker panels to guide targeted therapies in ER+BC,
 - that can be the basis for the development of new diagnostic devices by the MESI-STRAT partner NIN and collaborator QuantumDX (see letter);
 - that can be marketed together with drugs interfering in signaling networks, developed by our collaborating pharma companies (1.3.a, consortium description)
 - improving and developing services provided by SMEs to systems medicine, creating a business case in particular for the data/model management platforms developed by HITS.
 - deriving a novel bottom-up strategy for mathematical model based analyses for faster and efficient drug development in preclinical research, and for predictive marker-panel development and improved clinical trial and therapy design for the pharma industry
 - as developed and marketed by SBS,
 - and as a basis for own industry engagement (see below, exploitation).
 - quick and cost-efficient monitoring of emerging ET resistance and relapse in patients using MESI marker panels in biological fluids. Currently no marker panels are available for this purpose in ER+ BC.
- Commercial innovation will be measureable by the number of students educated and hired by SBS, patents applied for and granted for MESI models, marker panels and diagnostic tests licensed to partnering or external SMEs and companies, and the outcome of the feasibility studies for a possible own industry engagement.

c) Integration of new knowledge: giving new life to old drugs

Our bottom-up approach can (*i*) identify predictive MESI network marker panels to select patients at ET onset for additional drugs or combinations thereof, (*ii*) detect marker panels that correlate with progression under ET, and (*iii*) predict drug combinations to target the associated ET resistance mechanisms. A broad range of drugs interfere with the mTOR and MAPK signalling and metabolic networks depicted in **Figure 1**. Among these are inhibitors of PI3K, Akt, CDK4/6, MEK-ERK, and mTOR (everolimus and other rapalogs), and metabolic modulators, such as IDO and PARP inhibitors, and metformin, which interfere with Trp degradation, NAD and energy metabolism, respectively. Several of these drugs have been in clinical use, with known safety and toxicological profiles. Thus, the model-enhanced identification of MESI-STRAT marker panels for repurposing these drugs for specific ET-resistant BC patient subgroups and new indications can considerably speed up clinical trials and use in patients. Drug repurposing can also prolong the drug lifecycle for the companies holding the patents.

d) Other environmental and socially important impacts

Improvement of **patient welfare and literacy** is a major goal of MESI-STRAT. The BC patient organisation PATH has directly contributed to our research direction since the earliest project planning and the BC patient expert and communication coach Doris Schmitt and the European BC patient organisation Europa Donna are on the MESI-STRAT advisory board. PATH also collaborates with the MESI-STRAT partner German Cancer Information Service (SW, KID/DKFZ) and its European partners to act as multipliers communicating MESI-STRAT findings to BC patients and their families, and implementing patients' feedback into the MESI-STRAT programme. They will also raise public awareness for the issues and opportunities that systems medicine offers for BC therapy.

2.1.2 Barriers and obstacles

A general obstacle is imposed by variation in the ethical regulations for patient data and sample handling in the countries covered by our European consortium. For example, the required level of anonymization and accessibility of data can differ. Also the lack of clear comparative guidelines (i.e. lack of knowledge about such differences) can slow down patient data and sample collection, and usage by MESI-STRAT. Our consortium will address this challenge by strictly implementing the national regulations that apply in each partner country (see Section B5 and annex). However, we deem it an important EU regulatory task to harmonize ethical and data security regulations to enhance opportunities for pan-European data exchange for systems medicine and clinical study efforts.

Another issue is the accessibility of patient tissues and biological fluids, which is often in the hands of single pathologists or clinicians. The lack of clear legislation to make such materials accessible to other researchers, and to document sample quality for follow up studies, often limits the possibilities for validation of findings in larger sample panels. MESI-STRAT overcomes this issue by conducting own clinical trials and by associating with trials conducted by the partnering BC biobank PATH, partnering and collaborating clinical scientists and pharma companies. Strict SOPs, as developed by PATH, UKL-HD/NCT (see letter), and UMCG, will be applied for sample collection and biobanking. Again, harmonization of clinical sample access and standards of handling by the EU would greatly enhance the opportunities for pan-European systems medicine. The European Biobanking

and BioMolecular resources Research Infrastructure Consortium (BBMRI-ERIC, <http://www.bbmri-eric.eu/>) is a step towards this by providing tools to share aggregate information on European biobanks. PATH, UKL-HD and UMCG all contribute to BBMRI (as detailed in WP1), thus ensuring that the biological samples collected in the frame of MESI-STRAT will remain available to the scientific community.

Pan-European trials are possible but require extensive administrative efforts to account for different regulations in different partner countries. Therefore, MESI-STRAT will be supported by the partnering clinical trials competence center KKS Heidelberg, which is part of UKL-HD. As a small full-service contract research organisation (CRO), KKS provides support for our interventional clinical trials including protocol development, monitoring, data management, and reporting. Thus, KKS will manage the MESI-STRAT WOO trial, advise on IIT and umbrella trial design, and ensure their conduct in accordance with European regulations. KKS will also advise on regulatory issues regarding usability of our longitudinal sample collection (PATH) and other collected samples across the pan-European MESI-STRAT consortium. We will also use the EC initiative on breast cancer (ECIBC) Guidelines Platform, another resource targeted at harmonizing the care for BC patients across Europe. Thus, MESI-STRAT activities and trials will conform with high quality, evidence-based guidelines at the European level.

2.2 Measures to maximise impact

The **MESI-STRAT dissemination and exploitation plan** (2.2.a/2.2.1) maximises impact through dissemination to a broad range of professional users in science and healthcare management (2.2.1.1), and through exploitation in research, healthcare, and industry (2.2.1.2). The **MESI-STRAT communication plan** (2.2.b/2.2.4) complements this by focusing on scientific, medical, and commercial stakeholders as well as societal actors and non-specialist stakeholders. Our **data management plan (DMP)** (2.2.2) and **intellectual property rights (IPR) management plan** (2.3) are key to maximise dissemination while protecting patients' rights, observing regulatory aspects, and preserving exploitation opportunities by timely protection of IPR. Furthermore, **internal communication** is seminal for effective innovation management, and is implemented by the MESI-STRAT management plan (WP8, and Section 3.2).

Table 4. Measures to maximise impact of MESI-STRAT

Measure to maximise impact	Aims	Target audience
1) Dissemination and non-commercial exploitation (2.2.1)	- Maximise use of MESI-STRAT results by scientific and medical stakeholders, and health care management (e.g., in hospitals, insurances)	Scientific experts and professionals from basic and medical sciences and health care management, companies in diagnostics, systems medicine and pharma, patients and families
2) Commercial exploitation (2.2.1)	- Maximise use of MESI-STRAT results by commercial stakeholders - Conduct feasibility studies for own commercial engagements	Companies in the fields of pharma development, diagnostics, and services for systems medicine
3) Management of data and knowledge (2.2.2) & intellectual property (2.2.3)	- Promote effective innovation management - Respond to external or internal opportunities	MESI-STRAT partners and collaborators: - Internal communication - Regulations: grant and consortium agreements
4) Communication (2.2.4)	- Communicate MESI-STRAT results to scientific, medical, and commercial stakeholders, societal actors and non-specialists - Implement the goals named under responsible research and innovation (RRI) and public engagement, incl. the gender dimension in the MESI-STRAT research team, decision making, and R&I content	- All previously mentioned stakeholders - Healthcare providers and healthcare professionals - Patients and families - Policymakers - EU citizens

a) Dissemination and exploitation of results: MESI-STRAT Draft Dissemination and Exploitation Plan

2.2.1 Dissemination and exploitation, and data to monitor impact

Central to the MESI-STRAT dissemination policy and actions is the dissemination and exploitation plan for the MESI-STRAT results outlined below and in WP9. This plan is jointly led by the partnering SME SBS and the patient organization PATH, and regularly reviewed by the strategic board (SB) to reflect results obtained during the project. It contains the following elements: (i) key goals; (ii) target audiences; (iii) mediums and means for dissemination and exploitation; (iv) dissemination frequency/timing; (v) impact monitoring. The **key goal** of MESI-STRAT's dissemination and exploitation activities is to achieve a significant and durable impact on EU citizens' health by the implementation of MESI model based stratification.

2.2.1.1 Plan for dissemination and non-commercial exploitation of MESI-STRAT results

The basis for all dissemination and exploitation of the MESI-STRAT results is the systematic validation of the predictive power of our MESI models and marker panels in clinical studies in ER+BC patients, laid out in section 1.3.b (Methodology / Clinical Trial strategy) and implemented through WPs 6 and 7.

Dissemination of MESI-STRAT results will further

- **basic and medical research**

- MESI model construction as a new bottom-up approach for marker panel development (WP5)
- Novel concepts and methods to connect metabolic and signalling computer network models across different time scales and omics scales (genome, transcriptome, signalling/ proteome, metabolome) (WP5)
- Novel methods to parameterize multiscale MESI network models based on multiscale data (genome, transcriptome, proteome, metabolites) (WPs 3-5)
- MESI marker panels to stratify patient cohorts, and correlate the subgroups with multilevel omics scale data to identify ET-resistance mechanism-based MESI marker panels in biological fluids (WPs5-7) that
 - predict tumour progression
 - enable optimal therapy design
 - allow monitoring of therapy response and relapse.

- **clinical research and cost effectiveness for health care management**

- A novel, pharmacogenomic approach for ET resistance-mechanism-based tumor characterization by MESI model-derived metabolite marker panels, which complements classical histology-based phenotyping
- New, modeling-enhanced concepts for clinical trial design and management
- Modeling-derived and bottom-up approach-driven MESI-STRAT marker panels that can guide therapy design, ET response and relapse monitoring. Measuring the MESI marker panels in biological fluids allows quick and cost-efficient monitoring of arising ET resistance and relapse in patients where no tumor material is available (i.e., at any time following initial surgery). Currently no marker panels are available for this purpose in ER+BC.

The main target groups

of the MESI-STRAT dissemination strategy will be medical and clinical researchers and health professionals including policy makers for health care management, e.g. at hospitals and insurances.

The activities, detailed in Table 5, will generally include the following:

- i. Open Access publishing and Open Research Data Pilot (see 2.2.2 Data management plan and 2.2.3 Management of knowledge and IP, and WP2)
- ii. close interaction with other consortia active in the field of systems medicine of BC and inclusion of consortia representatives in the MESI-STRAT international advisory board (IAB)
- iii. presentations of interim and final results at national and international conferences;
- iv. active involvement of policy makers at insurances and hospitals who decide on health care management to raise awareness of the increased cost effectiveness offered by MESI models (see Table 3).
- v. information about the project and its aims to scientific stakeholders via a continuously updated MESI-STRAT website and press releases
- vi. a concluding symposium at the end of the project, with presentation of the results and hands-on workshops aimed at the scientific community active in systems medicine and BC research.

Major instruments in MESI-STRAT's dissemination policy will be to

- **publish advances beyond the state-of-the-art** in open access peer-reviewed scientific journals, and to share them at high impact scientific meetings. Several MESI-STRAT partners, including AS & SS (UKL-HD), DS (PATH), CSC (UMCG), NC (UNEW) regularly attend major national and international BC conferences (detailed in table

5), both as invited speakers and attendees. We anticipate that disseminating our research in high-impact papers will seed and strengthen research lines in systems oncology focusing on the interactions between signalling and metabolism to target cancer by individualized therapies. MESI-STRAT strives to implement open access and open data wherever possible. However, we need to consider the boundaries set by the requirement to protect patients' data, and to enable exploitation by allowing IPR protection prior to dissemination of our results. Hence, a trade-off needs to be made between the requirement of open data and the protection of patient privacy and IPR. A dissemination and exploitation committee (DEC, WP9) – led by the SME SBS and the patient organisation and co-coordinator PATH – will oversee this process and will take decisions on timelines of keeping data non-public.

- **closely collaborate with other BC systems consortia** to optimally exploit synergies and enhance the national and European investments in BC systems medicine. Representatives of BC systems medicine consortia are on our IAB to maximise the synergies among our projects: the European Working group of Breast Cancer Research, the EU funded BASIS project (breast cancer somatic genetic study), the ICGC (International Cancer Genome Consortium), the Oslo2 study (> 2500 samples incl. molecular data), METABRIC, and the ITN EpiPredict (epigenetic regulation of ET resistance in breast cancer and systems medicine approaches to predict ET outcome). Based on the knowledge of these other consortia, our IAB will foster synergies with MESI-STRAT by identifying and initiating opportunities for exchange and collaboration.

Table 5. MESI-STRAT draft plan: scientific dissemination and non-commercial exploitation (/a = per year)

Key goals	Target audience	Medium and means *one-way **two-way interaction	Timing of implementation	Impact monitoring = reaction of target audience
• Promote new models for patient stratification to inform clinical decision making. • Set new method standards to connect metabolic and signaling models for systems oncology (methodological approaches, data/modelling standards)	systems biologists & systems medicine scientists	**present new models at systems biology conferences, e.g., ICSB, SBHD, and others	throughout and after project	- conference invitations ($\geq 2/a$) - size of audience (≥ 50)
		* open access publications in high-impact systems biology journals, e.g. Nat. Commun., MSB, Science Signal., PloS Comput. Biology, EMBO J., etc.	start in year 2, throughout and after project	- number of papers ($\geq 3/a$) - number of citations, impact of citing journals
		**final symposium at the end of MESI-STRAT project including hands-on workshops	end of project	number of attendees (≥ 200)
• Accelerate the translation of MESI-STRAT biomedical and clinical research results to medical use, in particular new MESI marker panels and models for clinical decision making	BC researchers (basic and clinical) BC healthcare professionals BC patients	**present ER+ BC diagnostics/therapy results at cancer conferences: <ul style="list-style-type: none">• Annual European Breast Cancer Conference (EBCC)• Annual meeting of the German Society for Senology (DGS). AS, UKL-HD is vice president 2017 (senologiekongress.de).• SABCS, ABC (Advanced Breast Cancer) and annual meetings of AGO (AG Gyn. & Oncology), GBG (German Breast Group), St. Gallen Consensus Conference, etc.	throughout and after project	- conference invitations ($\geq 5/a$) - size of audience (≥ 100)
		* open access publications in high-impact and highly visible medical journals, on clinical studies and new routes to BC therapy, e.g., NEJM, Clin Breast Cancer, Eur J Cancer, etc.	start in year 2, continued after project (partners, collaborators)	- number of papers ($\geq 3/a$) - number of citations, impact of citing journals
		**identify and use synergies with other consortia and initiatives on BC systems medicine, e.g., European Working group of BC Research, BASIS (breast cancer somatic genetic study), the ICGC	since early project preparation (project representatives invited for MESI-STRAT IAB)	- joint publications with other BC related consortia and initiatives (at least 3 during the project)

Table 5 (continued)

		(International Cancer Genome Consortium), the Oslo2 biobank, METABRIC, ITN EpiPredict, etc.	continued throughout and after project	- number of citations, impact of citing journals
• Promote the emerging field of systems oncology	cancer researchers/ oncologists (basic and clinical)	**present new strategies in oncology research at cancer conferences, e.g. ASCO, ESMO-ECCO, AACR & Cell Symposia, DKK (German Cancer Congress)	throughout and after project	- conference invitations ($\geq 2/a$) - size of audience (≥ 50)
		open data access publishing in cancer journals: 1) new strategies in systems oncology, e.g., in Nature, Science, Nat. Comm. 2) new molecular mechanisms in cancer, e.g. in Cell, Cancer Cell, Cancer Discovery	start in year 2, continued after project (partners, collaborators)	- number of paper ($\geq 3/year$) - number of citations, impact of citing journals
• Promote the implementation of novel MESI-STRAT concepts (models and marker panels) by the health care sector to increase cost effectiveness in comparison to already established practices	health care managers and policy makers (insurances, hospitals, politicians)	** invite health care managers from the partnering hospitals to the annual MESI-STRAT meetings. Increase network inviting further hospital representatives in subsequent years ** invite health insurance representative and politicians active in health politics to annual meetings and final conferences	annually, start in year 2 year 4+5	- number of participants from health care policy at conferences ($\geq 2/a$; at least 5 at concluding conference)

2.2.1.2 Plan for commercial exploitation: Increased research and innovation opportunities for SMEs

The MESI-STRAT activities for the commercial exploitation plan are detailed in table 6, and ensure effective commercial exploitation of MESI-STRAT results. Having adequate IP protection is imperative both for licensing and internal development and therefore the consortium will seek patent protection of new results and findings (foreground IP). This will be supported by the TTOs within the MESI-STRAT consortium (e.g., UIBK, DKFZ), who have extensive experience in licensing procedures. The IPR management plan is outlined in 2.2.3.

MESI-STRAT results suitable for commercial uptake will be

- new computational models for marker development, clinical trial, and therapy design for the pharma industry, as developed and marketed by SBS, and/or as a basis for a possible own industry engagement.
- New marker panels for targeted therapy of ER+BC, which can be
 - marketed together with drugs interfering in signalling and metabolic networks – as done by pharma companies with whom the MESI-STRAT partners collaborate for clinical BC trials and/or which are on the MESI-STRAT IAB (see 1.3 (a), The MESI-STRAT consortium)
 - the basis for the development of new diagnostic devices as developed by the MESI-STRAT partner NIN and collaborator QuantumDX (see enclosed letters)
- services provided by companies to systems medicine, such as data/model management platforms by HITS.

The main target groups of the MESI-STRAT exploitation strategy are

its partnering SMEs NIN, SBS and HITS, several collaborating SMEs including QuantuMDX and CELLEC BIOTEK, and its contacts with the pharmaceutical industry (see 1.3.a).

Major activities in MESI-STRAT's exploitation policy will be implemented with our partnering SMEs:

(i) Pipeline for customization of computational models for use by pharma industry, and assessment of their marketing potential by SysBioSim B.V. (SBS)

Jointly with the partnering SME SBS, MESI-STRAT will setup a pipeline, which allows us to systematically assess and customize the computational models developed within MESI-STRAT for the pharma industry. This pipeline also entails the transfer of expert knowledge and personnel from the academic partners to the partner SMEs. Currently there is a limited workforce in the field of systems biology/systems pharmacology, which is a serious bottleneck for SBS, and the field. The major commercial interest of the MESI-STRAT academic partners is to license their computational models to the industry. This will be greatly enabled by the experience of SBS in customizing and marketing computational models for customers in the pharma sector. Due to confidentiality agreements, SBS cannot detail its pharma customers in this proposal, but will be able to act as a mediator linking the MESI-STRAT academic partners with pharma industry.

Our pipeline will consist of the following steps:

1. **Training of master students in computational biology** in the frame of model development within MESI-STRAT at the academic partner sites UIBK, UMCG, CHAB, UNEW, UiT. The training will be led by UIBK, and students will be sent for internships to the partner institutions, which conduct modelling work in the frame of MESI-STRAT (CHAB, UNEW, UiT).
2. **MESI-STRAT model customization by trained modelers at SBS.** The modelers who earned their master of science in computational biology under the supervision of MESI-STRAT modelling PIs (UIBK, UMCG, UNEW, CHAB, UiT) and have been trained in the development and use of MESI-STRAT models will join SBS. Under the supervision of a senior modeler at SBS (funded by MESI-STRAT), the newly trained modelers will customize the MESI-STRAT models for use in the pharma industry.
3. **Trial licensing of MESI-STRAT models to SBS.** While customizing MESI-STRAT models for pharma stakeholders, SBS will constantly assess the marketing potential of these models. SBS will be granted trial licenses at favourable conditions for limited time periods. SBS will initiate contacts with pharma companies to develop and execute projects utilizing the MESI-STRAT models. During this time, SBS will assess the market potential of the MESI-STRAT models based on measures such project prospects and acquisitions, the time and cost for customization, licence fee and the market estimation of project fee. In case the trial period confirms a positive market value and viable commercial opportunities, parties will evaluate the market potential and decide on a licence fee that is beneficial for both parties.
4. **For models with positive licensing trials,** SBS will obtain long-term royalty bearing licenses from each partner to provide services to the pharma industry for patient stratification for targeted therapies.

(ii) Development and commercialization of diagnostic tests to detect MESI marker panels in patients' body fluids by Neuroimmun GmbH (NIN)

The partnering SME NIN develops ELISA-based diagnostic tests for various disease markers relating to amino acids and biogenic amines, including Trp and its metabolites (for products see www.neuroimmun.com). MESI-STRAT will explore metabolites in biological fluids as markers for ER+BC therapy response, progression, relapse, and patient stratification for targeted therapies. Strong evidence in the MESI-STRAT consortium suggests that Trp metabolites may drive ET resistance and ER+BC relapse. If the predictive power of Trp metabolites is validated, they will be patented by MESI-STRAT partners (see 2.2.3 Management of knowledge and IP). NIN has the diagnostic tests and related patents for the detection of the metabolic marker panels and can directly market them and develop multiplex tests for this application. MESI-STRAT will likely also identify additional metabolites that are predictive of ER+BC therapy response to be evaluated by NIN for commercial assay development. NIN will receive trial licenses for candidate markers and develop diagnostic tests; if successful, long-term licenses will be obtained. Developed ELISAs will be validated according to criteria defined by the GMP guideline ICH Q2.

(iii) Additional developments to openSEEK providing a test case for the long-term business model of Systems Medicine data management activities at HITS gGmbH

The openSEEK software used for MESI-SEEK in the FAIRDOMhub is open source under BSD license. While the software is free to end users, funding is needed for maintenance and extension. HITS expects to build extensions to SEEK that directly benefit the project and the broader systems medicine community, improving FAIRDOM services, as well as SEEK's use in the context of systems medicine projects. The resulting code will be open-source while it is developed. The long-term business model is based on charging users for administration, service, advice, and training. Service includes contract development, and curation, which is crucial for the long-term vision of this investment for the community. Being part of MESI-STRAT is an important step for HITS towards elaboration of such a business model.

(iv) Commercialisation, licensing and marketing by academic partners

In addition to specialist computational models and diagnostic tests for ER+BC, MESI-STRAT will derive

- clinically validated MESI marker panels for ER+BC therapy monitoring and design.
- preclinically validated MESI target molecules for potential new drugs.

Given our novel approach to identify metabolite-based MESI markers and targets for ER+BC, their added value is potentially clinically significant. New MESI marker panels and targets will be evaluated for a direct fit with project partners for advanced development or for sale to third parties. The related IP protection and licensing will be coordinated by the TTOs within the MESI-STRAT consortium.

The main objective of the licensing strategy is to benefit ER+BC patients, and for this purpose two main options will be considered:

- **Licensing to third parties**

Foreground IP on developed MESI-STRAT models, biomarkers, and their associated assays, shall be licensed to the partnering and collaborating systems medicine, diagnostic, and pharma companies, but may also be of interest to companies outside MESI-STRAT. Partnering companies will have the first option as detailed in the consortium agreement. A license to a third party can include a license to multiple results (foreground IP) in order to increase the interest of parties. Potential licensees should have a significant presence in the field of BC (e.g., Novartis, Celgene, Pfizer, Roche, and others, see 1.3.a), services for systems medicine (e.g., SBS), or development of diagnostic tests (e.g., NIN, QuantuMDX). Our licensing vision is that we will license to parties (internal and external to the MESI-STRAT consortium) who are interested in establishing further research collaborations with the MESI-STRAT partners to combine state-of-the-art science with the requirements of the envisaged application and market. Combining the diagnostic opportunities with drug development will also provide licensing opportunities and enable the licensee to monitor and improve the therapeutic effect of their drugs and new lead compounds. As outlined above (in “(ii) Development and commercialisation of diagnostic (...) by NIN”), there is already serious interest for the development of diagnostics by the partnering SME NIN, based on the to-be-identified biomarkers (see partner description NIN). QuantuMDX is also interested in applying the new markers for diagnostic devices, which, for example, would enable BC patients to monitor their therapy responses by themselves.

- **Evaluate the potential of an own industry engagement**

In certain cases, it might be more effective to advance development by creating a spin-off company, ensuring full dedication and offering an opportunity to attract funds and venture capital to support pre-clinical development and the initial clinical trials. Depending on the results of the clinical proof of concept, a larger industrial partner would potentially be involved during the clinical studies to enable late clinical studies and marketing of the drugs or biomarkers. This route has been shown to be successful and is supported by the TTOs of UIBK and DKFZ (see letters). The decision to license foreground IP to third parties or to advance the development through spin-off companies depends on the MESI-STRAT outcome and will be subject to evaluation by the dissemination and exploitation committee (DEC, WP9) and on feasibility studies conducted by the partner TTOs to evaluate the added value of combining the technology and findings of MESI-STRAT with a corporate approach. The study will include the value proposition, both patient and market perspectives, a financial evaluation of investments required and potential revenues, as well as IPR position, business strategy and potential partners.

Table 6. MESI-STRAT draft plan for commercial exploitation (/a = per year)

Key goals	Target audience	Medium and means *one-way **two-way interaction	Timing of implementation	Impact monitoring = reaction of target audience
<ul style="list-style-type: none"> • increase research and innovation opportunities, particularly for SMEs active in diagnostics and pharma companies → gain internal and external partners for out-licensing and commercialization → evaluate own commercial involvement 	companies in pharma sector & diagnostics	<p>** develop diagnostic tests/devices/services with partner NIN and collaborators QuantuMDX and CELLEC BIOTEK</p> <p>** work/collaborate with companies that sell relevant drugs and conduct large clinical trials (e.g., Novartis, see letter), and contacts already established via the clinical trials in which MESI-STRAT participates (see 1.3.a, WP1,6,7, clinical annex)</p> <p>** approach new collaborating companies</p> <ul style="list-style-type: none"> - via existing networks (of TTOs and of partners) - by presenting patents at patent information fairs and conferences - via feasibility study by partner TTOs 	from the beginning, throughout and after the project	<p>number of interactions with companies ($\geq 10/a$)</p> <p>- number of patent applications (≥ 4)</p> <p>- number of licensing requests ($\geq 2/a$)</p>

Table 6 (continued)

<ul style="list-style-type: none"> Increase research and innovation opportunities, particularly for SMEs active in systems medicine 	partnering SMEs: service providers for systems medicine	<p>**HITS partners a broad range of systems biomedicine infrastructure projects. Participation in MESI-STRAT gains sustainability experience and promotes use of open source and open data.</p>	since early project planning, throughout and after the project	functionality customization and first-hand advice (≥ 10 interactions/a within MESI-STRAT and with external customers)
		<p>**SBS develops and customizes computational models for the pharma sector. In MESI-STRAT, SBS customizes models for pharma use and hires students educated at academic partners, licenses models, and commercializes them with pharma partners.</p>	since early project planning, throughout and after the project	request for development of customized computational model-based analyses for drug development/ Drug Candidate/Target Assessment Projects (≥ 10 interactions/a within MESI-STRAT and with external customers)

2.2.2 Data management plan (DMP)

Table 7. MESI-STRAT draft data management plan: Data types, standards, sharing/accessibility, curation/preservation

Citations for resources mentioned in the table are as follows: PSI³⁶, MSI³⁷, SBML³⁸

Data types & estimated volumes	Description	Standards	Data sharing & accessibility for verification and re-use	Curation and preservation
Patient data Relational searchable database 10 MB	Pseudonymized, organized as patient history, samples (blood, urine, tissue), associated cell lines and PDX models	We conform to EU directives, NFU (Netherlands Federation of University Hospitals), and law of the protection of personal data (LDLG-BW) directives in Germany, agreed by the ethical councils of all data holders involved. All clinicians will be GCP trained, all department procedures will be defined in SOPs available on a protected website.	Shared with consortium members via MESI-SEEK platform, always following patient and data privacy regulations including the new REGULATION (EU) 2016/679, and other specific limitations based on the informed consent obtained.	Entries will be manually curated by WP1 and entered into the database.
Raw omics data, computational models, and relevant clinical data 10-20 TB	<p>Output of high-throughput experiments: sequencing, proteomics, metabolomics</p> <p>Computational models</p> <p>Scientifically relevant pseudonymized clinical data, depending on the informed consent obtained and data privacy regulations</p>	<ul style="list-style-type: none"> Sequencing data: MINSEQE standard for data clarity and reproducibility. Proteomics data: PSI standards. Metabolomic data: Metabolomics Standards Initiative (MSI), which combines SMRS, ArMet and MIAMET. Computational models: Model formats will adhere to COmputational Modeling in Biology' NEtwork (COMBINE) standards http://co.mbine.org/. SBML is a free and open interchange format which will mainly be used for MESI-STRAT models. SED-ML will be used for storing numeric model experiments in a reproducible manner. 	<p>We expect medium to large amounts of data. To ensure distribution within MESI-STRAT and open data access after publication, EMBL-EBI are our chosen collaborators. Data will be uploaded to their servers as generated, and made publicly available and open access at the time of publication via EMBL-EBI. De-identified clinical and demographic data will form part of these datasets to allow re-use by future systems oncology studies.</p> <p><u>Controlled access</u> applies to all data types that may be unique to an individual and requires user certification, following established TCGA procedures https://tcga-data.nci.nih.gov/docs/publications/tcga/datatype.html. This applies, for example, to RNAseq data.</p>	<p>Data annotation/ curation will be performed at the point of submission.</p> <p>Data will be securely hosted as follows:</p> <ul style="list-style-type: none"> sequencing data in ENA, RNAseq data in ENA & Expression Atlas, proteomics in PRIDE & IntAct, metabolomics in MetaboLights, published and patent-protected computational models at BioModels. <p>In addition, RNAseq data will be deposited in NCBI/GEO https://www.ncbi.nlm.nih.gov/geo/. This redundancy further ensures long-term accessibility.</p>

To maximise access to and re-use of MESI-STRAT data, our consortium participates in the ***Open Research Data Pilot***. As detailed in section 2.2.3, the decision on mode and timing of open access publishing of documents and data must include protection of patient privacy, and IPR protection of MESI-STRAT findings, in keeping with regulatory aspects for clinical studies and commercialization. The MESI-STRAT data management plan will follow guidelines specified under ***FAIR data management*** ('F' stands for findability, 'A' for accessibility, 'I' for interoperability, 'R' for reusability of data). Our data management strategy is fully compliant with the H2020 drive towards FAIR data management. It has already been agreed across the consortium, and will be formally delivered as a data management plan in month 6 of MESI-STRAT. Our data management platform, MESI-SEEK will be based on the FAIRDOM (FAIR Data, Operations, Models) project, which provides the openSEEK platform, and the FAIRDOMHub site for data sharing. Our openSEEK platform MESI-SEEK is characterized by a transparent, searchable structure, interlinking processed data to raw data, metadata and computational models according to ISA standards. MESI-SEEK will contain all experimental data including analysed omics data, shared protocols, and mathematical models and relevant pseudonymized clinical information. The ownership of uploaded data and models will remain with the groups that produced them. All the uploaded data will be accessible to all project partners. Standard Operating Procedures (SOPs) for experimental procedures will also be stored and linked to the data.

WP2, dedicated to the implementation of the MESI-STRAT DMP, is led by the SME HITS, one of the core FAIRDOM partners that have contributed to the FAIRDOM guidelines document. We will collaborate closely with the FAIRDOM data management project for issues concerning data and metadata management and storage, data curation and annotation, technical modeling support, and publication of project data. ***Preservation of the data*** stored in MESI-SEEK will be guaranteed for at least 10 years beyond the end of the project. Raw data will be submitted to ***public repositories***, and we will collaborate with EMBL-EBI to guarantee open access upon publication of MESI-STRAT results (see attached letters). EMBL-EBI databases are member projects of ELIXIR, which will guarantee wide reusability of our data. We will also interact with the ELIXIR Human Genomics and Translational Data team to ensure that our methods evolve with current best practice. ***Clinical data*** will be kept in the MESI-REPOSITORY set up at the central DataCenter of the IT Core Facility of the DKFZ, which complies with all regulations of data safety necessary for storage of personal data and the protection of confidentiality of individual records (for details see 5.1.4 Personal Data). Access to sequencing data that potentially allow identification of individuals will be restricted as detailed in Table 7.

Costs for data curation and preservation

Data and models will be annotated and curated by the MESI-STRAT partners who generate and publish them (WP3-7). This process and adherence to strict SOPs and data standards (Table 7) will be overseen by HITS, the leader of WP2. Setup, maintenance, and extension of the MESI-SEEK data and model management platform is covered by MESI-STRAT budgets during the running time of our project. HITS guarantees long-term maintenance of the data stored centrally. Long-term maintenance of data stored at other partner institutions will be provided by the respective partner centers. The data management plan will detail contingency plans emphasizing the longevity of the data. Deposition of all published data and models in open access databases at EMBL-EBI and NCBI/GEO is covered by public funding and ensures adherence to data standards, long-term accessibility and re-use of MESI-STRAT data by future systems oncology efforts.

2.2.3 Plan for management of knowledge and Intellectual Property (IP) protection

The management of knowledge and intellectual property will be monitored by the Coordinator subject to the decision of the Strategic Board (SB, WP8), the dissemination and exploitation committee (DEC, WP9) led by SBS and PATH, and the Consortium Agreement. The Consortium Agreement, and the Grant Agreement will be based on the DESCA model, which is the most broadly used consortium agreement model for H2020 projects. The model will be adapted to accommodate MESI-STRAT related principles such as data management, the terms for favourable licensing for evaluating the market potential of MESI-STRAT models by SBS and other potential licensees, and the details on collection, storage and use of patient data.

At the critical times of (1) patenting, (2) licensing, or (3) own industrial initiatives, the contributions of all involved consortium members up to this point will be documented and frozen to define what the object of the license will be. The efforts of the leading institutions for patenting, licensing, feasibility analyses for establishing a possible spin-off will be continuously documented, to reward continuing investment. The following aspects will be the basis for detailing the DESCA model to the specific needs of MESI-STRAT:

Ownership of MESI-STRAT Results (i.e., Foreground): All MESI-STRAT participants shall keep laboratory books showing ownership, date of generation and progress in generation of knowledge. These notes will also

reflect contributions to jointly developed foreground (i.e., results). Where no individual ownership can be ascertained, partners will establish their respective shares of ownership based on contribution, for example through effort. The consortium agreement will further detail management issues such as sharing of the costs arising from legal protection procedures and exploitation of the jointly owned foreground.

In case of transfer of ownership, the assignor shall conclude appropriate arrangements to ensure that its contractual obligations with respect to dissemination, use, and the granting of access are passed on to the new owner, as well as by the latter to any subsequent assignee. In certain cases, prior notice shall be given to other participants and to the European Commission.

Protection of MESI-STRAT Results (i.e., Foreground): Foreground with potential for commercial exploitation shall be protected in an adequate and effective manner. MESI-STRAT participants shall aim at making collective decisions concerning the best strategy to protect foreground, which may include a decision not to protect the foreground, for example, due to a lack of commercial opportunity. In all cases and in an appropriate time frame (making sure protection is not harmed), outcomes shall be disseminated via journal publication or other means of putting foreground in the public domain. When necessary, an invention shall be kept confidential with postponed application and dissemination activities.

The consortium agreement will include further details on:

- the number of days (at least 14) prior to the intended publication to inform all partners;
- procedures on the method and content of informing the other participants;
- procedures on the methods and content of written objections by other partners to the intended publication.

Access rights for implementing the project: Access rights to background and foreground needed for implementing the project will be granted on a royalty-free basis.

Access to another participant's results (foreground) or background: The access shall be granted if the requesting participant needs it in order to carry out the project or to exploit one's own foreground. Any additional conditions such as the definition of 'needed', and if necessary, exclusion of specific background from the obligation to grant access, will be stated in the consortium agreement. In case of sublicensing, the terms and conditions shall be agreed in writing.

Measures to provide open access and open data

The decisions on IPR protection in relation to timing of open access publishing will be taken by the SB (WP8), supported by the dissemination and exploitation committee (DEC, WP9), together with the partners involved. In accordance with Horizon 2020 regulations, MESI-STRAT will grant free-of-charge access to peer-reviewed scientific publications and underlying data to the end user. Implementation of open access data sharing will occur via the grant agreement. All data generated, whether primary raw data or analysed secondary data, will be documented in a traceable manner in the MESI-SEEK database (see section 2.2.2 Data management plan and WP2) to aid further meta-analysis and reuse within and outside the consortium.

Data dissemination will occur principally in conjunction with open access scientific publications in national and international specialized publication organs and peer-reviewed journals. Publication of datasets and models in structured, searchable and citable databases at EMBL-EBI or NCBI/GEO will enhance reuse of data and models (see section 2.2.2 Data management plan and WP2). DOI references to data guarantee long-term citability. Open access scientific publications will be achieved by self-archiving in institutional repositories, following a possible embargo period after journal publication of 6 - 24 months (green open access). Several partner institutions and nations have come to agreements with publishers ensuring that costs for gold open access publishing are waived or reduced for publications co-authored by members of these institutions (see e.g., <http://www.rug.nl/library/open-access/oa-finances>). HITS has ring-fenced internal funds for open access. Where possible, costs for gold open access will be applied for at the partner institutions and national funding bodies (e.g. Stimuleringsfonds Open Access, NWO, NL). To further ensure gold open access publishing in our consortium, a dedicated budget for additional costs of open access publishing will be reserved by the coordinator and can be distributed to the partners if they cannot access other funding support.

b) Communication activities

2.2.4 The MESI-STRAT Communication Plan

Our comprehensive communication plan, central to WP9 jointly led by the patient organisation PATH and the SME SBS, complements our dissemination and exploitation strategy by communicating MESI-STRAT results to and receiving input from a broad group of stakeholders including scientists, healthcare professionals and commercial stakeholders - also addressed by our dissemination and exploitation measures - plus societal stakeholders such

as patients and their families, policy makers, and EU citizens. Table 8 shows MESI-STRAT's draft plan for communication, including measures for monitoring the impact of the communication activities.

MESI-STRAT key communication activities

(1) MESI-STRAT patient days for patients participating in the clinical studies of MESI-STRAT will be organized by the patient organization PATH and the German Cancer Information Service (KID) at DKFZ. Our partner DS is PATH co-chair and BC patient expert, communication coach, and advisory board member for several clinical trials (see letter and DS's CV in the annex). The impact of the patient days will be proportional to the number of attendees. Therefore, MESI-STRAT representatives (PATH, KID), SB, partnering scientists and clinicians) will visit each of the clinical partner centers (Heidelberg, Groningen) and clinical centers collaborating with PATH at least twice during the project for on-site patient days to present and discuss the MESI-STRAT results, to receive input from patients on their urgent needs (e.g. guidance on targeted therapies, treatments of co-morbidities or therapy side effects), to discuss how to implement these needs in the MESI-STRAT studies, and to motivate patients to continue participating in clinical studies. Patient days will provide patients with high-quality reliable information essential to empower patients and their families to deal with their fears and to actively take part in the decision making on their therapies. Addressing fear by informed decision making is also important to strengthen therapy adherence. Patient-centered communication is key to reach this goal. Therefore, SW (DKFZ / KID) and DS (PATH) will advise on frequent questions that are relevant to BC patients and on how to best communicate the results of MESI-STRAT. For example, it is important to clarify to patients the timeline for a MESI-STRAT result to be translated to the clinic, and to choose ways of communication that motivates patients to be involved in decisions regarding their own therapy.

In particular, we aim to

- inform patients about the latest MESI-STRAT results, and receive their input on therapies to take to the next steps in the MESI-STRAT work plan;
- listen to the needs of patients and what they expect from MESI-STRAT;
- translate this information into measures to further specify deliverables in the course of the project.

We will interact and collect feedback from patients in two ways:

(i) through discussion rounds of MESI-STRAT partners – including patients, patient experts, communication experts, clinicians and scientists (e.g., SW+CO, DKFZ; DS, PATH; KT, UIBK, CSC, UMCG; SS+AS, UKL-HD), to be documented and implemented by the Strategic Board (SB) into the scientific objectives, policy, and strategic orientations of MESI-STRAT;

(ii) through questionnaires designed with KID/DKFZ and PATH in WP9 and distributed during patient days and as electronic polls via the MESI-STRAT website to collect opinions and feedback in a formalized manner.

In addition to the patients themselves, MESI-STRAT will also actively invite other stakeholders from the public (patient families and partners, other patient organisations for cancer/tumour diseases, public invitation via internet to attract wider audience), the scientific community (professional networks from other medical centers, to be contacted via email), and the political community (e.g. invitation of clinical opinion leaders and representatives from national funding bodies for basic and clinical science) in order to ensure that results of the project are endorsed by multiple stakeholders throughout Europe.

(2) A European telephone survey on frequent questions by breast cancer patients, relevant to MESI-STRAT.

KID (DKFZ) supports 6,000 breast cancer patients per year by phone counselling, and ER+BC patients are also counselled by KID's European partner organizations in the UK, Norway and The Netherlands who collaborate via the International Cancer Information Service Group (<http://icisg.org/>). KID and its European partners will monitor questions relevant to MESI-STRAT by questionnaires for their co-workers who offer phone counselling for BC patients. SW (KID, DKFZ) will analyse them and report on the results at the annual MESI-STRAT meetings.

The questionnaires will collect information on • type of caller (patient with diagnosed BC, patient under suspicion of BC, relative), • sex of caller and/or patient, • age of caller and/or patient, • origin of caller and/or patient (country), • disease localization (breast), • specification of disease (DCIS, LCIS, breast cancer), • situation of the patient (diagnosis, first treatment block, maintenance therapy, relapse, palliative situation, etc.), • tumor receptor status (ER, PR, Her2, not known), • endocrine therapy, • prognostic markers, • predictive markers

Based on the results of this survey, SW will advise the MESI-STRAT strategic board as well as health care professionals and patient organizations in and associated with MESI-STRAT on how to implement the patients' questions into the project, and how to effectively communicate MESI-STRAT results to patients.

(3) Communication of MESI-STRAT results at patient events and platforms, incl. those for male BC (cross cutting priority gender). MESI-STRAT aims and results will be communicated at BC patient events for female and male BC at partner and external institutions and internet platforms. This includes events such as the NCT

patient day (Heidelberg School of Medicine) at UKL-HD and DKFZ with 500-750 patient attendees per year, the yearly Patient Congress BOOG-BVN-Pink Ribbon (NL) with 200 attendees, and the annual symposium of the Dutch Breast Cancer Patient Society (Borstkanker Vereniging Nederland, BVN) with 200 attendees. **AS and SS (UKL-HD)** regularly speak at the NCT patient day. SS is part of the board of the German Society of Gynaecology and Obstetrics (DGGG) and has organized the congresses every second year with patients' contributions over the last 6 years. Being the head of the hereditary center at the women's clinic, she has organized meetings with the BRCA e.V network with an upcoming event in September 2017. CSC (UMCG) is chair of the Dutch Male Breast Cancer Consortium, steering board member of the EORTC-BIG Male Breast Cancer Consortium, and on the BVN scientific board. She regularly presents at the BVN symposia, patients events, and Public Academy lectures on BC at UMCG. Patient platforms for communication of MESI-STRAT results include the project "diploma patient" (www.diplompatientin.de, **DS (PATH)** is a member), run under the umbrella of the patient advocacy group mama-zone e.V., and the dialogue around breast cancer (www.dialogrunde-brustkrebs.de), a cooperation of Pfizer with MammaMia which focuses on patients with MBC. Importantly, DS is executive board member of the European patient academy EUPATI (<https://www.eupati.eu/>). EUPATI aims to support the integration of patient involvement over the entire process of drug development through a training tool box for patient involvement in setting research priorities.

(4) Website, electronic newsletters, podcasts and YouTube films, and social media. MESI-STRAT will create a public website and electronic newsletters with project information and results. WP9, led by PATH and SBS, will pro-actively work with the other partners to provide content for both. The website will also host the feedback collection from patients (see 1), and aid in newsletter distribution. Key lectures during MESI-STRAT annual meetings, patient days and at external events (see 3, and dissemination) will be available as podcasts and YouTube films and will be promoted via the MESI-STRAT website and social media (Facebook, Twitter). Access and download rates from the website and social media will be monitored to measure the impact.

(5) Professional training and patients' literacy

- **medical professionals and basic scientists.** Open workshops will be held at the annual MESI-STRAT meetings, announced via the MESI-STRAT website, electronic newsletters, social media, and professional and patient networks, where MESI-STRAT partners and collaborators will share their expertise and knowledge on recent developments in MESI-STRAT and systems oncology.
- **students studying to become medical or basic scientists.** All MESI-STRAT partners are actively involved in academic teaching at universities, medical centers, and international events such as workshops and summer schools (e.g. organised by SB@NL, or the DTKT <https://dktk.dkfz.de/en/training/dktk-summer-school/introduction>).
- **patients, their families and relatives, and EU citizens (i.e. 'the public')** who are interested in learning about the perspectives of systems oncology. The partners will disseminate developments in MESI-STRAT and systems oncology in the context of public lectures and discussion rounds, such as the *studium generale* at Heidelberg University (DKFZ, UKL-HD), and the Medical Public Academy (Medische Publieks-academie) at UMCG (www.umcg.nl/NL/UMCG/medische_publieksacademie), the project diploma patient and the European patient academy EUPATI (see 3).

(6) General measures to raise public awareness for systems oncology in Europe will be achieved by joint press releases of partner institutions for annual meetings, patient days, and scientific publications. In addition to scientific publications for an expert audience, we will also write reviews and give interviews in lay language to be published in national and regional newspapers as we have done in the past; such as *Telegraaf* (CSC, 02/2015, 'Oh, I am sorry, you are a man!' on male breast cancer), *Dagblad van het Noorden* (CSC: 02/2016, 'Breast cancer without a lump'; 11/2015 'No breast cancer is the same'), *NRC* (CSC, 10/2016 'Madam, you do/don't need chemotherapy'), *Deutsche Ärztezeitung* (AS, 10/2011, 'Tailored therapies for breast cancer'), *Facebook* (CO, 2011, Lindau Nobel laureate meeting, 'A Tough Balance: Cancer Research and Motherhood'), national internet platforms such as *bio-pro.de* (KT, 05/2015, The art of deciphering signalling), and broadcasted on TV, e.g. *ZDF* (AS, 02/2016, 'Volle Kanne, Focus topic Cancer'), or *YouTube* (AS, 03/2013, 'Gene signatures in clinical practice', interview with patient organization Mamazone e.V.).

Table 8. MESI-STRAT draft plan for communication. (/a = per year)

Key goals	Target audience	Medium and means *one-way **two-way interaction	Timing of implementation	Impact monitoring = reaction of target audience
<ul style="list-style-type: none"> • Accelerate the translation of MESI-STRAT biomedical and clinical research results to medical use, guided by patients' needs. • Promote rapid and better use of systems medicine research results • Support mutual learning, science literacy • Target MESI-STRAT to patients' needs • Perform participatory research 	cancer patients specifically ER+ BC patients	<p>**MESI-STRAT patient days implemented by BC patient organisation PATH and the Cancer Information Service KID (DKFZ)</p> <p>**Presence at patient days and patient-internet platforms to present project results and new directions in BC therapy, e.g. at partner BC centers, Breast Health Day (Europa Donna, on our IAB) http://www.breasthealthday.org/, 'diploma patient' congress focused on breast cancer patients. http://www.diplompatientin.de/index.html</p> <p>**European telephone survey of BC patient needs related to MESI-STRAT, implemented by European Cancer Information Services (led by KID, DKFZ)</p> <p>**questionnaires on needs of patients related to MESI-STRAT, circulated at patient days and on internet by PATH and KID</p> <p>**publications in journals and on websites read by BC patients, e.g., EUPATI European Patient Academy www.eupati.eu, MammaMia (ca. 20,000 copies, https://mammamia-online.de), mamazone MAG, Alliance again BC</p>	from project start on, throughout/ after project, at least twice at each partnering and associated BC center	≥200 patient attendees and partners/a
			throughout and after project at least 3 times/a	≥300 patient attendees and partners/a (500 at UKL-HD/DKFZ)
			from project start on, throughout project	≥6,000 patient contacts/a
			start in year 2, throughout and after project	≥100 responses of patients and partners/a from 2nd year on
			from beginning throughout the project	at least 2/a
<ul style="list-style-type: none"> • Align MESI-STRAT with needs & expectations of society in accordance with responsible research and innovation (RRI), with particular emphasis on gender issues • Foster socially relevant research and innovation outcomes of MESI-STRAT 	European citizens (including all other stakeholders, see section 2.2.1)	<p>* MESI-STRAT website</p> <p>* Newsletters electronic MESI-STRAT newsletters PATH print newsletter</p> <p>**polls/surveys on interest in systems oncology, understanding of principles, expectations regarding research goals and ethical aspects via the MESI-STRAT website</p> <p>**MESI-STRAT gender committee (GC) will discuss results relevant to male BC at meetings incl. those of the EORTC-BIG Male Breast Cancer Consortium</p>	<p>throughout the project</p> <p>during project, 2 newsletters/a before, during and after project, 1 newsletter/a</p> <p>from beginning throughout the project</p> <p>start in year 2, throughout the project</p>	<p>- monitor traffic on website (count clicks, downloads, divided by country)</p> <p>monitor download rates by country 7,500 copies</p> <p>response rate per country ≥200/a → present/ implement results at annual meetings</p> <p>≥2 presentations for male BC / a</p>

Table 8 (continued)

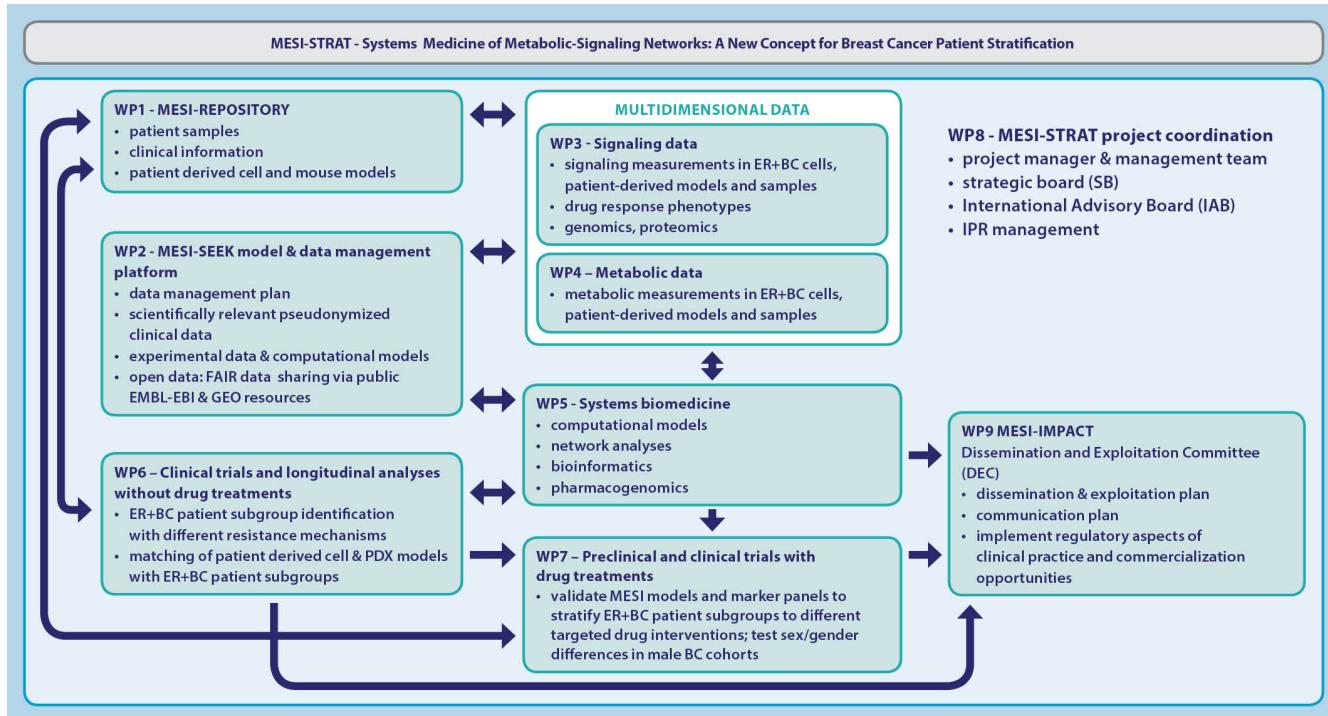
Key goals	Target audience	Medium and means *one-way **two-way interaction	Timing of implementation	Impact monitoring = reaction of target audience
Present project results with focus on chances, risks, and implementation of systems oncology to foster <ul style="list-style-type: none"> • awareness • mutual learning • science literacy • easier access to scientific results 	healthcare providers, health professionals	skills & training: **open workshops as part of annual MESI-STRAT meetings	each year throughout the project	≥15 attendees/a
	medical and basic science students at partner institutions and beyond	skills & training: **implement strategies and research of MESI-STRAT in academic teaching (courses and internships in partner's laboratories)	throughout and after the project	≥50 attendees/a
	skills & educational training for <ul style="list-style-type: none"> - patients and their families - EU citizens 	**invited lectures of MESI-STRAT partners in the context of public lectures at partner universities, medical centers and patient initiatives such as: diplompatientin.de	from beginning throughout the project	≥2 public lectures/a
Convey added value of transnational cooperation to lever systems oncology for patient stratification to inform clinical decision making	EU citizens	joint press releases of partner institutions for annual meetings, patient days, scientific publications from the consortium	from beginning throughout and after the project	≥3 joint press releases/a
		EU and MESI-STRAT logo and/or project number on all dissemination/exploitation/communication actions		≥20 releases/a that carry the MESI-STRAT/EU signature
Consideration of regulatory aspects of clinical practice: <ul style="list-style-type: none"> • Promote systems oncology in clinical guidelines • Enable implementation of systems oncology in disease management • Consider MESI-STRAT results for future grant programmes and industrial engagement 	policymakers: clinical opinion leaders	invitation of clinical opinion leaders <ul style="list-style-type: none"> - to annual MESI-STRAT meetings - to patient days 	from beginning throughout and after the project	≥3 opinion leaders participate in meetings and patient days

3. Implementation

3.1 Work plan — Work packages and deliverables (incl. Gantt and Pert charts)

3.1.1 Brief presentation of the overall structure and work plan

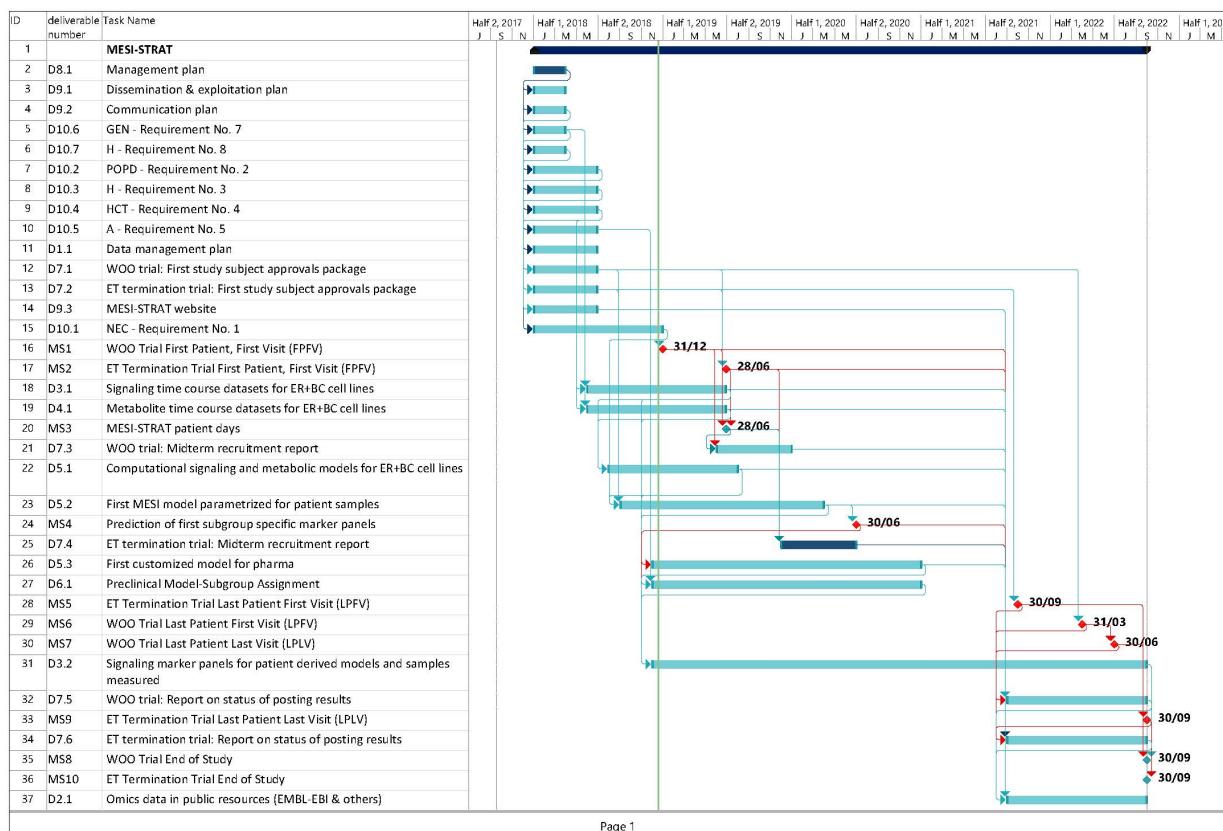
An overview of the MESI-STRAT strategy and summary of the WPs are given in section 1.3 (b). The strategy is shown in **Fig. 4**. WP8 will coordinate the work. The clinical WPs 1, 6, 7 will be led by clinicians, the theoretical WPs 2 and 5 are led by modelers, bioinformaticians and data management experts, and the experimental WPs 3 and 4 are led by experimentalists. WP9 focuses on maximizing the impact and is led by the partnering SME SBS and the patient organization PATH. The WPs provide technology platforms on which we run our work plan, following an iterative straightforward systems biomedicine concept.



3.1.2 Timing of the different work packages and their components (Gantt chart)

The project will operate on the core basis of 57 months active scientific and clinical work. To ensure a fast start, there will be a preceding period of 4 months for preparation and signature of the grant agreement, timely application for ethics votes, staff recruitment, working and business rearrangements, planning meetings. At the end there will be further three months for writing the final report.

Timeline: Full project duration: 57 months: months -4 to -1: preparatory work; months 1 to 57: active clinical and scientific work; months +1 to +3: final reporting.



Page 1

3.1.3 Detailed work description

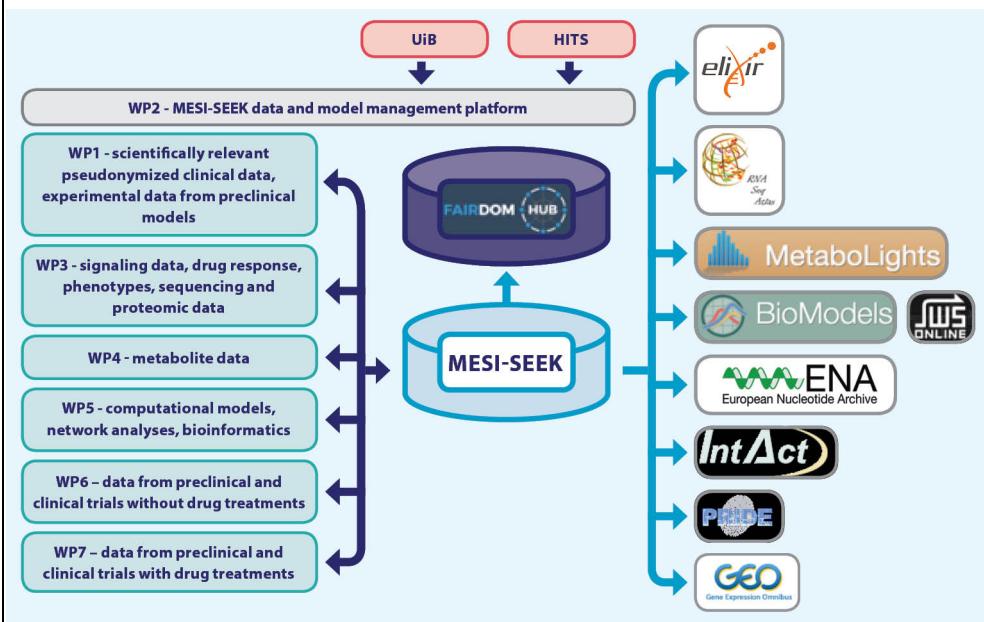
The description of implementation of the work contained in table 3.1.3 was migrated to Part A. Figures and tables which could not be entered in Part A are listed below with a precise reference to which WP and tasks in Part A they refer to.

Work Package 1

Task 1.1 Provision of sera and selected BC tissues at diagnosis from high-risk and low-risk ER+ BC patients Selection of ER+BC patients

Low risk	High risk
Tumor size less than 2 cm in diameter (pT1)	Premenopausal: tumor size more than 2 cm in diameter (\geq pT2-3) Postmenopausal: tumor size more than 5 cm in diameter (\geq pT3)
No cancer cells in any nearby lymph nodes (pN0)	Cancer cells have spread to 4 to 9 axillary lymph nodes, or have enlarged the internal mammary lymph nodes (\geq pN2)
Well-differentiated, slower growing cells (G1)	Less differentiated, faster growing cells (G 2-3)
No metastasis (M0)	No metastasis (M0)

Work Package 2



Task 2.2 Setting up the openSEEK database MESI-SEEK

- TCGA and METABRIC data sets for untreated tissues of ER+ BC patients

(*Provisional data; ** Sequencing, CNA, RNAseq-V2, microarray, miRNA, Methylation & RPPA)

Study	Samples	ER+ BC	Data Type	Patient Status	PMIDs
METABRIC	2509	1498	Sequencing	Patients were either naive to treatment, or treated in accordance to their corresponding clinical group.	22522925; 27161491
TCGA-BRCA*	1105	813	Multiple platforms**	Naive to treatment	23000897; 26451490

- GEO data sets with data from patient's BC tissue after receiving targeted treatments (*Anastrazole, Letrozole, Exemestane). The Tamoxifen data sets are selected examples of studies comprising > 100 samples.

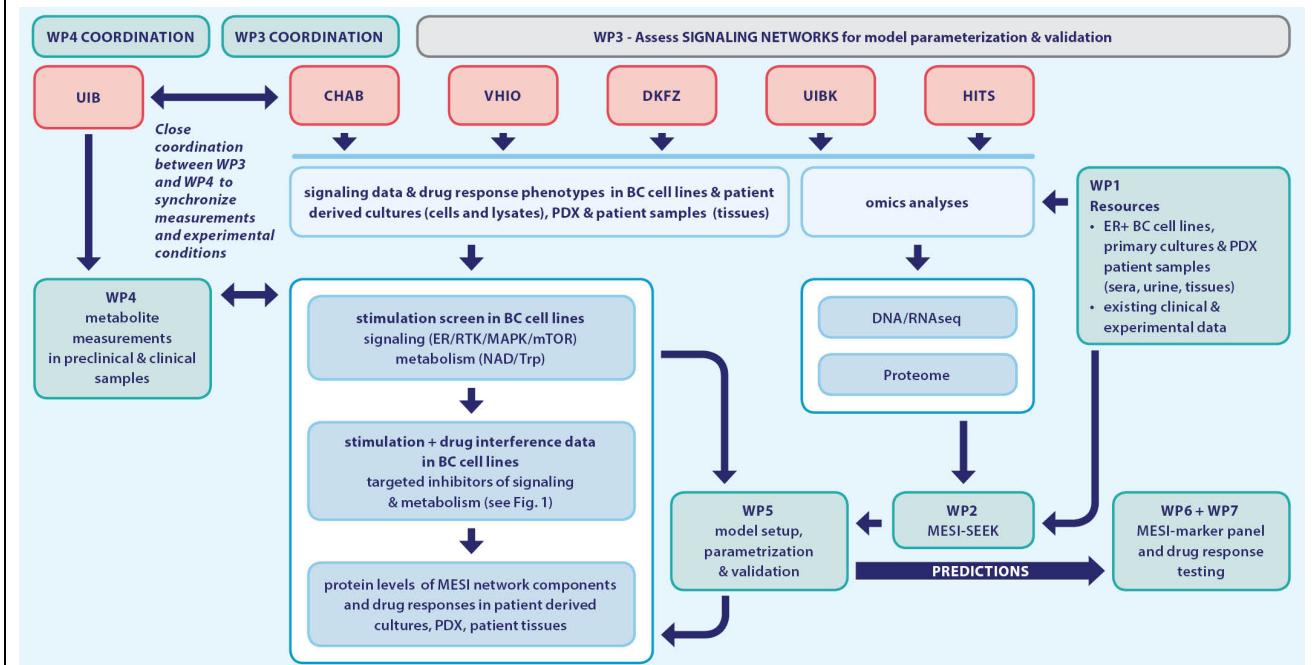
Targeted treatment	Studies	Samples	Data Type	Accessions	PMIDs
Tamoxifen	9	2105	RNA arrays	GSE6532; GSE17705; GSE22219; GSE22216; GSE9893; GSE37405; GSE12093; GSE12665; GSE6577	17401012; 18498629; 20479250; 20697068; 21737487; 21737487; 18347175; 22623953; 18821012; 21947828; 17404078

Fulvestrant	4	253	RNA arrays	GSE76040; GSE71791; GSE48905; GSE33658	27185372; 24916694; 24505287; 21792626
Trastuzumab	8	861	RNA arrays; SNP geno- typing	GSE22358; GSE66399; GSE50948; GSE76360; GSE58984; GSE42822; GSE55348; GSE44272	21373875; 26245675; 27484801; 24443618; 26842237; 23158478; 25164009; 26334217; 25330188
Aromatase inhibi- tors*	12	995	RNA arrays	GSE20181; GSE5462; GSE59515; GSE16391; GSE10281; GSE55374; GSE35186; GSE48906; GSE71791; GSE18378; GSE26544; GSE41994	20697427; 20646288; 17885619; 20646288; 26033813; 19573224; 19666588; 25100562; 26033813; 22722193; 24505287; 24916694; 20428938; 21777924; 24242068

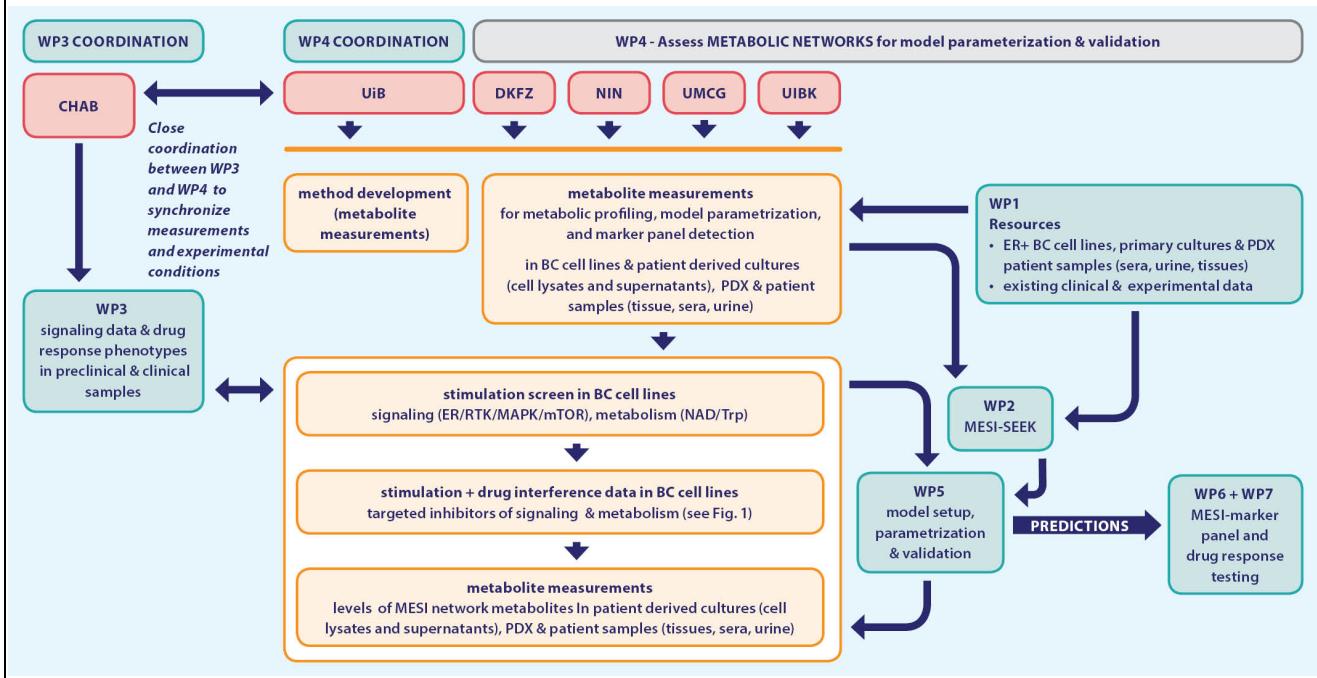
3) Data sets from GEO reporting data sets generated using male BC tumor tissue:

Accession	Samples	Data Type	PMIDs
GSE57087	75	Genome variation profiling by genome tiling array	26355282
GSE31259	74	Expression profiling by array	22333393
GSE50512	56	Genome variation profiling by genome tiling array	-
GSE17155	38	Non-coding RNA profiling by array	19664288
GSE23891	25	Genome variation profiling by array	21045282; 21547577

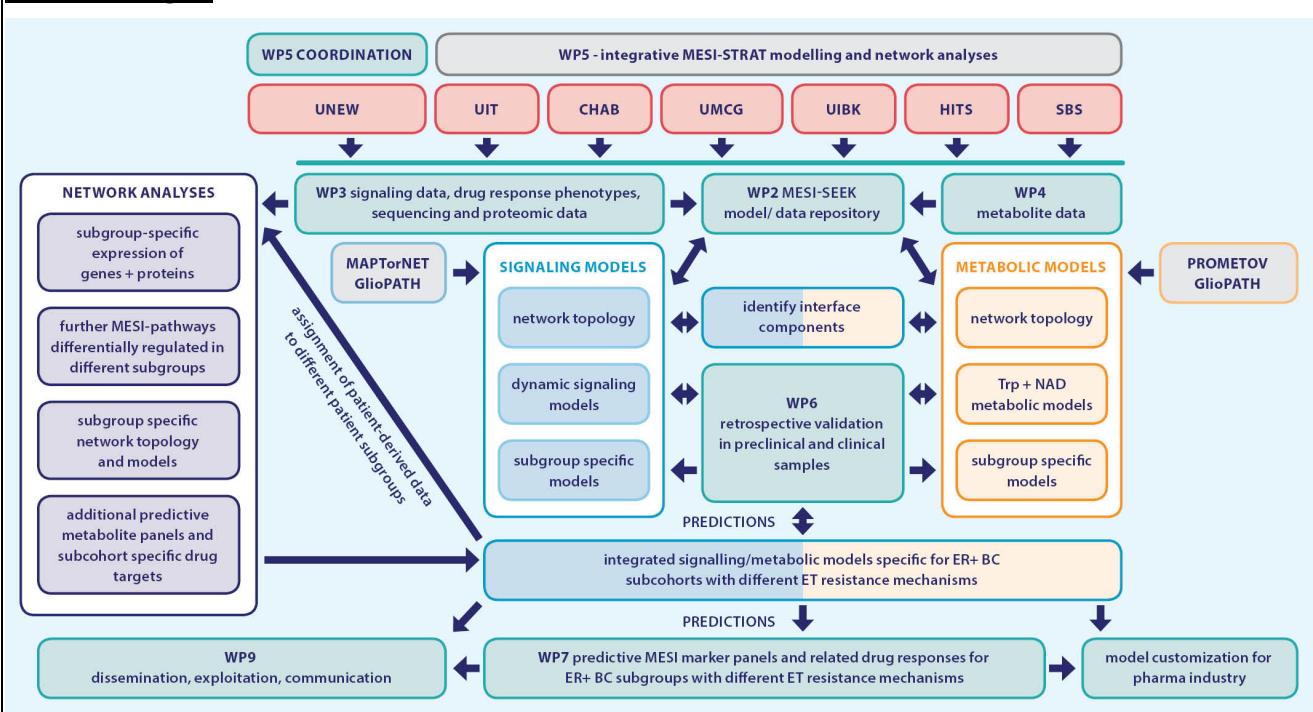
Work Package 3



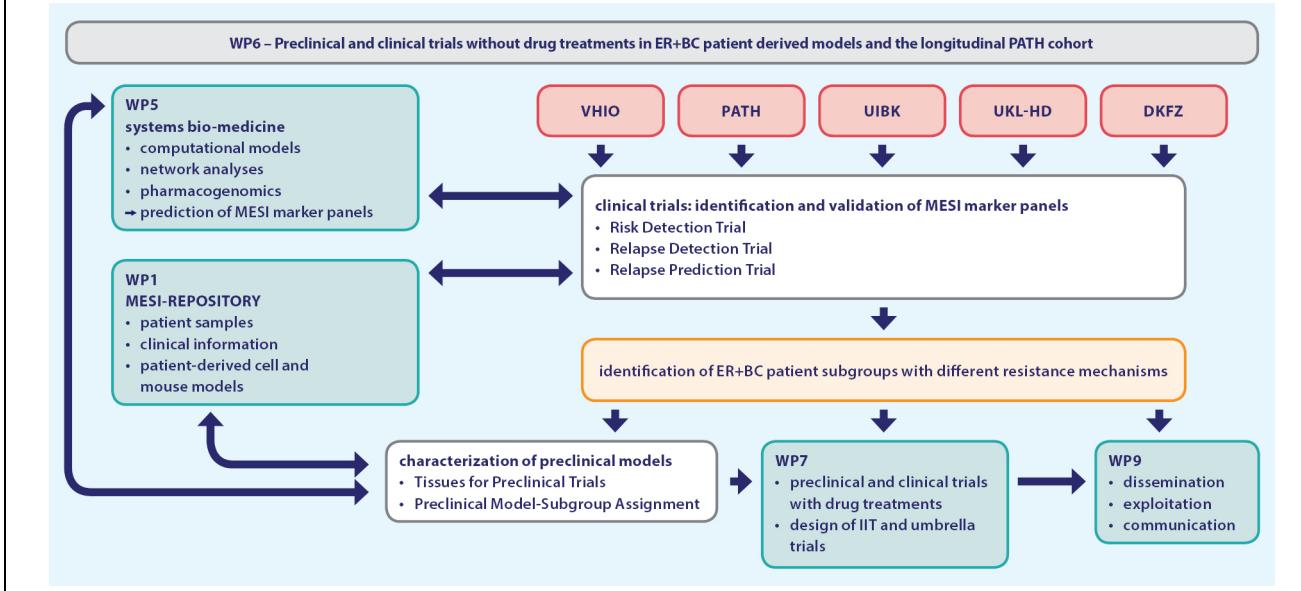
Work Package 4



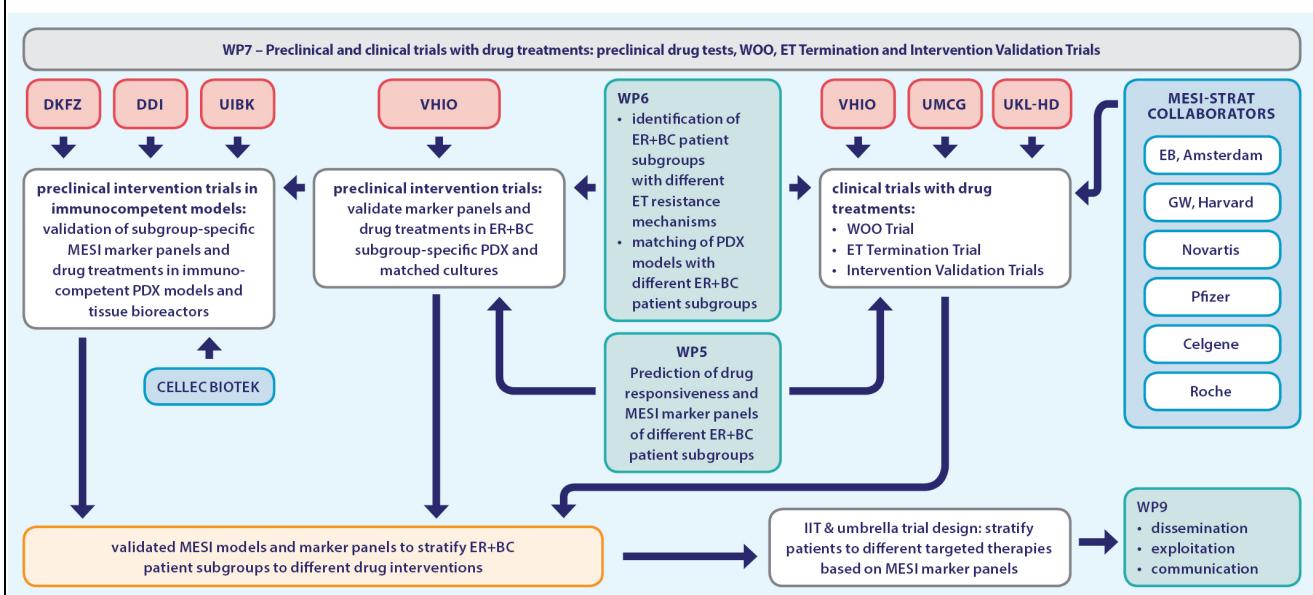
Work Package 5



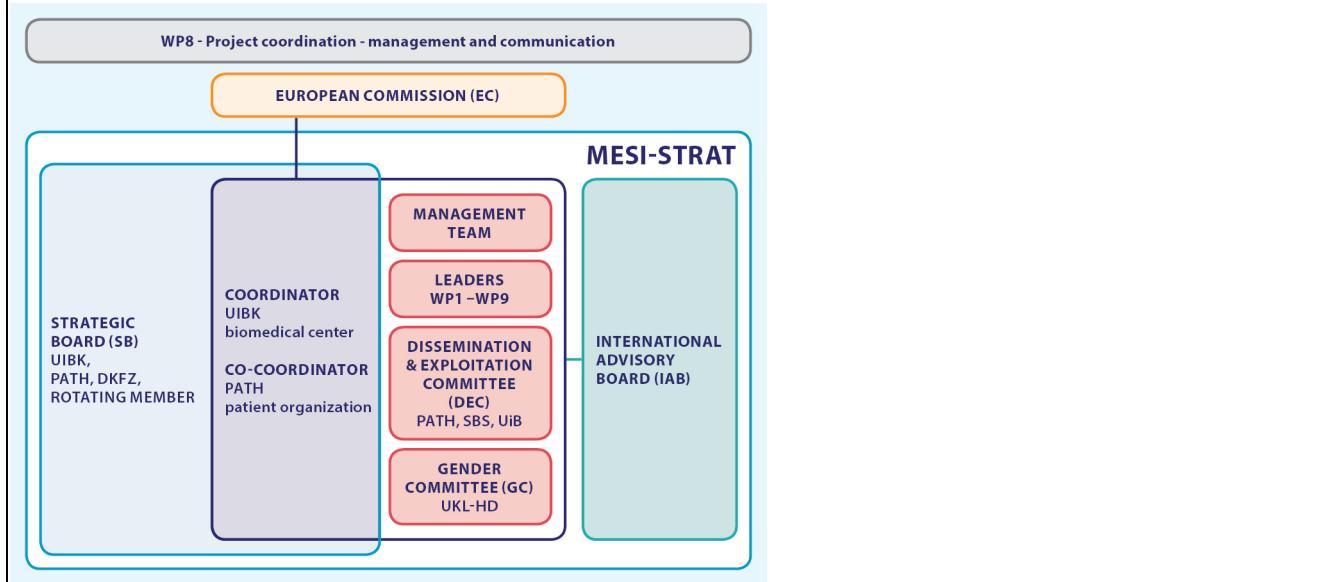
Work Package 6



Work Package 7

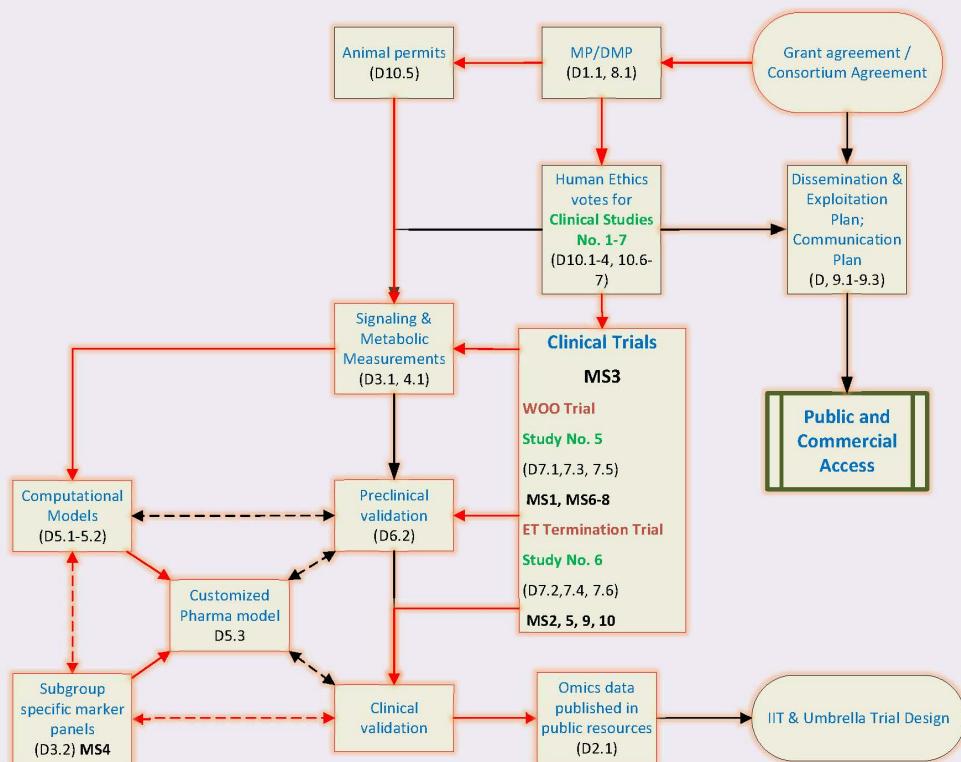


Work Package 8



3.1.4 Graphical presentation showing how the components interrelate (Pert chart) and list of deliverables.

Figure 9. PERT diagram: relationship between WPs and tasks. Shown are the most important connections between MESI-STRAT WPs and their deliverables and milestones.



3.2 Management structure and procedures

3.2.1 Organisational structure and the decision-making in relation to the complexity and scale of the project

The MESI-STRAT project brings together 14 partners. The Project Coordinator UIBK with Prof. Dr. Kathrin Thedieck (f) as relevant staff was unanimously appointed by all MESI-STRAT partners. KT is a young high profile and highly active female scientist in systems medicine, and has the full support from WP leaders in the MESI-STRAT consortium, representing an experienced panel of high profile systems biologists and medical scientists. WP8 is dedicated to the management and organization of the overall project, led by the Project Coordinator UIBK/KT and supported by a project manager (PM) and the host institution (UIBK). Project management covers a range of activities including project planning, and implementing deviations from planned actions where necessary; gathering intelligence to promote the generated results; and preparing and undertaking the exploitation.

Our project has a strong **team commitment** to the tasks of MESI-STRAT. The partners are closely linked by previous and ongoing collaborations in systems biology and medicine, evidenced by multiple joint publications and funding (Section 3.3, Consortium as a whole). **Each WP** has been designed by its own team, facilitated by meetings and close interactions across the consortium throughout the proposal preparation. The support for the successful stage 1 submission, and the composite set of plans for all WPs continues to be endorsed by all involved. Thus, MESI-STRAT starts with the advantage of shared vision and commitment, and mutual support for the leadership of KT and for the partner work streams.

The MESI-STRAT consortium structure and procedures as laid out below is further detailed in the Consortium Agreement which will be the basis for the Grant Agreement to be signed between the coordinator and the EC. The Consortium Agreement will be based on the DESCA model and includes provisions, procedures for convening ad hoc meetings and dealing with extraordinary events such as conflicts, partners leaving or entering the project.

Project management will be implemented at a **strategic level** and an **operational (day-to-day management)**. The **management structure is graphically shown in WP8**.

- **Strategic management**

In accordance with the consortium size and the project structure, the strategic management includes one governance body: the **MESI-STRAT Strategic Board (SB)**, consisting of the coordinator (UIBK/KT, systems biologist), the co-coordinator (PATH/TA, patient organization & clinician), a clinician and cancer metabolism expert (DKFZ/CO), and a fourth rotating member. The balanced representation ensures the efficient implementation of our systems bio-medicine project and strong involvement of patients as a main group of stakeholders. The rotating member will be appointed according to the major tasks or emerging risks at the different project phases. For example, in the beginning, the setup of the MESI-SEEK platform will be of major importance both to MESI-STRAT and to join the EC Pilot on Open Research Data by implementing a data management plan. Therefore, the leader of WP2 (data management) HITS will join the SB in this initial project phase. Decision-making will be supported by regular online meetings with all WP leaders and co-leaders, and by polls if decisions by vote are required. The SB sets annual scientific objectives, policy and strategic orientations of the project in accordance with the rules of the Consortium and Grant Agreements and the project programme; ensures proper administrative, legal and financial operations; monitors the progress of the project towards its objectives, deliverables and milestones, and prepares the reports to the EC; decides on the distribution of the EC pre-financing/interim payment; funding for open access publishing (open data); and modifications to the consortium such as inclusion/exclusion of beneficiaries, funding redistribution, corrective measures, and modification to the research programme.

The SB will be assisted by the **International Advisory Board (IAB)** providing strategic input and supervision of the activities of the MESI-STRAT program. The IAB is composed of global experts recognized in the fields of basic and clinical BC research, signaling & metabolism in BC, systems medicine, companies active in the pharma sector and systems medicine, and patient representatives. Together with the partnering and collaborating SMEs, the IAB will ensure scientific excellence as well as compliance with the needs of industry and society. It will promote dissemination, exploitation, and communication and provide visions for the structuring and operation of activities of **MESI-STRAT**.

Expertise	Name and Affiliation	m/f
Integrated Genomics of BC	Prof. emerita A.-L. Borresen-Dale, Dept. of Cancer Genetics, Inst. for Cancer Research, The Norwegian Radium Hospital, Oslo, NO	f
BC liquid biomarker discovery and trials	Prof. E. Boven, MD, PhD, Medical Oncologist, VU University Medical Center, Amsterdam, NL	f
BC metabolism	G. Wulf, MD, PhD, Assoc. Prof., Dana-Farber Harvard Cancer Center, Boston, US	f

BC patient expert	Doris Schmitt, PATH co-chair , executive board member of the European patient academy EUPATI , and patient-doctor communication coach , Konstanz, DE	f
European BC patient organization	Susan Knox, CEO, EUROPA DONNA – The European Breast Cancer Coalition , Milan, IT	f
BC drug development pharma	Dr. Eric Hoedemaker, Medical Director Oncology, Novartis , NL	m
Systems modeling for pharma drug discovery	Dr. Andreas Raue, Lead early stage immune-oncology development and biomarker discovery, Merrimack Pharmaceuticals , Cambridge, MA, US	m
Metabolic modeling and systems biology of epigenetics in BC	ITN EpiPredict Coordinator: Dr P.J. Verschure, University of Amsterdam, NL Prof. H. V. Westerhoff, Director Manchester Centre for Integrative Systems Biology (MCISB), University of Manchester, UK	f m

A **committee for exploitation and communication of results (DEC)** will be built by the SME SBS, the patient organization PATH, the clinical partner UKL-HD and the academic partner UiB/SG to represent all interest groups and expertise within the MESI-STRAT consortium. In regular meetings the DEC will evaluate the potential of MESI-STRAT results for scientific and commercial exploitation and advise on the next steps. The DEC will take care that access rights to background and foreground IP needed for implementing the project will be granted, and will monitor MESI-STRAT actions and results (i.e., foreground) to identify IP that requires protection prior to publication, always observing patients' interests and privacy regulations.

A **gender committee (GC)**, headed by our clinical experts SS (UKL-HD) and CSC (UMCG), both specializing on male BC, will focus on the consequent consideration and implementation of gender issues at all project levels. This concerns in particular the translation of results for female ER+BC to male ER+BC. SS (UKL-HD) and CSC (UMCG) both have a strong focus on male BC and access to large sample male BC collections (see WP1, 7). These are very precious as male BC is rare. Hence, the GC will evaluate and decide on the validation of strongly predictive MESI marker panels from female ER+BC subgroups in the male cohorts. Furthermore, the GC will constantly evaluate MESI-STRAT actions and results regarding the proper consideration of gender issues and consideration and validation for male BC wherever possible.

- **Day-to-day management**

The coordinator (UIBK/KT)

- is the dedicated contact person liaising with the EC on behalf of the MESI-STRAT consortium, transferring the reports and informing the EC of any major issues/modifications of the work plan.
- is responsible for the achievement of the project in line with the Grant Agreement,
- is the chairperson of the SB, ensuring coherence between decision-making bodies and to minimize the risk of bottleneck
- acts as the primary conduit between the SB and the IAB,
- mediates and settles disputes within the consortium.

The PM (project manager, to be appointed), is responsible for implementing the decisions of the SB and the day-to-day management of the project. The PM will provide an administrative link with the Commission Desk Officer, and partner institutions' administrations. The PM will oversee administrative, legal, and financial operations and reporting, and effective and efficient implementation of the project.

The Management Team (KT together with the PM)

- prepares the meetings, proposes decisions and prepares the agenda of the SB,
- is responsible for the proper execution and implementation of the decisions of the SB,
- monitors the effective and efficient implementation of the project;
- collects information at least every 6 months on project progress, examines that information to assess the compliance of the project with the technical annex and, if necessary, proposes modifications to the SB.

Meeting schedule

- monthly video conference of the SB + MT, including identification and discussion of any problems arising on progress, resources or other matters.
- monthly work and progress returns to the project office.
- bi-monthly video conference between all WP Leaders, to discuss progress, identify and resolve arising issues, and an alternating presentation on scientific progress in the partner labs.
- six-monthly face-to-face meeting of WP Leaders and co-leaders.
- annual meeting with the whole consortium.
- ad hoc meetings for addressing unexpected events.

- all WPs will hold monthly meetings, chaired by the WP leader or co-leader, to ensure progress and achievement of their milestones and deliverables and for timely identification and resolution of emerging risks.

The PM will prepare agendas for the listed consortium meetings, and promptly produce memoranda on agreements and actions. The **annual meeting** with the whole consortium will be held as a one-day event involving all MESI-STRAT partners. For efficiency, but also to enable good inter-personal linkage, the meeting will be preceded by half-day meetings of the WP Leaders and of the IAB; each WP will then have the opportunity to hold its own working meeting, and inter-WP discussions will be led by the tandems. Most members will thus attend for two days. To tighten the links and ensure commitment between the partners, the annual meeting will be organized and hosted by a different partner each year.

3.2.2 Effective innovation management in the management structure and work plan

The **MESI-STRAT** WPs are technology, expertise, and delivery centred. The technical expertise resident in the WPs is a constant that we draw upon to implement our **highly iterative systems medicine strategy**. In this approach, existing knowledge is formalized into mathematical models, and simulations are turned into predictions, which are then tested against experimental data. At each step, the test results will feed back into the theoretical models, where any discrepancies may reveal a missing knowledge and/or need to change our hypotheses. Resolution of such discrepancies typically requires multiple cycles of open-minded systematic analysis of existing data and brainstorming sessions with experimental, theoretical, and clinical partners. Followed by evaluation and prioritization of new ideas, implementation into models and further testing against experimental data.

The **MESI-STRAT innovation process**, implemented in WPs 8 and 9 and detailed in sections 2.2.1 (scientific dissemination, commercial exploitation), 2.2.2 (data management plan), 2.2.3 (IPR management & open data), and 2.2.4 (communication) follows this well-established iterative practice in systems approaches.

Collaborations, open internal communication, and mutual trust and respect are key to innovation management. These key aspects will be ensured by

- frequent virtual and on-site meetings (see previous section)
- a consortium whose partners have communicated closely and collaborated productively for many years, familiar with projects that involve cross-disciplinary communication, requiring the willingness to listen to partners from other disciplines and to try out their ideas.
- the **understanding of both market and technical problems, including commercial and medical regulatory aspects** due to the open communication between the SMEs, and scientific and clinical partners and patient experts in our consortium.

As a result, the guiding principle of all MESI-STRAT efforts will be the **continuous improvement through iterative development** within all WPs and their interactions. This gives MESI-STRAT the possibility for self-correction and the ability to respond to an external or internal opportunity.

3.2.3 Critical risks, relating to project implementation, and risk mitigation measures

Risk management will be given a high priority. (i) Risk identification: foreseeable risks identified by the consortium during the elaboration of the project are stated below; (ii) Risk treatment: identified risks (see below) and/or alternative plans to limit their impact will be drawn up, and followed up by the SB. Milestones will serve as an assessment tool, enabling risks to be monitored and corrective measures to be implemented. The WP leader(s) will monitor their milestones and report to the Coordinator and the SB for recommendations on continuation/implementation of contingency plans. The management team will ensure that relevant information and knowledge circulates efficiently between partners (see WP8).

Conflict resolution will be approached by consensus at the point of origin; if consensus cannot be reached, the SB and ultimately the coordinator will make the final decision: for any problems arising with individual partners we will first try to find a solution within the institution; secondly within the WP to try to cross-cover any work problems; and thirdly at project level to find a solution within the WP Leaders' meeting. As the last resort the Project Coordinator will have final decision. No partner will be allowed to exceed their budget without appropriate approval and resource transfer. If any partner seeks to (or does) undertake work not in the project plan, or not in accord with agreed procedures (especially with regard to ethics) that work will not be funded.

Decision-making process concerning the evolution of the consortium (entry of a new party, withdrawal of a party, change of coordinator) or suspension of the project will be made by unanimous vote. All other decisions within the consortium will always be made by a qualified majority of two-thirds (2/3) of the partners'.

3.3 Consortium as a whole

3.3.1 Match of the consortium with MESI-STRAT objectives, expertise and complementarity of the members, and value chain

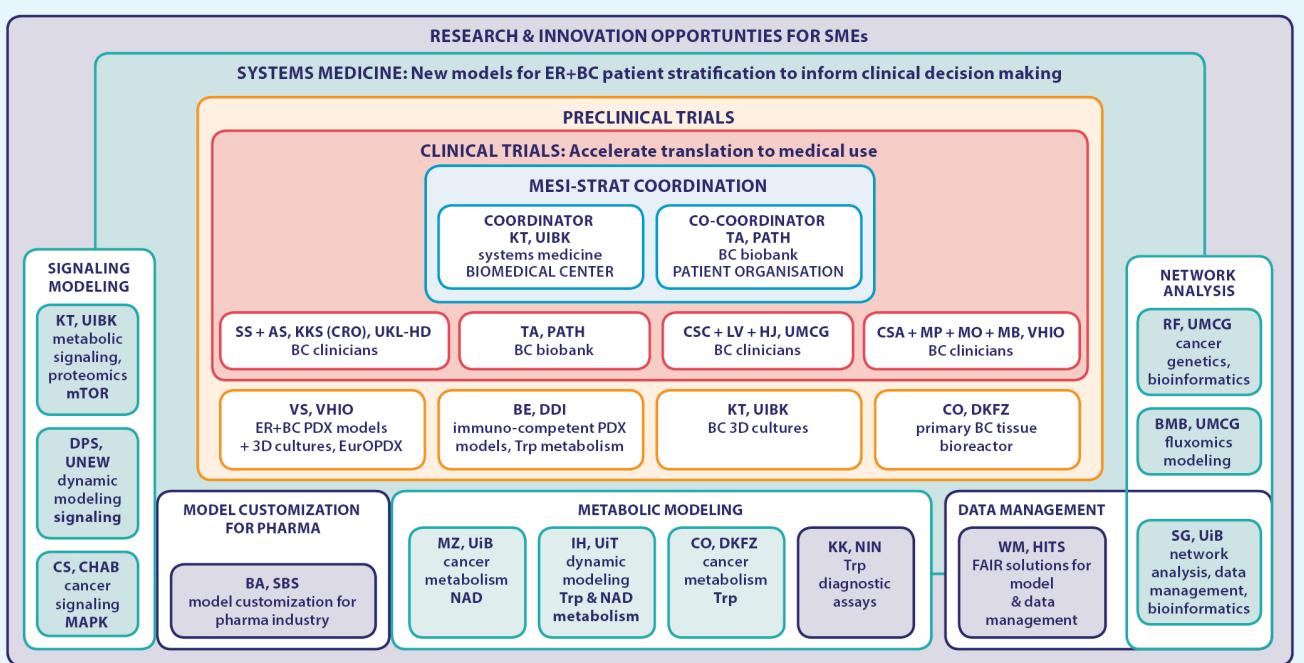
MESI-STRAT assembles the scientific excellence and essential multidisciplinary expertise (biology, medicine, mathematical modeling, bioinformatics, biobanking, and patients' expertise) to implement MESI-STRATs systems medicine approach to deliver and to preclinically and clinically validate novel concepts for ER+BC patient stratification (see also Section 1.3.a for short description). Key complementary expertise is assembled into **multidisciplinary expert teams** that link the work across the work packages and pan-European institutions (detailed in 3.3.2). The interconnection of academic and clinical partners with the partnering SMEs SBS, NIN, and HITS and collaborating SMEs and pharma companies ensures the implementation of the multi-level **MESI-STRAT value chain**, further detailed in 3.3.3.

As evidenced by joint papers and grants, the **MESI-STRAT consortium has close internal links**. Several partners cooperate within the GlioPATH (CO, IH, KT), MAPTorNET (CS, DPS, KT), PROMETOV (CO, KT) and EuroPDX (VS, SJ) consortia, which will deliver data and models to MESI-STRAT. Many partners are linked by a strong joint publication history (e.g., DPS+KT; IH+MZ; KT+SG; CO+KK+SS; VS+CS; VS+SJ; TA+AS, etc., see partner descriptions in section 4 for details). MESI-STRAT will link our separate initiatives into an integrated, synergistic effort that enables European systems biology (CISBAN, SBC-EMA, DKFZ) and BC (VHIO, UKL-HD, UMCG, DKFZ) centres to develop new models for disease-mechanism-based stratification of ER+BC patients for targeted therapies.

3.3.2 Roles and resources of the project partners

The **coordination tandem** encompasses systems medicine (UIBK/KT) and clinical BC and biobanking expertise (PATH/TA.). The role of the patient organization PATH as a co-coordinator not only ensures the timely, longitudinal collection of ER+BC patient tissues to reach our scientific and clinical aims; but the PATH patient expert DS together with the cancer information service (DKFZ/SW) also ascertain that the patients' perspective is embedded at all project levels, from the earliest planning throughout implementation and actions for dissemination, exploitation and communication.

Figure 10. The MESI-STRAT consortium as a whole. Roles of the consortium partners.



The **interdisciplinary MESI-STRAT expert teams** consist of modelers and experimentalists/clinicians who specialize in different aspects of cancer signalling and metabolism, and preclinical and clinical BC research. The expert teams will focus on (*i*) **signaling** (KT, DPS, CS), (*ii*) **metabolism** (IH, CO, MZ, KK, BMB), and (*iii*) **network analysis** (RF, BMB, SG, WM), (*iv*) **preclinical trials** (VS, BE, SJ, KT, CO), (*v*) **clinical trials** (SS+AS, TA, CSC+LV+HJ, MP+MO+MB), and (*vi*) **model customization for pharma industry** (BA + MESI modeling expert teams) (**Figure 10**). Relying on their joint biological/clinical expertise and their synergistic methodological expertise, the expert teams will bridge the method-focused WPs to run and develop the

MESI-STRAT systems medicine project plan. Effective cooperation is ensured by the MESI-STRAT management plan (WP8) and continuous information management (described above). The bioinformatics **MESI-SEEK platform** (WM, SG) will collaborate closely with EMBL-EBI (see enclosed letters) and the **dissemination and exploitation committee** (DEC, headed by TA and BA). This will enable the integration of biological and medical research data with computational modeling and to make MESI-STRAT data openly accessible (open data) while ensuring commercial exploitation opportunities and patients' interests and privacy. The **gender committee** (GC, headed by SS, UKL-HD + CSC, UMCG) will ensure the implementation of gender aspects throughout, particularly focusing on the validation of MESI panels, identified in female ER+BC, in male BC cohorts.

As detailed in 3.4 all partners have **significant resources** that are tailored according to their respective tasks. This is particularly important for the clinical partners, as the mandatory clinical trials are costly and their implementation is key to the success of MESI-STRAT; and for the patient organization PATH and the partnering SMEs who all have key roles in our consortium, which is also highlighted by their leadership or co-leadership in WP1 (PATH), WP2 (HITS), WP8 (PATH), and WP9 (SBS, PATH).

3.3.3 Industrial/commercial involvement in MESI-STRAT: structure of the consortium to support exploitation and to build the MESI-STRAT value chain (see also Section 2.2).

The combined clinical and scientific expertise provide a unique opportunity for synergistic efforts to develop and implement a pipeline that covers the earliest steps of model development for ER+BC patient stratification up to validation in preclinical and clinical trials, and customization of our MESI-STRAT models for the pharma industry. Our pipeline entails (i) the education of students for model development at the academic partner centers; (ii) their subsequent employment at the **SME SBS** where they further develop and customize the MESI-STRAT models for pharma clients, under the supervision of experienced computational SBS experts; and (iii) trial licensing of MESI-STRAT models by SBS to explore their potential for expanding the SBS services to the pharma industry. All **stakeholders** of this **value chain** including the SME SBS, pharma clients (Novartis, Merrimack, and others), clinicians and patients are integral parts and/or close collaborators of MESI-STRAT. Moreover, the MESI-STRAT IAB covers the full stakeholder chain (clinicians, patients, pharma, and systems oncology companies) and can hence effectively assist in implementing our value chain. Our new models for clinical decision making will increase cost-effectiveness for clinical trial design (due to smaller cohorts necessary to observe statistically significant effects) and ER+BC therapies (due to avoidance of ineffective treatments and side effects by stratifying patients for targeted therapies). Hence, the commercial value of well-characterized predictive computational models for ER+BC patient stratification is potentially high – resulting in a market advantage for SBS. Initially tailored for ER+BC our models can be adapted to all cancers that affect the molecular networks addressed by MESI-STRAT. As most cancers show dysregulated mTOR/MAPK signaling and/or energy and Trp metabolism the MESI-STRAT models will be broadly applicable and hence have a market potential far beyond ER+BC. In addition, the implementation of our value chain will help SBS gain new well-educated computational personnel – which is currently a serious bottleneck for all companies active in the computational sector.

The **SME HITS gGmbH** has partnered with MESI-STRAT to support data management and to further develop its own platforms and customer services. Participating in MESI-NET constitutes a reference collaboration for HITS gGmbH in systems medicine for the openSEEK platform and the FAIRDOMHub, and enables the enhancement of systems biology infrastructure business models.

The **SME NIN** develops diagnostic assays for amino acid metabolites. Thus NIN can directly exploit the MESI-STRAT results to design new diagnostic assays for MESI marker panels with known and new prognostic metabolites. Like SBS, also NIN will profit from favourable conditions for trial licensing to explore the potential of MESI-STRAT results for commercial exploitation, and, if successful, will strive to acquire long-term licenses.

Wherever possible the MESI-NET consortium will involve additional industrial partners and/or advisors to ensure that the developments stay in line with market demand and requirements. The level of involvement will depend strongly on the stage of development and the time required to reach the market. The **SMEs QuantuMDX** and **CELLEC BIOTEK** are contributing to the programme as associate partners (see enclosed letters). Their expertise in diagnostics and tailored solutions for preclinical drug testing will be valuable in evaluating the MESI-STRAT results and in obtaining the proper focus to match our results with the market demand. For therapeutic developments, MESI-STRAT will work closely with pharma companies already involved in clinical cooperation with UKL-HD, UMCG, VHO, DKFZ, UNEW and DDI (see section 1.3.a) to maximize the window of opportunity for commercial exploitation (Section 2.2).

3.3.4 Other countries and international organizations

All MESI-STRAT partners are based in countries eligible for EU funding.

3.4 Resources to be committed

All partners involved in the MESI-STRAT project are committed to achieve a significant breakthrough in the field of systems medicine by developing new concepts and models for BC patient stratification. The resources and facilities that each organization dedicates to the project (see B4 partner descriptions) further demonstrate their determination to successfully implement the tasks ascribed to this project. The following figures provide an overview of the resources to be committed within the project.

Figure 11: Total effort (PM) distributed per Work Package

The total project effort is of 694 person months (PM), out of which 90,13% are fully dedicated to RTD (Research and Technological Development, WP1-7) activities. All together the 7 WPs dedicated to RTD represent a significant effort of 625,5 PM. 68,5 PM (9,87% of the total) are devoted to management activities (including IP management, WP8) and to the MESI-STRAT impact (dissemination, exploitation, and communication, incl. regulatory issues for commercialization, WP9). WP1 and WP2 (9% of total PM) are dedicated to management of samples and clinical data (MESI-REPOSITORY) and scientific data (MESI-SEEK), and WP6 and WP7 (23% of PM) are dedicated to clinical trials, incl. ethics and medical regulatory issues.

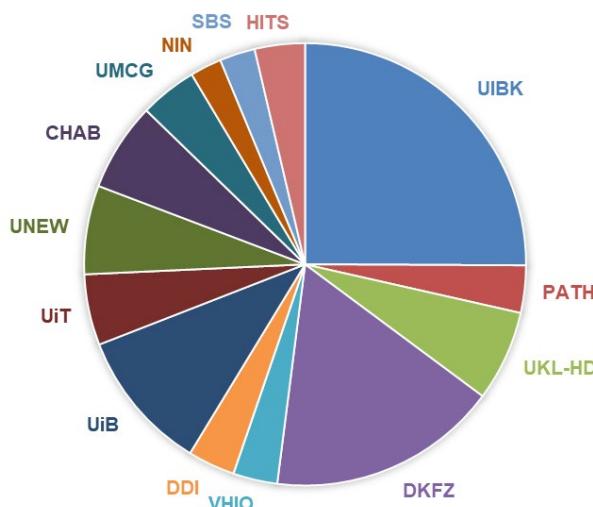
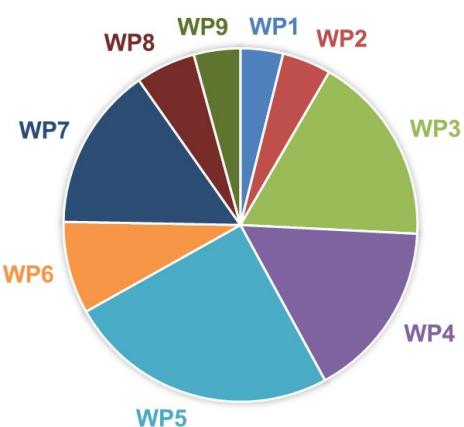


Figure 13: Budget distribution per partner (in EUR)

The total budget of MESI-STRAT distributed among 14 partners amounts to 5,949,964 EUR. The partners UIBK (AU) and DKFZ & UKL-HD (DE) receive 48% of the total requested EU budget for the same reason as indicated in figure 12.

Figure 12: Total effort (PM) distributed per partner

The total staff effort to the MESI-STRAT project is divided among 14 partners. Partners UIBK (AU) and DKFZ & UKL-HD (DE) are allocated 49% of the total staff effort. This is due to the fact that these partners host the clinical studies and multiple measurements and modeling efforts, which require different expertise from experimentalists, clinicians, and computational scientists. Furthermore, UIBK hosts the project coordination (WP8).

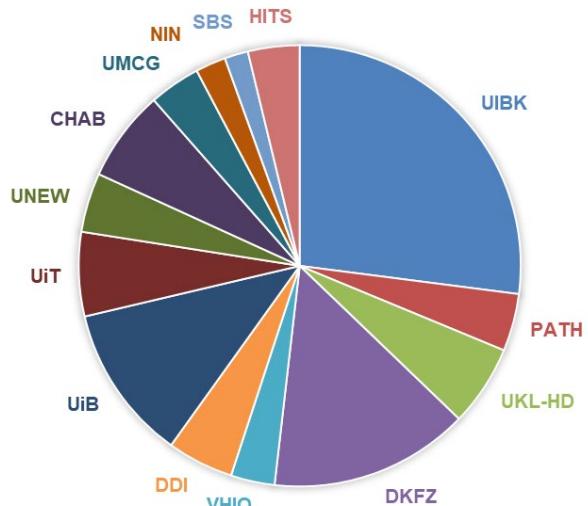


Table 3.4b: ‘Other direct cost’ items

This table justifies the costs for ‘travel’, ‘equipment’, and ‘goods and services’ where the total sum exceeds 15% of the personnel costs for a given participant (see budget table in form A).

1. UIBK	Cost (€)	Justification
Travel	18,729	Travel budget for coordinator, physicians, and research postdocs to consortium + WP leader meetings, patient days, and European systems medicine conferences.
Equipment	19,900	Specialised computer for modeling (5,000 EUR), bioreactor for cancer tissue culture (14,900 EUR).
Other goods and services	278,113	Standard consumables. Extra budgets for proteomics and metabolic measurements (WP3, 4: 80,000 EUR); MESI-STRAT consortium management (WP8, 78,820 EUR) incl. organisation of consortia and WP leader meetings, IAB travel costs; measures to raise impact (WP9 23,293 EUR) incl. open access publishing, daily rates patient organisation Europa Donna, feasibility studies, website; Certificates on the Financial Statements (CFS) (2,000 EUR)
Total	316,742	
2. PATH	Cost (€)	Justification
Travel	8.000	Travel budget for PI and medical scientist to join consortium meetings.
Other goods and services	25,000	Extra budget for the organization of 3 European patient days in WP9 (Dissemination).
Total	33,000	
3. UKL-HD	Cost (€)	Justification
Travel	8,080	Travel budget WOO trial manager, and PI and medical scientists to consortia and WP leader meetings
Other goods and services	56,625	Standard consumables. Extra budgets for clinical trials incl. sample and data processing for 70 patients (36,261 EUR), competent and local authoritie(s) fees (4,425 EUR), trial insurances (4,200 EUR), ethics committee and national institution fees (6,300 EUR), trial audit costs (2,000 EUR) for WOO Trial.
Total	64.705	
4. DKFZ	Cost (€)	Justification
Travel	12,000	Travel cost for PI and 2 scientists to join consortia and WP leader meetings.
Equipment	29,800	2 Bioreactors for primary culture of cancer tissue.
Other goods and services	170,080	Standard consumables. Extra budgets for primary cell culture media and reagents (32,000 Euros); metabolomics columns /consumables; panel seq & RNAseq (25,480 Euros), NCT tissue bank (2,000), bioreactor consumables (21,600 Euros), and Certificates on the Financial Statements (CFS) (5,000 EUR).
Total	211,880	
5. VHIO	Cost (€)	Justification
Travel	4,000	Travel cost for PI to join consortia meetings
Other goods and services	85,000	Standard consumables. Extra budgets for the collection of tumor tissue and blood; animal costs (60,000 EUR) incl. chemosensitivity tests, and establishing two new ER+BC PDX models (20,000).
Total	89,000	
6. DDI	Cost (€)	Justification
Travel	8,000	Travel costs for 2 persons to all consortia meetings.
Other goods and services	60,000	WP7 requires budget for establishing up to four immunocompetent PDX BC mouse models, and running up to two preclinical therapy trials in these models (animal housing for long term in vivo studies, and anticancer therapeutics, incl. IDO 1 inhibitor (Epacadostat).
Total	68,000	
10. CHAB	Cost (€)	Justification
Travel	8,000	Travel budget for PI and postdoc to join consortium meetings.
Other goods and services	42,000	The amount of 40,000 Euros for consumables exactly equals 15% of the personnel costs. This is needed to carry out signaling studies in WP3 (cell culture reagents incl. media, fetal calf serum, additives, antibiotics); compounds and reagents (RNAi, CrisprCas9) for perturbation screens and analyses; antibodies, BioPLEX analysis (multiplex kits), Incucyte consumables for growth/survival/migration analysis; general lab consumables (plastic, chemicals etc.).
Total	50,000	
12. NIN	Cost (€)	Justification
Travel	3,900	Travel budget for researcher to join consortium meetings.
Other goods and services	29,500	Standard consumables. Additional budget for materials for L-Kyn, Trp, Serotonin, KA, QA metabolite diagnostic assays (15,000), IDO1 protein assays (2,500), and multiplex assay development (12,000).
Total	33.400	

- **Please note:** No costs of large research infrastructure are requested

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MESI-STRAT

Systems Medicine of Metabolic-Signaling networks -
A New Concept for Breast Cancer Patient Stratification

Technical Annex Section 4-5

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Section 4: Members of the consortium

4.1. Participants (applicants)

Partner 1 – UIBK – Universitaet Innsbruck, Austria

UIBK takes coordination and tasks over from UMCG as of 01.02.2019.

Details are given in amendment request letter.

Description of the Institution

The University of Innsbruck (UIBK) was founded in 1669, and today comprises 16 Faculties. In 2011, the UIBK was Austria's best university with an overall worldwide rank of 187 according to the Times Higher Education World University Ranking, and has since maintained good rankings within the top 350 universities as the best or second-best ranking among Austrian universities. Notably, the UIBK receives far above-average ratings regarding the research impact of its scientists, and also excels by its highly supportive and successful research and teaching environment. The UIBK receives funding from national and international sources, in particular by the Austrian Science Fund (FWF, 356 projects in the last five years) and the European Commission (55 projects in the last five years). The UIBK collaborates extensively with the Medical University of Innsbruck and has a long-standing record of successful collaborations with the industry, in particular in the fields of cell biology and biochemistry.

Experience and role in the project

The Institute of Biochemistry, of which KT is the designated head, is embedded at the Faculty of Chemistry and Pharmacy of UIBK, recognised as one of the leading European institutions in its field. The faculty's professional and methodical capabilities in basic and applied research also provide the basis for state-of-the-art teaching. The Faculty comprises more than 100 staff members, nearly 100 postdoctoral associates and visiting fellows and about 100 PhD students from all over the world, engaged in cutting-edge research of highest international standing. This is reflected by numerous prestigious prizes and honours awarded to staff and graduate students and by the large number of outstanding publications in top quality international scientific journals. The Faculty excels in multi- and interdisciplinary research in the life sciences, advanced materials with particular emphasis on nanotechnology, and in theoretical and computational chemistry and biology. These research topics provide the basis for the Faculty's prominent role in the University's „Center for Molecular Biosciences“ (CMBI), the research initiative „Advanced Materials“, and the „High-Performance Computing“ (HPC) platform. A large number of partnerships and co-operation programmes with institutions all over the world provide excellent staff and student exchange facilities and highest internationality in research networking.

Research at the **Institute of Biochemistry** is focused on the (patho) physiology of mammalian nutrient signaling and metabolism, from cells to the entire body. Specific fields of interest are systems approaches to study the linkage between signaling and metabolism in cancers, congenital disorders and metabolic disease. The institute has long standing expertise in signalling and metabolic research, with emphasis on biochemical and mass spectrometry based proteomics and metabolomics, and imaging.

Its embedding within the **Center for Molecular Biosciences (CMBI)** further strengthens the biomedical focus of the Institute of Biochemistry. The CMBI is an integrative and multidisciplinary research and graduate teaching institution, currently comprising 20 research groups from the Faculties of Biology, Chemistry and Pharmacy, and Mathematics, Informatics and Physics. The CMBI mission is to advance knowledge on the structure, function, and interaction of biological macromolecules and simple compounds, relevant for cellular growth, metabolism, and development.

Located at the Center of Chemistry and Biomedicine (CCB) jointly run by the UIBK and Innsbruck Medical University, in direct vicinity to the Biocenter Innsbruck (Medical University), the Institute of Biochemistry builds on strong ties with biomedical and clinical expertise in its direct surrounding.

Oncological research at the Medical University of Innsbruck ranges from basic research using the latest genetic, cellular, molecular and systems biology approaches to translational and clinical research. This includes the complete clinical development of new drugs from early phase I/II studies to approval or therapy optimization studies. The focus on oncology is highlighted by the participation in various national and international oncology research networks. Over the last ten years, the oncology focus has been supported by the very successful SFB-021 "Cell proliferation and cell death in tumors", which was also decisive for the implementation of Oncotyrol. The **Comprehensive Cancer Center Innsbruck**

(CCCI) has currently been founded according to the criteria of the US-American National Cancer Institute. This interdisciplinary research center is at the interface between theory and the clinic and is jointly supported by the **Medical University of Innsbruck, the Tyrol Clinics, the Tyrolean Cancer Research Institute and Oncotyrol**. This environment, focused on highly translational studies, provides a fruitful asset for the MESI-STRAT project.

Main Tasks undertaken in the consortium

UIBK is leader of **WP8**, and hosts the **coordination of the project**. UIBK will contribute to measurements in **WP 3 and 4** and the modeling in **WP5**. UIBK supports pre-clinical and clinical trials (**WP6+7**) for identification and validation of predictive MESI marker panels in patient derived cultures, PDX models, and patient samples. Together with the colleagues at UKL-HD, DKFZ, and VHIO, UIBK will coordinate the decision making processes for the selection of treatment strategies and marker selection throughout the project (**WP3-WP7**) including clinical studies and for IIT and umbrella trial design (**WP7**). Note that the tasks in WP6 and WP7 relate either to coordinative tasks (Tasks 6.2 and 7.4) or to preclinical analyses of cells and primary tissues (Task 7.1). Thus, UIBK/KT does not conduct clinical tasks.

Operational capacity to carry out the tasks described in the project:

- As the coordinator at UIBK, KT also has the coordinative capacities to support all coordinative tasks within MESI-STRAT, including in tasks 6.2 and 7.4.
- The UIBK tasks in 7.1 as well as in the other scientific tasks require expertise in cell biology and biochemical analyses, which are both core expertises of KT (see her track record), and for which there is excellent equipment and outstanding infrastructure at UIBK. Specifically, KT (and hence MESI-STRAT) will have access to own high end cell culture, microscopy, protein and metabolite analytics, and mass spectrometry units, and excellently equipped core facilities for mass spectrometry and imaging, to conduct their tasks. Furthermore, the German Cancer Research Center (DKFZ/CO) will closely collaborate with UIBK/KT to establish/refine techniques for primary cell and tissue cultivation, where needed. Next to KT's own expertise in systems studies (see track record), the „High-Performance Computing“ (HPC) platform at UIBK will be an excellent framework for computational tasks in WP5.
- Being embedded in the Center of Chemistry and Biomedicine (CCB), jointly run by UIBK and the Medical University of Innsbruck, KT will have close ties with oncological research and the newly founded Comprehensive Cancer Center Innsbruck, where capacities, knowledge and infrastructure for planning and conduction of clinical trials are available. This will not be necessary for the operational capacity of MESI-STRAT, but it is available for advisory purposes if required. Of note, MESI-STRAT clinical trial coordinator Dr. med. Christiane Opitz (partner DKFZ, German Cancer Research Center) closely collaborates with KT and advises her on clinical questions, whenever necessary.

CV of PI and other people involved (including gender)

Prof K. Thedieck, PhD (F) [KT] (www.metabolic-signaling.eu) joins the UIBK, Innsbruck (AU) in February 2019 as a full professor and designated institute head of the Institute for Biochemistry. Previously, she was appointed at the UMCG, Groningen (NL) and Oldenburg University (D) since 2013 in the frame of the European Medical School (EMS) as an Adjunct Professor of Metabolic Signalling. KT has studied since 10 years the control of metabolic homeostasis by the mTOR network, by means of cell biology, biochemistry, proteomics, and systems biology in cancer cells. KT's technological background is in proteomics and cell biology analyses of signalling networks (Schwarz et al, 2015, Mol. Cell. Proteomics). Furthermore, she has made seminal additions to the study of mTOR in cancer by systems medicine, by developing, jointly with Daryl P. Shanley (DPS, UNEW, partner 9) one of the first systems approaches to the mTOR network (Dalle Pezze et al, Science Signaling, 2012). This is further developed ever since by KT and DPS (Dalle Pezze et al, Nature Comm., 2016), and other labs (83 citations). Her work on systems approaches, and the crosstalk of mTOR with other cancer signalling (Thien et al. Dev Cell 2015; Ruf et al., Autophagy 2017) and cancer stress networks (Thedieck et al, Cell 2013) is funded among others by the EU (Transcan-2 JTC 2014 call: PROMETOV; FP6 NoE LifeSpan), the German Research Society (DFG), and the German Ministry for Research and Education (BMBF). The promise

in KT as a scientist and her research line continues to be acknowledged by fellowships of the Rosalind Franklin Program (University of Groningen, NL), the Schlieben-Lange-Program (Federal state of Baden-Württemberg, D), the FRIAS Freiburg Institute for Advanced Studies (D), and the Engelhorn Foundation. Having worked in an industrial SME (BioVisioN AG, D), before starting her academic career, KT is well aware of the opportunity and importance of IPR protection and industrial collaboration. Therefore, KT and DPS jointly hold one of the first European patents for computational systems oncology models (WO2012163440). KT continues to be active in patenting therapeutic cancer targets (WO2014108532). Together with the UMCG TTO (see attached letter), KT initiated a feasibility study to exploit the results of this and other systems oncology consortia in an own spin-off, and we plan to continue these activities in the frame of MESI-STRAT (see section 2.2 of this proposal). KT's capability in bringing together basic and clinical scientists and commercial stakeholders from different cancer-relevant disciplines in successful multi-center systems medicine collaborations is evidenced by the author lists of her papers, all highlighting the strong collaborative character of KT's work. Several of her papers are co-authored by MESI-STRAT members. KT's enthusiasm and effort over the last seven years in developing systems oncology to target metabolism and signaling networks have seeded the German MAPTorNET (coordinated by CS, CHAB, partner 10) and GlioPATH consortia, as well as the European ERA-NET Transcan-2 PROMETOV consortium (both coordinated by CO, DKFZ, partner 4). These efforts now cumulate in the setup of the pan-European MESI-STRAT project. KT has successfully built up her lab and reputation in the field as evidenced by 10 PhD students (3 graduated, 7 ongoing), and so far 20 peer-reviewed publications, an h-index of 10 (top papers with 125 – 218 citations), with key publications in Cell, Nature, and Science journals. KT acts as an editorial board member for Pharmacological Research and PLoS Genetics, and reviews for numerous key journals in life sciences and systems medicine and for several national and European funding organizations.

5 relevant publications/products/services/software/other achievements relevant to the call content: § denotes corresponding authorships

Please note:

Joint activities between KT (UIBK, coordinator) and DKFZ, UiT, UiB, UNEW, and CHAB are indicated in their partner descriptions as well.

A full record of KT can be found at www.metabolic-signaling.eu.

1. **Adam I, Dewi DL, Mohapatra SR, Sadik A, Berdel B, Keil M, Sonner JK, **Thedieck K**, Rose AJ, Platten M, **Heiland I**, Trump S, **Opitz CA**§. Upregulation of tryptophanyl-tRNA synthethase adapts human cancer cells to nutritional stress caused by tryptophan degradation. Oncoimmunology. 2018 Sep 5;7(12)
2. **Riemer P, Rydenfelt M, Marks M, van Eunen K, **Thedieck K**, Herrmann B, Blüthgen N, **Sers C**, Morkel M. Oncogenic β-Catenin and PIK3CA instruct network states and cancer phenotypes in intestinal organ-oids. Journal of Cell Biology. 2017 Apr 25
3. **Dalle Pezze P, Ruf S, Sonntag AG, Langelaar-Makkinje M, Hall P, Tölle R, Schwarz JJ, Horvatovich P, Fäßler E, Schäuble S, Hahn U, **Shanley DP**§, **Thedieck K**§. A systems study reveals concurrent activation of AMPK and mTOR by amino acids. Nature Communications. 2016 Nov 21; 7: 13254.
4. Ruf S, Heberle AM, Langelaar-Makkinje M, Gelino S, Wilkinson D, Gerbeth C, Schwarz JJ, Holzwarth B, Warscheid B, Meisinger C, van Vugt MATM, Baumeister R, Hansen M, **Thedieck K**§. Polo-like kinase 1 inhibits mTOR complex 1 and promotes autophagy. Autophagy. 2017 Jan 19:0.
5. ****Thedieck K**§, Holzwarth B, Prentzell MT, Boehlke C, Kläsener K, Ruf S, Sonntag AG, Maerz L, **Grellscheid SN**, Kremmer E, Nitschke R, Kuehn EW, Jonker JW, Groen AK, Reth

**Publications and grants with other consortium members

M, Hall MN, Baumeister R. Inhibition of mTORC1 by astrin and stress granules prevents apoptosis in cancer cells. Cell. 2013 Aug 15;154(4):859-74

List of up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. ****KT and CO (DKFZ) and IH (UiT)** collaborate in the frame of the **e:Med BMBF GlioPATH** consortium (Comparison of central metabolic routes and signaling pathways in IDH mutant and wildtype gliomas), and **KT and CO (DKFZ)** collaborate in the **ERA-NET Transcan-2 project PROMETOV** (Translational research on human tumour heterogeneity to overcome recurrence and resistance to therapy on ovarian cancer).
2. ****KT, CS (CHAB) and DPS (UNEW)** collaborate in the frame of **e:Med BMBF MAPTor-NET** (MAPK-mTOR network model driven individualized therapies of pancreatic neuro-endocrine tumors). **KT and DPS** have collaborated in the frame of **NoE LifeSpan** which was a FP6 Network of Excellence (2007-2011) of 17 leading ageing research centres. LifeSpan seeded the collaboration between **DPS and KT**, and KTs entry into systems biology.
3. ** **KT, BMB (UMCG), and SG (UiB)** are elected members of the International Scientific Advisory Board of the **International Study Group for Systems Biology (ISGSB)**

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

- The Institute of Biochemistry at the CCB hosts its own mass spectrometry unit, with excellent analytical and data scientists, and technical personnel, and is equipped with high-end instrumentation, including an Orbitrap Fusion™ Lumos™ Tribrid™ Mass Spectrometer to conduct cutting edge proteomic and metabolomics analyses, including fluxomics. Thus, the institute hosts the MS instrumentation, infrastructure and expertise to smoothly conduct the MESI-STRAT project.
- This excellent framework is complemented by the Core Facility for Mass Spectrometry at the CCB/Medical University of Innsbruck. The facility specializes in providing researchers with equipment, expertise and customized services for the recognition, characterization and quantification of proteins, peptides and metabolites. The facility maintains a suite of state of the art instrumentation including a MALDI TOF/TOF 4800 plus Analyzer (Applied Biosystems), a Hybrid FT-Mass Spectrometer LTQ Orbitrap XL (ThermoScientific), various Capillary Electrophoresis and HPLC Systems and a Solaar M6 Dual Zeeman Spectrometer (ThermoScientific) for trace element analysis.
- Furthermore, the CCB houses the Biooptics Core Facility, which offers advanced equipment, training and expertise in the field of light microscopy. This includes confocal imaging, FRET, FRAP, photoactivation, 3D imaging, TIRF, Spinning Disc confocal and combinations thereof, 2D-STORM, superresolution, gSTED, and multi position live cell fluorescence imaging.

Any other supporting documents specified in the work programme for this call
Not applicable.

Partner 2 – PATH - Patients' Tumor Bank of Hope Foundation, Biobank, Munich, Germany

Description of the Institution

PATH was founded in 2002 by BC survivors and its biobank is intended for the sole purpose of supporting BC research. The samples of the PATH cohort were collected in 7 certified breast cancer centres in Germany

1. Bonn: Evangelische Kliniken Bonn gGmbH, Johanniter-Krankenhaus; Universitäts-Frauenklinik Bonn;
2. Dortmund: St. Johannes-Hospital Dortmund, Brustzentrum;
3. Bochum/Herne: Universitäts-Frauenklinik Marienhospital Herne, Kooperatives Brustzentrum Bochum/Herne; St. Annahospital, Kooperatives Brustzentrum Bochum/Herne;
4. Kassel: Klinikum Kassel GmbH, IBZ- Interdisziplinäres Brustzentrum;
5. Marburg: Klinik für Gynäkologie, gynäkologische Endokrinologie und Onkologie, Universitätsklinikum Gießen und Marburg GmbH, Standort Marburg, Brustzentrum Regio;
6. Offenbach: Klinik für Gynäkologie und Geburtshilfe, Klinikum Offenbach GmbH;
7. Regensburg: Klinik für Frauenheilkunde und Geburtshilfe der Universität Regensburg am Caritas-Krankenhaus St. Josef.

PATH has a unique collection of fresh-frozen tumor tissues, normal adjacent tissues and sera, as well as longitudinal therapeutic follow-up datasets as far back as 2004 from **more than 9200 BC patients** (out of which >7400 ER+), processed and stored according to strict SOPs.

PATH Foundation Biobank is an independent, charitable research resource organized as a public foundation under German civil law, which acts as a no-profit, non-governmental organisation. The work is financed by donations, sponsoring and cost recovery fees.

Experience and role in the project

PATH Biobank has longstanding expertise in biobanking and contributes to the European BBMRI-ERIC initiative. For the storage of the samples PATH has established a decentralized biorepository. The samples are processed and stored according to strict SOPs, including immediate freezing and storage at ultralow temperatures. Every patient has signed informed consent, and detailed clinical and therapeutic data sets annotate the samples. Follow-up information is available. To annotate the samples PATH runs a centralized database using Oracle® software and a LIMS Software developed in-house. Data sets comprise standardized clinical data as well as follow-up data.

Main tasks undertaken in the consortium

PATH Foundation Biobank is leader of **WP1** and **WP9** and is scientific and clinical co-coordinator of the project. In the frame of WP1 PATH Biobank will coordinate the setup and maintenance of the MESI-REPOSITORY. In WP9 PATH will coordinate the dissemination, exploitation and communication actions of MESI-STRAT, supported by the co-leading SME SBS (partner 13) and the coordinator KT (UIBK). PATH will have a special focus on patients' interests, needs and communication, and regulatory aspects of patient data privacy. Furthermore, PATH participates in **WP6+7** by providing tumor tissue and blood serum samples from its longitudinal collection and by prospectively collecting serum and urine samples, and follow-up data.

CV of PI and other people involved (including gender)

T. Anzeneder MD (M) [TA], Manager Biobanking at PATH Foundation, committed his entire career to building-up and improving the PATH Biobank as a valuable research resource for breast cancer. He monitors all biobanking activities at the seven PATH sample source sites, organizes the data collection and analyses as well as coordinates the discussions with researchers who want to use PATH Biobank as a research resource. Since 2008 he has arranged the allocation of biological samples and annotating datasets for more than 20 scientific projects. His passion is to promote high-quality biobanking and clear and unbiased access policies to biomaterials for well-planned and rewarding research by presenting the work of PATH Biobank at national and international meetings and symposia.

D. Schmitt (F) [DS] is a patient expert, patient-doctor communication coach, and breast cancer survivor. She is PATH co-chair, executive board member of the European patient academy EUPATI, and consultant in national and international Advisory Boards and Panels for clinical breast cancer studies including the PACT Study (Patient Compliance Study concerning Aromatase Inhibitors), ALTTO-Study

(Phase III Study in the adjuvant treatment of HER2 positive breast cancer), SUCCESS A and C Studies (Phase III Adjuvant Chemotherapy Breast Cancer Studies), and DETECT III Study (Phase III Study in HER2 positive metastatic breast cancer). She studied Psychology and Communication Sciences and works as a coach for patient-doctor communication, focusing on patient literacy and counselling, as well as communication and observation of the patient's aims as well as justified and unjustified concerns by the treating physician.

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. **Thewes V, Simon R, Hlevnjak M, Schlotter M, Schroeter P, Schmidt K, Wu Y, **Anzeneder T**, Wang W, Windisch P, Kirchgässner M, Melling N, Kneisel N, Büttner R, Deuschle U, Sinn HP, **Schneeweiss A**, Heck S, Kaulfuss S, Hess-Stumpf H, Okun JG, Sauter G, Lykkesfeldt AE, Zapatka M, Radlwimmer B, Lichten P, Tönjes M. The branched-chain amino acid transaminase 1 sustains growth of antiestrogen-resistant and ER α -negative breast cancer. *Oncogene*. 2017 Mar 20.doi: 10.1038/onc.2017.32.
2. Rudolph M., **Anzeneder T**, Schulz A., Beckmann G., Byrne A.T., Jeffers M., Pena C., Politz, O., Köchert, K., Vonk, R., Reischl, J. "AKT1E17K MUTATION PROFILING IN BREAST CANCER: PREVALENCE, CONCURRENT ONCOGENIC ALTERATIONS, AND BLOOD-BASED DETECTION." *BMC Cancer* 16(1): 622, 2016
3. Peters E., **Anzeneder T**, Jackisch C., Dimpfl T., Kunz G., Katalinic A., Waldmann A. "VERSORGUNG PRIMÄRER MAMMAKARZINOME BEI ÄLTEREN FRAUEN MIT ADJUVANTER THERAPIE." *Dtsch Arztebl International* 112(35- 36): 577-584, 2015
4. Garczyk S., von Stillfried S., Antonopoulos W., Hartmann A., Schrauder M. G., Fasching P. A., **Anzeneder T**, Tannapfel A., Ergonenc Y., Knuchel R., Rose M., Dahl E. "AGR3 IN BREAST CANCER: PROGNOSTIC IMPACT AND SUITABLE SERUM-BASED BIOMARKER FOR EARLY CANCER DETECTION." *PLoS One* 10(4): e0122106, 2015
5. **Thewes V., Simon R., Schroeter P., Schlotter M., **Anzeneder T**, Büttner R., Benes V., Sauter G., Burwinkel B., Nicholson R. I., Sinn H.-P., **Schneeweiss A**, Deuschle U., Zapatka M., Heck S., Lichten P. "REPROGRAMMING OF THE ER α AND ER α TARGET GENE LANDSCAPE TRIGGERS TAMOXIFEN RESISTANCE IN BREAST CANCER." *Cancer Research* 75(4): 720- 731, 2015

Up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. Establishing a sustainable breast cancer biobank for more than 14 years as well as successfully supporting more than 20 research projects in different areas of interest with high-quality samples and comprehensive annotating clinical and follow-up data sets
2. Setup, monitoring and maintaining of a decentralized and specialized breast cancer biobank
3. Uniform biobanking SOPs implemented at all sample source sites
4. Programming and operation of an Oracle® database specially designed for biobanking purposes
5. Support to basic science research with clinical knowledge and background

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

- Biobanking infrastructure and hardware, e.g. liquid nitrogen sample storage tanks

Any other supporting documents specified in the work programme for this call

Not applicable

**Publications and grants with other consortium members

Partner 3 – UKL-HD - University Hospital Heidelberg, Germany

Description of the Institution

The Medical Faculty of Heidelberg is the oldest medical faculty in Germany. With its 44 specialized clinical departments Heidelberg University Hospital is one of the leading medical centers in Europe. Every year, hundreds of thousands of patients from all over Germany and many other countries make use of our modern treatment facilities. The highest standards of medical care are guaranteed by our world-renowned professors, distinguished physicians and committed nursing staff. Heidelberg University Hospital is constantly developing new methods of diagnosis and treatment at the forefront of biomedical science for the benefit of all patients.

Experience and role in the project

The Department of Obstetrics and Gynecology with the National Center of Tumor disease (NCT) is among the leading diagnostic and therapeutic gynecology units within Germany with over 500 primary breast cancer cases per year, around 170 with an neoadjuvant chemotherapeutic treatment and around 320 with ER+ CBC. There are currently over 70 phase I-III studies ongoing in the field of womens' cancers. The strong national infrastructure and high reputation brings a lot of patients to Heidelberg to enter clinical trials. The experience in translational medicine is outstanding and a focus of academic research at UKL-HD. The department of Obstetrics and Gynecology is very active in biomedical research and holds several international patents. The University has its own TTO, which supported the spin-off of over 10 start-ups in the last 10 years. A biomarker project for early BC detection was licensed recently and was awarded by the national funds for start-up development.

The Coordination Centre for Clinical Trials (KKS) Heidelberg, located at Medical Faculty Heidelberg, Germany was initially funded by the German Ministry of Education and Research (BMBF) and the Medical Faculty. More than 45 staff members support the whole spectrum of clinical research in patients to ensure that rights and well-being of study participants are protected and investigators comply with the protocol and the international guidelines, e.g. Good Clinical Practice (ICH-GCP). The KKS Heidelberg has been working effectively since 2000, mainly in clinical drug trials phase I-III, and has continuously been evaluated by different audits, inspections and expert assessments with successful outcome concerning quality and efficiency.

Main Tasks undertaken in the consortium

UKL-HD (SS + AS) lead **WP7** and have the expertise and the infrastructure to lead and conduct the interventional clinical studies in MESI-STRAT. Ongoing studies like PREAGNANT, GEKKO, GENOM have been established over years and have focused on biomarker sampling. SS has established an infrastructure to provide biobanking at a professional level. UKL-HD will conduct the WOO trial in WP7. KKS at UKL-HD will provide Study Management incl. Regulatory Affairs, Clinical Monitoring, Pharmacovigilance, Data Management incl. eCRF for the WOO trial conducted in WP7. UKL-HD will also support the observational clinical trials in **WP6**, and contribute clinical data/samples to MESI-REPOSITORY (**WP1**). Due to SS' longstanding experience not only in female but also male breast cancer, she will act on the **gender committee (GC, WP8+9)**.

CV of PI and other people involved

PD Dr. med. Sarah Schott, MD PhD (F) [SS] Head of the Division Translational Gynecology, Clinic of General Gynecology and Obstetrics with Polyclinic and Head of familial Cancer and clinical chair of the German consortium for hereditary breast and ovarian cancer representing Heidelberg. She is a gyneco-oncology surgeon and a senior breast surgeon. She is also a fellow of the German Cancer Consortium (DKTK) and has specialised in translational research. She coordinates all biobanking at the university women's hospital and provides several multicentre studies with material, she is clinical partner in several national projects such as the LIBRE study (<http://www.uni-kiel.de/download/pm/2014/2014->

057-libre-studie.pdf), the GEKKO Study, GENOM and Mammascreen study as well as the EU Transcan PROMETOV consortium. The group of translational medicine compromises 5 residents aiming for a PhD and 5 medical students.

Dr. Schott is a board member of the national board of obstetrics and Gynecology (DGGG eV), she has co-organized the national congress with over 5000 participants in 2012, 2014 and 2016 and she is a member of the steering committee of the FOKO congress, the biggest congress for outpatient gynecologists. She is also a member of the AGO Trafo (translational medicine in gyncooncology) group and co-organizes the annual scientific meeting.

She has given over 100 talks at German translational, obstetrician and gynecological as well as breast cancer meetings including international meetings, e.g., at the Royal College, the ASCO meeting.

Prof. Andreas Schneeweiss, MD (M) [AS] is the head of the division of Gynecologic Oncology at the National Center for Tumor Diseases (NCT) as well as the Chief of the Clinical Trial Unit and the Oncological Clinics section at the University of Heidelberg. He is the vice-chairman of the Cooperative Oncological Group for Breast Cancer and Gynecological Cancers at the NCT. His main fields of interest are a.) innovative systemic treatments of breast cancer and gynaecological cancers in phase I to IV studies and b.) the detection and evaluation of prognostic and predictive molecular markers. Prof. Schneeweiss is a member of multiple organizations, such as the European Society of Medical Oncology (ESMO), the German Cancer Society (DKG) and the American Society of Clinical Oncology (ASCO). He is currently involved in more than 35 active clinical studies in breast cancer.

Dr. Steffen P. Luntz (M, KKS) [SL] is board certified anaesthesiologist. After six years of clinical experience, incl. conducting clinical studies he joined the KKS in 2001. After working as project manager in different types of clinical trials he directs the KKS since 2005. Mr. Luntz had an extensive training in clinical pharmacology and is lecturer at the Medical School of Heidelberg for topics in clinical research and clinical pharmacology. He is member in different executive boards.

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. **Dewi, D.L., Mohapatra, S.R., Cabañes, S.B., Adam, I., Patterson, L.F.S., Berdel, B., Kahloon, M., Thürmann, L., Loth, S., Heilmann, K., Weichenhan, D., Mücke, O., **Heiland, I.**, Wimberger, P., Kuhlmann, J.D., **Kellner, K.-H.**, **Schott, S.**, Plass, C., Platten, M., Gerhäuser, C., Trumpp, S., **Opitz, C.A.**, (2017): Suppression of indoleamine-2,3-dioxygenase 1 expression by promoter hypermethylation in ER-positive breast cancer. *Oncoimmunology*. 2017;6(2):e1274477. doi: 10.1080/2162402X.2016.1274477.
2. Tang Q, Holland-Letz T, Slyko A, Cuk K, Marime F, **Schott S**, Heil J, Qu B, Golatta M, Bewerunge-Hudler M, Sutter C, Surowy H, Wappenschmidt B, Schmutzler R, Hoth M, Bugert P, Bartram CR, Sohn C, **Schneeweiss A**, Yang R, Burwinkel B. DNA methylation array analysis identifies breast cancer associated RPTOR, MGRN1 and RAPSN hypomethylation in peripheral blood DNA. *Oncotarget*. 2016 Sep 27;7(39):64191-64202
3. Madhavan D, Peng C, Wallwiener M, Zucknick M, Nees J, **Schott S**, Rudolph A, Riethdorf S, Trumpp A, Pantel K, Sohn C, Chang-Claude J, **Schneeweiss A**, Burwinkel B. Circulating miRNAs with prognostic value in metastatic breast cancer and for early detection of metastasis. *Carcinogenesis*. 2016 May;37(5):461-70. doi:10.1093/carcin/bgw008.
4. Peng C, Wallwiener M, Rudolph A, Ćuk K, Eilber U, Celik M, Modugno C, Trumpp A, Heil J, Marmé F, Madhavan D, Nees J, Riethdorf S, **Schott S**, Sohn C, Pantel K, **Schneeweiss A**,

**Publications and grants with other consortium members

[Proposal number 754688] [Proposal acronym  MESI-STRAT] – Part B

[Page number 59]

Chang-Claude J, Yang R, Burwinkel B. Plasma hyaluronic acid level as a prognostic and monitoring marker of metastatic breast cancer. Int J Cancer. 2016 May 15;138(10):2499-509. doi: 10.1002/ijc.29975.

5. Schneeweiss A, Chia S, Hegg R, Tausch C, Deb R, Ratnayake J, McNally V, Ross G, Kiermaier A, Cortés J. Evaluating the predictive value of biomarkers for efficacy outcomes in response to pertuzumab- and trastuzumab-based therapy: an exploratory analysis of the TRYPHAENA study. Breast Cancer Res. 2014 Jul 8;16(4):R73. doi: 10.1186/bcr3690

List of up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. LIBRE study (<http://www.uni-kiel.de/download/pm/2014/2014-057-libre-studie.pdf>) - Lifestyle intervention for women with hereditary breast and ovarian cancer
2. GEKKO Study (<https://www.nct-heidelberg.de/en/for-physicians/studies/preventiv/gekko.html>) – NCT together with the UKL-HD, aim of this study: Discovery and evaluation of new early detection tests that can be used to identify cancer and its precursors
3. GENOM and Mammascreen study (<https://www.klinikum.uni-heidelberg.de/index.php?id=141304&L=1>)- MammaScreen Test, to precisely detect breast cancer in women at early stage
4. **PROMETOV (<http://www.transcanfp7.eu/abstract/prometov.html>) - Proteogenomic and targeted metabolomic analysis of ovarian cancer heterogeneity and its contribution to recurrence and therapy resistance
5. Participation at NCT patient days

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

- Largest breast cancer unit within Germany
- PI experience in multicenter studies and biobanking ovarian, endometrium and breast cancer
- DKT Partner: The DKT network is the largest alliance among translational research within Germany. <https://dktk.dkfz.de/en/home>
- KKS will assure that the clinical WOO trial will be performed according to well established and harmonized Standard Operating Procedures (SOPs), which are based on ICH-GCP guidelines and current laws.

Any other supporting documents specified in the work programme for this call

Not applicable

Partner 4 – DKFZ - German Cancer Research Center, Germany

Description of the Institution

The German Cancer Research Center (DKFZ, www.dkfz.de) in Heidelberg, a member of the Helmholtz Association, was established in 1964 as a center for cancer research excellence. This vision has been realized through the highly competitive publication track record of DKFZ research groups crowned by two Nobel Prize winners in Medicine (Prof. Harald zur Hausen, 2008) and Chemistry (Prof. Stefan Hell, 2014). Providing state of the art research facilities and imbuing research excellence in various fields of cancer research, DKFZ is highly regarded as a center of excellence for Systems Medicine. DKFZ dedication to systems medicine is underscored by the fact that several DKFZ departments are involved in e:Med projects. Heidelberg extends DKFZ resourcefulness in tackling urging systems medicine issues with the on-going collaborations of surrounding partner institutes and through the renounced BioQuant interdisciplinary center at Heidelberg University which is dedicated to research and training in systems biology (comprising up to 40 different research groups from the University of Heidelberg, DKFZ, EMBL, HITS and the MPI for Medical Research).

Experience and role in the project

Over and above, DKFZ cooperation extends to numerous surrounding clinics and hospitals exploiting opportunities to link basic and clinical research, which is best exemplified by DKFZ “Bench to bed side” translational research. DKFZ together with the Heidelberg University Medical Center, founded the first “Comprehensive Cancer Center” in Germany (National Center for Tumor Diseases, NCT), providing an exceptional environment for translational biomedical research in terms of infrastructure and expertise. DKFZ prides itself as the host of one of the biggest conglomerates of international scientists in Europe. The highly competitive nature of selection (5 year appraisal) and the support DKFZ scientists receive (State of the art facilities, hosting international scientists, project management, technology transfer, capacity enhancement and extended international collaborations) is attracting the best calibres in cancer research driving DKFZ state of the art interdisciplinary research.

Dr. Opitz (CO) is a physician-scientist with a strong expertise in tryptophan metabolism in cancer. Her clinical as well as basic scientific backgrounds make her an ideal candidate to work on a systems medicine project in her area of expertise, cancer metabolism. The new analytical techniques developed by her to multiplex tryptophan metabolism will be instrumental for the analysis of tryptophan metabolism in ER+BC. In addition her lab has developed important tools to modulate Trp and NAD metabolism in cancer cells, which will also be used in the frame of this project.

Dr. Weg-Remers (SW) is head of the German Cancer Information Service (KID, Krebsinformationsdienst) at DKFZ. As physician scientist, she has a strong background in both clinical and basic cancer research and science management / science communication. CIS was founded in 1986 to provide evidence-based, quality-secured information to cancer patients, their relatives and the general public. As a National Reference Center for Cancer Information in Germany, KID has recently opened up its information resources also to health professionals.

Main Tasks undertaken in the consortium

CO will lead **WP6** to derive MESI marker panels that identify clinically relevant ER+ BC patient subgroups and to find preclinical models (matched primary cells and PDX models) representative for the different ER+BC subgroups. CO will contribute to **WP1** (MESI-REPOSITORY) & **WP7** (preclinical analyses in primary patient tissues cultured in perfusion-based bioreactors), and will perform the measurement of Trp metabolites (**WP4**).

SW will contribute to **WP9** by co-organizing MESI-STRAT patient days together with the patient organization PATH at the clinical partner centers. In addition, her phone counseling team for cancer patients at the German Cancer Information Center (Krebsinformationsdienst, KID) will perform a telephone survey to identify frequent questions of European BC patients, relevant to MESI-STRAT.

CV of PI and other people involved (including gender)

Dr. Christiane A. Opitz (F) [CO] leader of the “Brain Cancer Metabolism Group” at the German Cancer Research Center (DKFZ) is specialized in the analysis of tryptophan and NAD metabolism in cancer. Her group develops and applies advanced analytical methods to measure tryptophan and its metabolites and is involved in the development of inhibitors of tryptophan metabolism. She is coordinator of the BMBF-funded systems medicine consortium “Comparison of central metabolic routes and signaling

pathways in IDH mutant and wildtype gliomas (WHO°II-IV) – GlioPATH” consisting of 4 national and 1 international partners, aimed at establishing NAD, Trp, mTOR and AHR network models to derive novel treatment paradigms in glioma, thus building a resource for connecting signaling to metabolism. Furthermore, she coordinates the Transcan-2 JTC consortium PROMETOV, partnered by KT (UIBK); in which ovarian cancer heterogeneity will be analysed by proteogenomics and targeted measurements of tryptophan metabolism.

Positions and Employment: 02/2013-present Leader of the Group “Brain Cancer Metabolism” at the DKFZ and Resident in the Neurology Clinic, University Hospital Heidelberg; 2007-2012 Postdoc in the Experimental Neuroimmunology Unit at the DKFZ and Resident in the Neurooncology Department, University Hospital Heidelberg; 2006: Postdoc at the Hertie Institute for Clinical Brain Research, Tübingen and Resident in the Neurology Department, Eberhard-Karls-University Tübingen; 11/2005-1/2006 Postdoc at the Krannert Institute of Cardiology, Indianapolis, USA; Academic Education:

1998-2005: Medical school at University of Heidelberg, Germany; 2001-2004 International Master of Molecular Cell Biology (MCB) at the University of Heidelberg Achievements and Awards:

11/2014 Award of the Berlin-Brandenburg Academy of Sciences; 01/2013 Bayer Early Excellence Award in Science; 07/2012 Hella-Bühler-Award for Oncological Research; 05/2012 Sibylle-Assmus-Foundation Award for Neurooncology; 2010-2013 Postdoctoral Fellowship of the Medical Faculty, Heidelberg; 1999-2005 Scholarship of the German National Academic Merit Foundation

Dr. Susanne Weg-Remers (F) [SW] is head of the Cancer Information Service (KID) at the German Cancer Research Center (DKFZ) in Heidelberg. She holds an MD PhD degree and a Master degree in Public Administration. After graduation, she has worked in both clinical and basic cancer research and science management / science communication.

Positions and Employment: 2012-present Head of the German Cancer Information Service at DKFZ, Heidelberg; 2007-2012 Head of the Staff Unit Strategy and Programs at DKFZ, Heidelberg; 2004-2007: Head of Institute's Administration, Institute of Toxicology and Genetics (ITG), Karlsruhe Institute of Technology, Karlsruhe; 1998-2004 Postdoctoral Scientist at ITG; 1994-1998 Physician Scientist, University Medical Center, Homburg; Academic Education: 2004-2005 Master of Public Administration, Deutsche Hochschule für Verwaltungswissenschaften, Speyer, 1986-1994 Medical School at Universities of Bochum and Cologne

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. **Dewi, D.L., Mohapatra, S.R., Cabañes, S.B., Adam, I., Patterson, L.F.S., Berdel, B., Kahloon, M., Thürmann, L., Loth, S., Heilmann, K., Weichenhan, D., Mücke, O., **Heiland, I.**, Wimberger, P., Kuhlmann, J.D., **Kellner, K.-H.**, **Schott, S.**, Plass, C., Platten, M., Gerhäuser, C., Trump, S., **Opitz, C.A.**, (2017): Suppression of indoleamine-2,3-dioxygenase 1 expression by promoter hypermethylation in ER-positive breast cancer. *Oncoimmunology*. 2017;6(2):e1274477. doi: 10.1080/2162402X.2016.1274477.
2. Litzenburger UM*, **Opitz CA***, Sahm F, Rauschenbach KJ, Trump S, Winter M, Ott M, Ochs K, Lutz C, Liu X, Anastasov N, Lehmann I, Höfer T, von Deimling A, Wick W, Platten M. Constitutive IDO expression in human cancer is sustained by an autocrine signaling loop involving IL-6, STAT3 and the AHR. *Oncotarget*. 2014 Feb 28;5(4):1038-51. (*contributed equally)
3. **Opitz CA***, Litzenburger UM*, Sahm F, Ott M, Tritschler I, Trump S, Schumacher T, Jestaedt L, Schrenk D, Weller M, Jugold M, Guillemin GJ, Miller CL, Lutz C, Radlwimmer B, Lehmann I, von Deimling A, Wick W, Platten M. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature*. 2011 Oct 5;478 (7368):197-203. (*contributed equally)

**Publications and grants with other consortium members

Patents:

4. Means and methods for treating and/or preventing natural AHR ligand-dependent cancer International patent (PCT) application, filed September 7 2012 (Application n° PCT/EP2012/067504, published March 14 2013 under n° WO 2013/034685).
5. Patent: Isotopic method for measurement of tryptophan and metabolites thereof International patent (PCT) application, filed October 31 2016 (Application n° PCT/EP2016/076265).

List of up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. Development of a novel method to multiplex tryptophan and its metabolites using isobaric mass tags and LC-MS/MS
2. Development and evaluation of inhibitors of Trp metabolism
3. **Coordinator of the Era-NET Transcan 2 European Consortium PROMETOV “Proteogenomic and targeted metabolomics analysis of ovarian cancer heterogeneity and its contribution to recurrence and therapy resistance”, of which **KT and SS are PIs**.
4. **Coordinator of the BMBF-funded systems medicine consortium “Comparison of central metabolic routes and signaling pathways in IDH mutant and wildtype gliomas (WHO°II-IV) – GlioPATH” (**KT is PI; IH, UiT** is international collaborator)
5. **DAAD Norwegian-German research exchange (project no. 244770/F11): joint travel grant with **KT, MZ and IH**.

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

Since 1989, the German Cancer Information Service (KID) provides cancer information for patients, their families, the general public, and health care professionals. A team of physicians answers 35,000 individual enquiries per year (among them more than 6,000 related to breast cancer) per telephone or e-mail for free, and provides comprehensive information on many aspects of cancer on www.krebsinformationsdienst.de. All information is independent, up-to-date, and based on the best available evidence. In the International Cancer Information Service Group (ICISG), founded in 1996, the KID closely interacts with colleagues in a worldwide network of more than 70 organizations that deliver cancer information. Members share information and expertise and assist groups interested in starting a Cancer Information Service.

Any other supporting documents specified in the work programme for this call

Not applicable.

**Publications and grants with other consortium members

[Proposal number 754688] [Proposal acronym  MESI-STRAT] – Part B

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Partner 5 – VHIO - Vall d'Hebron Institute of Oncology, Spain

Description of the Institution

The Vall d'Hebron Institute of Oncology (VHIO) was founded in 2006 out of the necessity to bring together the basic, clinical and translational oncology research activities at the Vall d'Hebron University Hospital (HUVH) campus and the aim of responding to the challenges at the forefront of oncological research. HUVH is the largest public teaching hospital in Barcelona and one of the largest hospitals in Spain.

VHIO's organizational structure is part of the HUVH, so its researchers have exceptional access to multidisciplinary clinical facilities, cancer patients and clinical samples. The institution is internationally known for the development of early clinical trials with pathway-targeted inhibitors and novel diagnostic/prognostic tools in cancer. VHIO's outstanding **Clinical Research Program** is integrated by more than 30 staff medical oncologists, in addition to research fellows, clinical study coordinators, research nurses, pharmacists, etc. In 2016, the institution conducted 340 clinical trials in solid tumors and 115 phase I clinical trials with novel targeted agents, and a total of 1129 patients participated in therapeutic trials (453 in phase I trials). The **Preclinical and Translational Research Programs** enhance the bench-bedside-bench principle, adopting a purely translational and multidisciplinary approach with the development of sophisticated research tools (i.e. xenograft models to mimic patient's disease and study tumor development in optimized research models). They translate advances in molecular research to patient care as rapidly as possible, tackling the disease from all possible angles and generating synergies between molecular and clinical research in Oncology, playing a key role in the drug development process.

Experience and role in the project

The institution has been built by scientists and physicians working together to link basic science and clinical research, with the aim of developing research of excellence to improve prevention, early diagnosis and cancer treatment. In nine years of life, VHIO has empowered its scientific programs, increased the number of principal investigators in the basic sciences, increased the number and complexity of its early clinical trials program (one of the top Units in Europe) and expanded its collaborations with renowned institutions around the world. This situation, in addition to the existing equipment and laboratory structure for basic research in a newly 3.500 m² facility facilitates a highly productive model in cancer research. As an example, under European competitive funding, VHIO has been involved in 13 FP7 and 3 H2020 projects including being coordinator of a large PHC project.

Main Tasks undertaken in the consortium

For **WP6** and **WP7**, VHIO conducts preclinical trials in ER+BC patient derived xenograft models (PDX) and matched cultures and generates new subgroup-specific ER+BC models if necessary (VS), and contributes to the Intervention Validation Trials and design of IIT and umbrella trials (CSA, MP, MO, MB). In addition, VHIO will contribute to the MESI-REPOSITORY (**WP1**).

CV of PI and other people involved (including gender)

Violeta Serra, PhD (F) [VS] completed her PhD in Newcastle University, UK, in 2001, and performed several postdocs at international reowned institutions before joining Vall d'Hebron Institute of Oncology (VHIO) under José Baselga's mentorship in 2006, where she is leading a group since 2014. Her career at VHIO has been focused on exploring the mode of action and mechanisms of resistance to PI3K-pathway inhibitors and more recently on targeted therapies in triple negative breast cancers -- specifically PARP inhibitors. She is member of the *American Association of Cancer Research* (AACR), and serves on the Editorial Board of *Clinical Cancer Research*.

Cristina Saura, MD (F) [CSA] graduated in Medicine at the University of Barcelona in 2002 and carried out her training in Medical Oncology at the Vall d'Hebron University Hospital, Barcelona, where she has been working in the Department of Medical Oncology since 2007. Currently, Dr. Saura is the Head of the Breast Cancer Unit at the Vall d'Hebron University Hospital. Dr. Saura has participated as Principal Investigator and Co-Investigator in several clinical trials in Breast Cancer with special focus in Precision medicine and PI3K inhibitors and anti-HER2 treatment. She is the author of several publications and communications in national and international congresses.

Marta Palafox, PhD (F) [MP] obtained her master's degree in Therapeutics Targets and Signaling working on the identification of antitumor drugs targets in human cancer cells. During her PhD, she made important contributions clarifying the role of RANK/RANKL pathway in development and progression of human breast cancer. Since 2015 she holds a post-doctoral position in Dr. Serra's lab where her research is focused on the identification of response biomarkers to CDK4/6 inhibitors in ER+/Her2+ breast cancer.

Mafalda Oliveira, MD (F) [MO] graduated in Medicine at University of Lisbon in 2003 and completed her training in Medical Oncology at Instituto Portugues of Oncology. In 2012 she joined the Breast Cancer Unit at the Vall d'Hebron University Hospital as clinical investigator where she is now carrying out 12 clinical trials in phase I/II with drugs involving the PI3K/AKT/mTOR pathway being principal investigator of 5 and is author of several publications in the field.

Meritxell Bellet, MD PhD (F) [MB] has more than 20 years of experience in conducting clinical trials with therapies for ER+ breast cancer. Also she is author of more than 100 articles in the breast cancer field including several high impact publications in New England Journal of Medicine and Journal of Clinical Oncology. Also, she is principal investigator of several clinical trials with targeted therapies and has participated in the clinical development of most of the therapies included that nowadays constitute the standard of care

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. ***Interrogating open issues in cancer precision medicine with Patient-Derived Xenografts.* Byrne et al (41 authors including **Serra V**). Nat Rev Cancer. Jan 20. doi: 10.1038/nrc.2016.140.
2. *A Biobank of Breast Cancer Explants with Preserved Intra-tumor Heterogeneity to Screen Anticancer Compounds.* Bruna A, Rueda OM, Greenwood W, Batra AS, Callari M, Batra RN, Pogrebniak K, Sandoval J, Cassidy JW, Tufegdzic-Vidakovic A, Sammut SJ, Jones L, Provenzano E, Baird R, Eirew P, Hadfield J, Eldridge M, McLaren-Douglas A, Barthorpe A, Lightfoot H, O'Connor MJ, Gray J, Cortes J, Baselga J, Marangoni E, Welm AL, Aparicio S, **Serra V**, Garnett MJ, Caldas C. **Cell.** 2016 Sep 22;167(1):260-274.e22.
3. *Gain- and Loss-of-Function Mutations in the Breast Cancer Gene GATA3 Result in Differential Drug Sensitivity.* Mair B, Konopka T, Kerzendorfer C, Sleiman K, Salic S, **Serra V**, Muellner MK, Theodorou V, Nijman SM. **PLoS Genet.** 2016 Sep 2;12(9):e1006279
4. *Early adaptation and acquired resistance to CDK4/6 inhibition in estrogen receptor positive breast cancer.* Herrera-Abreu M*, **Palafox M***, Asghar U, Rivas MA, Cutts RJ, Garcia-Murillas I, Pearson A, Guzman M, Rodriguez O, Grueso J, **Bullet M**, Cortés J, Elliott R, Pancholi S, Baselga J, Dowsett M, Martin LA, Turner NC*, **Serra V***. **Cancer Research.** 2016 Apr 1;76(8):2301-13.
5. *A First-in-Human Phase I Study of the ATP-Competitive AKT Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors.* **Saura C**, Roda D, Roselló S, **Oliveira M**, Macarulla T, Pérez-Fidalgo JA, Morales-Barrera R, Sanchis-García JM, Musib L, Budha N, Zhu J, Nannini M, Chan WY, Sanabria Bohórquez SM, Meng RD, Lin K, Yan Y, Patel P, Baselga J, Tabernero J, Cervantes A. **Cancer Discov.** 2017 Jan;7(1):102-113.

5 relevant previous projects or activities, connected to the subject of this proposal

1. Targeting PI3K and CDK4/6 in breast cancer.

Instituto de Salut Carlos III (Spanish Ministry of Health)

**Publications and grants with other consortium members

[Proposal number 754688] [Proposal acronym  MESI-STRAT] – Part B

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Ref.CP14/0028
01/01/2015 – 31/12/2017

2. Targeting PI3K and CDK4/6 in Breast Cancer: Integrative Biomarkers of Response

SUSAN G. KOMEN BREAST CANCER FOUNDATION, INC

Ref.CCR15330331
22/10/2015 – 21/10/2018

3. Inhibición de la vía de PI3K en cáncer de mama: estudio en profundidad de los factores predictivos de respuesta y diseño racional de terapias combinadas

Instituto de Salut Carlos III (Spanish Ministry of Health)

Ref.PI13/01714
01/01/2014 – 31/12/2016

4. Rational Therapy for Breast Cancer (RATHER)

European Commission (Seventh Framework Program).

Ref. 258967.
01/01/2011- 12/12/2015.

5. Investigating mechanisms of resistance to PI3K inhibition by taselisib and the efficacy of combination treatments utilizing patient derived PDX models in a coclinical trial study

GENENTECH INC
06/04/16 – 05/04/2019

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

The Breast Cancer and Melanoma Group is dedicated to working on complex clinical trials with drugs in development (Phase II-III trials) focusing on novel targets, the UTIM, has already established itself as an international reference in developing new drugs based on identifying the molecular profile of each tumour and optimizing treatment regimens using combinations of new drugs with existing ones. To successfully do so, the unit has a day hospital dedicated to breast cancer patients. The animal experiments planned in the proposal will be carried out in the Animal Facility. This is located within the research laboratory building at the VHIO and provides accommodation for experimental animals maintenance, care and welfare, provides researchers with help and equipment to carry out adequate experiments. Close proximity of the Hospital with the VHIO accelerate the transfer of human material from the Hospital to the laboratories (less than 15 minutes) that is essential in order to obtain fresh patient-derived tumors to be efficiently implanted into mice.

Any other supporting documents specified in the work programme for this call
Not applicable

Partner 6 – DDI - DE DUVE INSTITUTE, Belgium

Description of the Institution

Founded in 1974 by Nobel Prize Laureate Christian de Duve, the de Duve Institute is a renowned multidisciplinary biomedical research institute located on the Brussels campus of the Université catholique de Louvain (UCL), next to the Cliniques Universitaires Saint-Luc. It hosts several laboratories of the Faculty of Medicine of UCL, as well as the Brussels Branch of the Ludwig Institute for Cancer Research. The de Duve Institute hosts about 250 scientists active in diverse biomedical fields, including biochemistry, immunology, bacteriology, developmental biology, cell biology, cancer biology, tumor immunology, metabolism, virology, human genetics and molecular biology. Equipped with a number of up-to-date technical platforms, the de Duve Institute provides a vibrant environment of highly collaborative multidisciplinary research. Research priorities at the de Duve Institute are based on three principles: (i) priority to fundamental research and to the freedom of the investigators, (ii) special attention to medical benefits potentially resulting from fundamental discoveries, and (iii) multidisciplinary collaboration within a critical mass of competences. For more information, please visit: www.deduveinstitute.be.

Experience and role in the project

The tumor immunology group of the de Duve Institute specialises in studying the mechanisms of immunological responses in various tumors. One of the current fields of interest is the study of immunosuppressive properties that tumours acquire to resist destruction by immune cells, with the aim to improve the efficiency of cancer immunotherapy as well as to determine the right treatment for a patient. The group has strong expertise in immune cell biology, genetics, metabolism and signalling pathways. It performs basic research, but is also involved in translational research, e.g. through a close collaboration with the Cliniques Universitaires Saint-Luc. The group has participated in many EU funded projects and has coordinated the FP6-project CANCERIMMUNOTHERAPY ([FP6-LIFESCIHEALTH](#)).

More specifically, the group of Benoît Van den Eynde has a strong experience in metabolic changes in the tumor microenvironment that cause immunosuppression. In particular, the group did pioneering work showing that tryptophan catabolism by indoleamine dioxygenase (IDO) or tryptophan dioxygenase (TDO) results in immune tolerance of growing tumors. Furthermore, they showed that immune rejection of those tumors can be restored by pharmacological inhibition of IDO or TDO, and they developed novel inhibitors of these enzymes, as potential cancer therapeutics.

In 2012, they launched a spin-off biotech, iTeos Therapeutics, to further develop such inhibitors towards clinical development. These efforts were successful, and their flagship compound, a new IDO inhibitor, is now in Phase I clinical trials, with a First in Human (FIH) in September 2016, in partnership with Pfizer.

This unique experience in developing, up to the clinical arena, new pharmacological agents targeting cancer resistance mechanisms will be extremely useful for the MESI-STRAT consortium. Indeed, over the years, the group has acquired a strong expertise in fields that are highly relevant for MESI-STRAT, such as the study of tryptophan metabolism in tumors, and the preclinical and clinical development of new pharmacological agents to modulate tumor metabolism. They have developed relevant syngeneic immunocompetent preclinical models, as well as xenogeneic immunocompetent PDX models, reconstituted with human lymphocytes, which will prove very useful in MESI-STRAT, in which human breast cancers will be developed and studied in PDX models.

Main Tasks undertaken in the consortium

Given this experience, the Van den Eynde group will contribute to **WP6** and **WP7**, by developing immunocompetent PDX models of breast cancers, which will be used for preclinical testing of new compounds targeting resistance pathways identified within MESI-STRAT.

The Van den Eynde group has also produced a unique monoclonal antibody to human IDO, and has developed an immunohistochemistry assay that can be used to stratify patients according to IDO expression, which is useful for clinical development of IDO inhibitors. This assay can be used on routine paraffin-embedded clinical samples, and will be useful for **WP4**.

CV of PI and other people involved

Benoît Van den Eynde, MD, PhD (M) [BE] is a scientist working in the field of tumor immunology. Born in 1962, he is currently Director of the Brussels Branch of the Ludwig Institute for Cancer Research. He also holds the positions of Full Professor at the *Université catholique de Louvain* (UCL) and co-director of the de Duve Institute in Brussels. In 2012, he co-founded iTeos Therapeutics, a spin-off focused on the development of immunomodulators for cancer therapy. In 2016, he was also appointed Professor of Tumour Immunology at the University of Oxford.

In the nineties, Van den Eynde was one of the investigators involved in the first identification of tumor antigens recognized by T lymphocytes on mouse and human tumors, a landmark discovery that allowed rebirth of the field of tumor immunology and ultimately led to the clinical development of various cancer immunotherapy approaches. He developed preclinical models to evaluate the efficacy of cancer vaccines, and was one of the first to show that the efficacy of cancer immunotherapy was limited by the ability of some tumors to block the immune response by producing immunosuppressive factors, such as tryptophan-degrading enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), which suppress T lymphocyte activity by locally depleting tryptophan in the microenvironment. This led to the clinical development of small-molecule inhibitors of these enzymes.

In parallel, Van den Eynde also gained strong international recognition for his research on the processing of tumor antigens, which are composed of peptides presented at the cell surface by class I molecules of the Major Histocompatibility Complex. These peptides derive from intracellular proteins that are degraded by the proteasome, an intracellular protease complex. Van den Eynde discovered that the proteasome was able not only to cleave proteins into peptidic fragments but also to splice peptidic fragments together, either in the right or the reverse order. This explains the production of "spliced" antigenic peptides derived from non-contiguous protein fragments. He also described new proteasome subtypes that are intermediate between the standard proteasome and the immunoproteasome, and produce distinct sets of peptides. Finally, he showed that other intracellular proteases such as insulin-degrading enzyme contribute to the production of antigenic peptides.

Altogether, he has published more than 135 scientific articles, which were cited more than 12,500 times (H factor = 44). He is full member of the Belgian Royal Academy of Medicine and has received a number of prestigious awards for his work.

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. Uyttenhove C., Pilote L., Théate I., Stroobant V., Colau D., Parmentier N., Boon T. and **Van den Eynde B.J.** *Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase* (2003) **Nature Medicine** 9(10): 1269-1274.
Citations: 1041. Impact factor: 30.550.
This manuscript described for the first time the resistance mechanism of tumors to immune rejection, based on tryptophan degradation by IDO. This enzyme, which is expressed in many human tumors, degrades tryptophan locally thereby producing an immunosuppressive tumor microenvironment. The manuscript also showed that immune rejection of IDO expressing tumors is restored by treatment of mice with an IDO inhibitor. This work paved the way towards clinical development of IDO inhibitors to combat this resistance mechanism, and indicated that patients can be stratified for such therapies by measuring IDO expression.
2. Pilote L., Larrieu P., Stroobant V., Colau D., Dolušić E., Frédéric R., De Plaen E., Uyttenhove C., Wouters J., Masereel B. and **Van den Eynde B.J.** *Reversal of tumoral immune resistance by inhibition of tryptophan 2,3-dioxygenase* (2012) **Proceedings of the National Academy of Sciences USA** 109(7): 2497-2502, 2012.
Citations: 135. Impact factor: 9.737.
This work described the expression in human tumors of tryptophan dioxygenase (TDO), another tryptophan-degrading enzyme, and the role of TDO in promoting tumor resistance to immunotherapy. The work also described a new TDO inhibitor, and showed that treating mice with this TDO inhibitor can restore the rejection of TDO-expressing tumors. This work paved the way towards the clinical development of TDO inhibitors and the stratification of patients according to TDO expression in their tumor.
3. Théate I., van Baren N., Pilote L., Moulin P., Larrieu P., Renaud J.C., Hervé C., Gutierrez-Roelens

I., Marbaix E., Sempoux C. and **Van den Eynde B.J.** *Extensive profiling of the expression of the indoleamine 2,3-dioxygenase 1 protein in normal and tumoral human tissues* (2015) **Cancer Immunology Research** 3(2): 161-172.

Citations: 19. Impact factor: 6.665.

This manuscript reports the development and validation of a new monoclonal antibody against human tryptophan-degrading enzyme IDO, and the use of this antibody to study expression of IDO in normal tissues and in a panel of about 900 human tumors. This immunohistochemistry assay, which can be used on routine paraffin-embedded section, can be used to stratify cancer patients in view of selecting those who are likely to respond to IDO inhibitors, which are currently in clinical development.

4. Vigneron N., Stroobant V., Chapiro J., Ooms A., Degiovanni G., Morel S., van der Bruggen P., Boon T and **Van den Eynde B.J.** *An antigenic peptide produced by peptide splicing in the proteasome* (2004) **Science**, 304(5670): 587-590.

Citations: 110. Impact factor: 31,853.

This is the first description of the production of spliced peptides by the proteasome. This knowledge increases the size of the antigenic repertoire of human tumors, and is very useful in the context of personalized cancer immunotherapy approaches, which aim at defining the (neo)antigens expressed by individual tumors and target them with vaccine or adoptive cell therapy approaches.

5. Granted **Patent EP 2132343** (29/08/2012): *Method for the determination and the classification of rheumatic conditions*. Inventors: B. Lauwers, **B. Van den Eynde**, F. Houssiau, I. Gutierrez-Roelens.

This patent describes a gene expression signature that can be used on synovial tissues to determine the origin of arthritis of unknown origin. This is an unmet medical need. This signature is currently developed clinically, together with a diagnostic algorithm, by the spin-off biotech called DNAlytics.

5 relevant previous projects or activities, connected to the subject of this proposal

1. Benoit Van den Eynde co-founded in 2012 iTeos Therapeutics, a spin-off biotech with the mission of developing immunomodulators to combat cancer resistance to therapy. iTeos' first major program was to develop inhibitors of tryptophan-degrading enzymes IDO and TDO in order to combat resistance mechanisms in cancer patients stratified for IDO/TDO expression.
2. In 2014, iTeos Therapeutics signed a major partnership agreement with Pfizer, for the clinical development of IDO and TDO inhibitors.
3. September 2016: First in Human (FIH) for the IDO inhibitor PF-06840003, developed by iTeos Therapeutics. This event has launched a Phase I clinical trial in cancer patients (glioblastoma).
4. Benoit Van den Eynde is chairman and member of the Scientific Advisory Board of iTeos Therapeutics and Amgen, respectively. Both companies develop preclinical and clinical programs aimed at combating cancer resistance mechanisms.
5. Benoit Van den Eynde currently directs the Brussels Branch of the Ludwig Institute for Cancer Research, a world-leading international cancer research Institute. One of the major programs of the Institute is to combat cancer resistance mechanisms. This affiliation grants Van den Eynde access to a unique network of world-leading cancer scientists (Bert Vogelstein, Bob Weinberg, Irving Weissman, Carl-Henrik Heldin, Web Cavenee, George Coukos, Peter Ratcliffe, etc). For more information, please see www.ludwigcancerresearch.org

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

The lab of Benoit Van den Eynde has access to technical platforms of the Ludwig Institute and of its host institution the de Duve Institute for NGS sequencing, FACS, mass spectrometry and microscopy. Other equipment for cell culture and basic day-to-day biochemical and immunological work is available within the lab at the Ludwig Institute, including L2 and L3 confinement laboratories. An up-to-date

animal facility with individually ventilated cages is available for experimental work, and a central animal production facility is available to host production colonies for genetically modified mice and immunodeficient mice (Nude, NSG).

Any other supporting documents specified in the work programme for this call

Not applicable.

Description of the Institution

The University of Bergen (UiB) is a young, modern university with about 16.400 students and 3.600 faculty and staff, making it a medium sized European University. Seven faculties cover most of the traditional university disciplines. Within the faculties are included more than 50 different specialized departments, multi-disciplinary research centres and institutes. The University is engaged in the European Union's Framework programme for research and innovation and is currently involved in 60 H2020 projects, 19 of which it coordinates, including six ERC Grants. The Department of Biomedicine is part of the Faculty of Medicine.

Experience and role in the project

The Department of Biomedicine has nearly 40 faculty staff (PIs), 38 PhD students and nearly as many postdocs and researchers. Research is focused on several major areas including cancer biology, neuroscience, protein structure and function, and physiology. The Department hosts three core facilities, proteomics (PROBE), molecular imaging (MIC) and biophysical instrumentation for initial drug screening approaches (BISS). Aiming at fundamental discoveries, the research addresses primarily biomedical problems. Therefore, most projects involve tight collaborations within the medical faculty.

Mathias Ziegler (MZ) has a medical background and has over many years studied molecular mechanisms of human bioenergetics, metabolism and signalling. His experimental competences and experiences include cell and molecular biology, protein chemistry and enzymology as well as protein modifications and metabolomics. Over the past years, his major focus has been on NAD biology with regards to both bioenergetics and signalling functions. He has developed a number of technologies permitting to analyse both the enzymology and the metabolic conversions of intermediates in NAD metabolism.

Main Tasks undertaken in the consortium

UiB will lead **WP4** and will measure NAD metabolites for **WP4**, NAD-dependent signaling for **WP3** and provide data for and verification of mathematical models to **WP5**. Among others, we will use LC-MS technology for quantitative analysis of large sets of metabolites and signalling molecules. We will determine cellular responses to pharmacological treatments and conduct targeted analyses for the verification of models.

UiB will further contribute to data management and deposition (**WP2**), and bioinformatics network analysis and analysis of RNAseq data (**WP5**).

CV of PI and other people involved

Prof. Mathias Ziegler, MD, PhD (M) [MZ], Head of Dept. of Biomedicine, has more than 15 years of relevant experience as independent researcher in cell biology, NAD metabolism and signalling, gene regulation, enzyme studies and metabolic modelling as well as project management. His research has been continuously funded by national and international sources (including EU). The results of his studies have been recognized as major contributions in the fields of signalling and metabolism, in particular, studies of the NAD metabolome in health and disease (Nat. Rev. Cancer, 2012). He has (co-)organized several international conferences and has been invited to major congresses (FEBS, EMBO). He is editor of the FEBS journal, the J. of Biol. Chem. and member of the editorial advisory board of the Biochem. J. He has a wide range of productive research collaborations (UK, D, N, I, NL, USA, Russia), in part also relevant to this application.

Dr. Sushma Grellscheid (F) [SG] has a strong track record in genomics research, especially focusing on next generation sequencing, genetics and RNA biology. She is the recipient of several fellowships and awards throughout her career, and is currently associate professor at the Department of Biosciences and the Computational Biology Unit, University of Bergen, and part-time assistant professor in RNA Genomics at the Department of Biosciences at Durham University, UK.

She has several publications in international peer reviewed journals resulting from national and international collaborations. She is a visitor at EMBL-EBI where she is involved in large collaborative projects involving sequencing and data management.

List of up to 5 relevant publications/products/services/software/other achievements relevant to the call content:

1. Chiarugi, A., Dölle, C., Felici, R., and **Ziegler, M.** (2012) The NAD metabolome - a key determinant of cancer cell biology. *Nature Rev. Cancer* **12**, 741-752
2. Love, N.R., Pollak, N., Dölle, C., Niere, M., Chen, Y., Oliveri, P., Amaya, E., Patel, S., and **Ziegler, M.** (2015) NAD kinase controls animal NADP biosynthesis and is modulated via evolutionarily divergent calmodulin-dependent mechanisms. *Proc. Natl. Acad. Sci. USA* **112**, 1386-1391
3. Skoge, R. and **Ziegler, M.** (2016) SIRT2 inactivation reveals a subset of hyperacetylated perinuclear microtubules inaccessible to HDAC6. *J. Cell Sci.* **129**, 2972-2982
4. Ghosh P, **Grellscheid SN**, Sowdhamini R. A tale of two paralogs: human Transformer2 proteins with differential RNA-binding affinities. *J Biomol Struct Dyn.* 2016 Sep;34(9):1979-86. PMID: 26414300.
5. Lahat, A and **Grellscheid SN**. Book Chapter in Field Guidelines for Genetic Experimental Designs in High-Throughput Sequencing. Editors: Ana M. Aransay, José Luis Lavín Trueba. ISBN: 978-3-319-31348-1. 2016

List of up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. Norwegian Cancer Society: Metabolic hub molecules as key factors in cancer development and prevention (2015-2019, **MZ**)
2. **German Academic Exchange Service (DAAD): Bridging the gap: Unravelling the interaction between metabolism and signalling in health and disease (2015-2016); joint travel grant of **MZ** with **KT** (coordinator), **IH** (UiT, partner 8), **CO** (DKFZ, partner 4)
3. EMBL-EBI STFS fellow 2011-2012, continued and existing collaborations with Enright and Expression Atlas groups at EMBL-EBI (**SG**).
4. **Current scientific advisory board member of ISGSB and organiser of the 2014 International systems biology conference (**SG, IH, KT, BMB**).
5. **Royal Society Travel Grant, UK: Translational control by mTOR and Stress Granules (2014-2015). (**SG and KT**)

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

MZ's core expertise is in cell biology, biochemistry, protein engineering and targeted metabolomics. Specific strengths include generation of engineered cell lines and methods (and their development) for protein structure/function analyses and enzymology.

The Department of Biosciences has an Orbitrap LC-MS system (to be used for the metabolomics studies), a protein analytics facility and strong bioinformatics competences.

Any other supporting documents specified in the work programme for this call

Not applicable.

**Publications and grants with other consortium members

Partner 8 – UiT - Arctic University of Norway Tromsø, Norway

Description of the Institution

UiT The Arctic University of Norway is the northernmost university of the world. UiT has approximately 15,500 students and 3 300 employees. The academic community is highly international with more than 20% of the academic and 10% of the student body from abroad. UiT holds three Norwegian Centres of Excellence (SFF), three Centres for Research-based Innovation (SFI) and one Centre of Excellence in Higher Education all granted by the Research Council of Norway.

Experience and role in the project

UiT has a strong track record in EU supported research projects. Although being a relatively small university, UiT has the second highest success rate in terms of granted EU proposals in both FP7 and H2020 compared to the other Norwegian universities. UiT was granted 39 FP7 projects, including 3 ERC-grants (and additional 2 coordinated projects). So far in H2020, UiT has been granted 24 projects from the first three years, including an ERC Proof of Concept project, the first granted in Norway, in addition to one Blue Growth project and one ITN both coordinated by UiT. UiT is furthermore one of the Norwegian nodes of the ELIXIR program for distributed infrastructure for life science information.

Main tasks undertaken in the consortium

Using data from **WP4** (metabolites) and **WP3** (signaling), UiT will conduct metabolic modelling focusing on Trp and NAD metabolism for **WP5**. She will contribute models to MESI-SEEK in **WP2**.

CV of PI and other people involved

Prof. Ines Heiland (F) [IH] holds a position as professor in molecular biology and bioinformatics since 2016, and is responsible to build up bioinformatics infrastructure, including mathematical modelling, at the Faculty of Biosciences, Fisheries and Economics at UiT. She is furthermore member of the leadergroup for competence and infrastructure of the Centre for Digital Life Norway and member of the national research school for bioinformatics and biostatistics NORBIS. In addition, she is board member of the International study group in systems biology (ISGSB) and has been involved in several systems biology projects in Germany from 2008 to 2012. She has coordinated a German-Norwegian systems medical research exchange involving 4 groups in 2015 and 2016 and is partner in a project funded by the Norwegian research council led by prof. Mathias Ziegler on ***The NAD metabolome of human cells***.

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. **Dyah L Dewi, Soumya R Mohapatra, Saioa Blanco Cabañes, Isabell Adam, Luis F Somarribas Patterson, Bianca Berdel, Masroor Kahloon, Loreen Thürmann, Stefanie Loth, Katharina Heilmann, Dieter Weichenhan, Oliver Mücke, **Ines Heiland**, Pauline Wimberger, Jan Dominik Kuhlmann, **Karl-Heinz Kellner**, **Sarah Schott**, Christoph Plass, Michael Platten, Clarissa Gerhäuser, Saskia Trump, **Christiane A. Opitz**, *Suppression of indoleamine-2, 3-dioxygenase 1 expression by promoter hypermethylation in ER-positive breast cancer*, Oncoimmunology 2017;6(2):e1274477.
2. Schäuble, S², A.K. Stavrum², P. Puntervoll, S. Schuster, and **I. Heiland**¹, *Effect of substrate com-petition in kinetic models of metabolic networks*. FEBS Lett, 2013. **587**(17): p. 2818-24.
3. Schmeisser, K., J. Mansfeld, D. Kuhlow, S. Weimer, S. Priebe, **I. Heiland**, M. Birringer, M. Groth, A. Segref, Y. Kanfi, N.L. Price, S. Schmeisser, S. Schuster, A.F. Pfeiffer, R. Guthke, M. Platzer, T. Hoppe, H.Y. Cohen, K. Zarse, D.A. Sinclair, and M. Ristow, *Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide*. Nat Chem Biol, 2013. **9**(11): p. 693-700

**Publications and grants with other consortium members

4. **Stavrum, A.K.², **I. Heiland**^{1,2}, S. Schuster, P. Puntervoll, and **M. Ziegler**, *Model of tryptophan metabolism, readily scalable using tissue-specific gene expression data*. J Biol Chem, 2013. **288**(48): p. 34555-66.
5. **Gossmann, T.I., **M. Ziegler**, P. Puntervoll, L.F. de Figueiredo, S. Schuster, and **I. Heiland**¹, *NAD(+) biosynthesis and salvage -a phylogenetic perspective*. FEBS J, 2012. **279**(18): p. 3355-63.

List of up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. Partner Norwegian Research Council funded project The NAD metabolome of human cells (2016-2019)
2. Partner in MARVAL – From unexploited marine biomass to high value products (strategic funding by the Arctic University of Norway) (2016-2020)
3. **International partner in the systems medicine project GlioPATH funded by the German ministry of education and research (BMBF) (2015-2018); joint project with **CO** and **KT**
4. **DAAD Norwegian-German systems biology research exchange (project no. 244770/F11) (2015-2016); joint project with **CO**, **KT**, and **MZ**.

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

The UiT is part of the Norwegian Metacenter for Computational Science that provides the national infrastructure for computational science in Norway. The project provides computational resources and services to individuals or groups involved in education and research at Norwegian universities and colleges. In this context UiT host the supercomputing unit FRAM for high performance computing. UiT is furthermore associated to NORSTOR the Norwegian national infrastructure for management, curation and long-term archiving of digital scientific data.

Any other supporting documents specified in the work programme for this call

Not applicable.

Partner 9 – UNEW - Newcastle University, UK

Description of the Institution

Newcastle University has more than 18,000 undergraduate students, 6000 postgraduate students and 2000 academic staff. It is ranked 16th in the UK in terms of research power, based on the results of the Research Assessment Exercise 2014, which found that the vast majority of research (84% in Medical Sciences) was placed in the top two categories of 4* (world leading) and 3* (internationally excellent). The University is a member of the prestigious Russell Group, comprising 24 leading research institutions in the UK and in the year ended 31 July 2016, its total research income equalled €116 million. It currently has 81 projects in Horizon 2020 worth €38 million to the University. As part of the University's commitment to excellence with impact, it has identified 3 institutional research challenge themes that address key societal issues; ageing and health being the first of these.

Newcastle University has developed and adopted a Charter for Changing Age as indication of its commitment to ageing research and its translation into interventions to make humans live better for longer. In 2014, it is extending ageing research into a novel university-wide Newcastle University Institute for Ageing (NUIA), which is becoming one of the largest and most powerful institutions in basic and translational ageing research worldwide, encompassing around 250 research groups and generating a yearly research grant income of more than €25 million.

Newcastle University has a strong reputation in cancer research, focussed largely in the Northern Institute for Cancer Research, NICR. The NICR has 120 academic staff, it is one of only 15 CRUK and 18 ECMC Centres in the UK and has an approximate annual income of £9.6m. Its research output is excellent and at the last Research Excellence Framework (REF) in 2014 in Unit of Assessment 1 – Clinical Medicine, we are officially classified as world-leading or internally excellent in terms of originality, significance and rigour. It has particular strength in PARP biology and PARP inhibitor development culminating in the recent approval of Rubraca (formerly known as rucaparib, which was co-developed by researchers in the NICR and the Pharmaceutical Industry) by the FDA.

Experience and role in the project

Newcastle University has a good record of success, facilitated by strong support and information mechanisms, in EU funded research. NUIA researchers have been involved in multiple FP projects and now contribute to a number of major H2020 projects including a response to the European Institute for Innovation and Technology call for a KIC in Lifelong Health and Active Ageing and a Teaming application for a Multidisciplinary Institute for Ageing in Coimbra (Portugal), for which Newcastle University is the teaming partner.

NICR has a strong track record in EU supported research projects, including 5 projects worth £2,362,370 between 2010 and 2017. The organisation has been the coordinator in 2 FP projects. Researchers at the NICR have contributed to 3 projects where we are partners but not the co-ordinators of EU grants. The organisation is at this moment part of a new EU project named **TransPot**.

Main Tasks undertaken in the consortium

UNEW is leader of **WP5** (DPS). NC will contribute expertise on pharmacological interventions to WP5 in close interaction with **WP3** and **WP4**. DPS has specific expertise in systems modeling of signaling and has collaborated with KT for several years on systems modeling of nutrient signaling. The working practise established, e.g., for communication, sharing data and models, will be adopted for interactions between WP5 with WP3 and WP4, and MESI-SEEK in **WP2**.

CV of PI and other people involved (including gender)

Dr Daryl P. Shanley (M) [DPS] is a Senior Lecturer in Systems Biology and is the Director of the Newcastle University, Centre for Integrated Systems Biology of Ageing and Nutrition (CISBAN). He has over 20 years experience in mathematical modelling the molecular mechanisms of ageing and has published high impact papers in the systems modelling of key processes such as nutrient sensing signalling (Google Scholar h index = 20). He has led several UK funded systems biology projects and helped co-ordinate the mathematical modelling work package of the EU FP6 NoE LifeSpan, aimed at understanding the influence of early life nutrition in older age.

Prof. Nicola Curtin (F) [NC] is a Professor of Experimental Cancer Therapy. She is a world expert in PARP biology, the DNA damage response and cancer drug discovery. Prof Curtin led the PARP inhibitor project in the NICR that led to the development of rucaparib (now licenced as Rubraca) and has 63 publications with a total of 7194 citations on this topic. She has developed pharmacodynamic and predictive biomarker assays to support clinical trials. She is author of 140 peer-reviewed publications, 20 as first author and 53 as last or corresponding author, including publications in *Nature*, *Nature Medicine*, *Nature Reviews Cancer*, *Lancet Oncology*, *Journal of the National Cancer Institute* (Google Scholar h index = 55). She is also an inventor on 16 patents. She has a mixed portfolio of funding including RCUK, National and local Charities and the Pharmaceutical Industry.

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. **Dalle Pezze P, Ruf S, Sonntag AG, Langelaar-Makkinje M, Hall P, Heberle AM, Razquin Navas P, van Eunen K, Talle RC, Schwarz JJ, Wiese H, Warscheid B, Deitersen J, Stork BR, Fayler B, Schauble S, Hahn U, Horvatovich P, **Shanley DP** and **Thedieck K** (2016). A systems study on amino acid stimulation reveals concurrent activation of AMPK and mTOR converging on ULK1 and autophagy. *Nature Commun.* 7:13254
2. Dalle Pezze P, Nelson G, Otten EG, Korolchuk VI, Kirkwood TBL, von Zglinicki T, **Shanley DP** (2014) Dynamic modelling of pathways to cellular senescence reveals strategies for targeted interventions *PloS Comp Biol* 10(8): e1003728
3. **P Dalle Pezze, AG Sonntag, A Thien, MT Prentzell, M Gödel, S Fischer, E Neumann-Haefelin, TB Huber, R Baumeister, **DP Shanley[§]**, **K Thedieck[§]**. A Dynamic Network Model of mTOR Signaling Reveals TSC-Independent mTORC2 Regulation. *SCIENCE Signaling* (2012) Vol 5 Issue 217 ra25
4. Drew Y, Mulligan EA, Vong W-T, Thomas HD, Kahn S, Kyle S, Mukhopadhyay A, Los G, Hostomsky Z, Plummer ER, Edmondson RJ and **Curtin NJ** (2011) Therapeutic potential of PARP inhibitor AG014699 in human cancer with mutated or methylated BRCA. *JNCI* 103(4):334-46
5. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, Kyle S, Meuth M, **Curtin NJ**, and Helleday T (2005). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose)polymerase. *Nature* 434 913-917.

Up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. ***LifeSpan EU FP6 NoE*: funded 2007-2011 PI *Rudi Westendorp and Bas Zwaan* LifeSpan was a FP6 Network of Excellence that involved 17 leading research centres to create a durable structure in which the multilateral exchange of data, knowledge, and methodology between partners that substantially advanced our understanding of ageing and age-associated diseases. This consortium seeded the collaboration between **DPS** and **KT**.
2. *Centre for Integrated Systems Biology of Ageing and Nutrition (CISBAN)*: BBSRC BB/C008200/1, funded 2005-2011, PI *Prof Tom Kirkwood with CoI Shanley and other*, £6.2 M. CISBAN is an interdisciplinary centre combining talents of biologists, statisticians, mathematicians, computer scientists and engineers. Its purpose is to apply a systems approach to the biology of ageing and nutrition. This includes a strong experimental biology component, and also a large *in silico* research group comprised of modellers, statisticians, computational systems biologists.
3. *Therapeutic potential of PARP inhibitors in cancers defective in BRCA1, BRCA2 or other defects contributing to a “BRCAness” phenotype*, Pfizer funded 7/08-12/09 £147K PI Curtin.

^{**}Publications and grants with other consortium members

Clinical Fellowship to Support the Phase II Proof of Principle Study of the Potent PARP-1 Inhibitor, AG014699, in known Carriers of BRCA1 and BRCA 2. CR UK 12/07-11/09 £125K PI Prof Plummer with CoI Curtin.

4. Biology of Ageing e-Science Integration and Simulation System (BASIS): BBSRC BEP17042, funded 2003-2005, PI Prof Tom Kirkwood with CoI Shanley and others £442K

The Biology of Ageing e-Science Integration and Simulation system (BASIS) was designed as a web-based Computational Systems Biology application serving the biology-of-ageing research community. The system: 1) offered SBML model building, storage and stochastic simulation via secure web services and 2) provided computing power that could be shared within the Systems Biology research community.

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

UNEW established a Centre specialising in the systems biology of ageing (CISBAN) in 2005, DPS is the current Director, and the extensive resources (software, hardware and existing models) and expertise (data handling and systems modelling) in place will be available to MESI-STRAT.

Dedicated systems modelling compute clusters offering over 128 cores of compute power and hosted by our University Computing Service that ensures maintenance of equipment, long term storage of models and data and industry standard back up strategy. We have the technical capacity to develop and simulate large biochemical network models using all the major open source (e.g. Copasi, SBMLToolBox, PottersWheel) and commercial software (Matlab). The Newcastle University, Digital Institute has specific expertise in cloud computing that will be available to this project.

Any other supporting documents specified in the work programme for this call

Not applicable.

Partner 10 – CHAB - Charité University Medicine Berlin, Germany

Description of the Institution

Charité University Medicine Berlin is among the largest university clinics in Europe. Charité has four locations within Berlin and a total staff of more than 13 000 people. Founded in 1710, Charité has produced a number of Nobel laureates including Emil von Behring, Robert Koch und Paul Ehrlich. Currently, Charité is among the German top centers in cancer research, cardiovascular disease, neuroscience, immunology, rare diseases and human genetics as well as regenerative therapies. This broad spectrum of research is accomplished by more than 4500 scientists with almost 150 M€ of grants in 2013. In addition, Charité now acts together with the internationally renowned Max Delbrück Research Center (MDC) as the Berlin Institute of Health with the unique focus on “Systemsmedicine”. Since 2012, Charité is one of the eight centers of excellence within the German Consortium for Translational Research with a strong focus on improved molecular diagnostics and therapy.

Experience and role in the project

Charité has a strong track record in coordination and participation in projects which combine experimental and systems biology approaches for cancer therapy, including the EU-funded project Oncotrack. Also a large number of systems biology consortia funded by the German Federal Ministry of Education and Research (BMBF) are coordinated by CHAB. For example, Prof. Christine Sers (CS) coordinates, e.g., the three systems oncology projects MAPTor-NET, ColoNET, OncoPATH, and ZeBANC for building up an interdisciplinary biobank at Charité Comprehensive Cancer Center.

Main tasks undertaken in the consortium

CHAB will coordinate **WP3** to generate quantitative and time-resolved signaling and omics data for network reconstruction (WP5), and perform validation experiments in preclinical and clinical samples (**WPs 6+7**). CS will work in close contact with the coordination of **WP4** (MZ, UiB) to synchronize measurements and experimental conditions for metabolite and signaling analyses. In **WP5** CS will contribute to the development of predictive models of signaling pathways with a focus on MAPK and the connections to the other signaling and metabolic networks studied.

CV of PI and other people involved

Prof. Dr. Christine Sers (F) [CS] is professor for Tumour Systems Biology at the Institute of Pathology, Charité. She has a strong track record in cancer research and systems biological approaches to understand signalling network circuits in cancer and to use such approaches for prediction of therapy response. She coordinates several BMBF research consortia, including MAPTorNET, partnered by **KT** and **DPS** (external partner). She is part of the German Consortium for Translational Cancer Research (DKTK), founding member of the Integrative Research Institute (IRI) for Life Science, funded by the German Research Foundation (DFG) and a faculty member of the Berlin School of Integrative Oncology (BSIO).

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. Mamlouk, S., Childs, L.H., Aust, D., Melching, F., Wolf, T., Oliveira, C., Durek, P., Schumacher, D., Bläker, H., von Winterfeld, M., Schäfer, R., Klauschen, F., Gastl, B., Heim, D., Möhr, K., Menne, A., Redmer, T., Lenze, D., Tierling, S., Morkel, M., Möbs, M., Weichert, W., Folprecht, G., Leser, U., and **Sers, C.** (2017). DNA copy number changes define spatial patterns of heterogeneity in colorectal cancer. *Nat Commun.* 2017 Jan 25;8:14093. doi: 10.1038/ncomms14093
2. Childs LH, Mamlouk S, Brandt J, **Sers C**, Leser U. SoFIA: a data integration framework for annotating high-throughput datasets. *Bioinformatics.* 2016 May 13. pii: btw302.
3. Fritzsche-Guenther R, Witzel F, Kempa S, Brummer T, **Sers C**, Blüthgen N. Effects of RAF inhibitors on PI3K/AKT signalling depend on mutational status of the RAS/RAF signalling axis. *Oncotarget.* 2016 Feb 16;7(7):7960-9. doi: 10.18632/oncotarget.6959.

4. Relógio A, Thomas P, Medina-Pérez P, Reischl S, Bervoets S, Gloc E, Riemer P, Mang-Fatehi S, Maier B, Schäfer R, Leser U, Herzog H, Kramer A, **Sers C**. Ras-mediated deregulation of the circadian clock in cancer. *PLoS Genet.* 2014 May 29;10(5):e1004338.
5. Riemer P, Sreekumar A, Reinke S, Rad R, Schäfer R, **Sers C**, Bläker H, Herrmann BG, Morkel M. Transgenic expression of oncogenic BRAF induces loss of stem cells in the mouse intestine, which is antagonized by β-catenin activity. *Oncogene.* 2014 Aug 11. doi: 10.1038/onc.2014.247

List of up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. **BMBF collaborative research consortium „MAPTor-NET“ (2015-2017), coordinator CS, partners **KT** and **DS** (UNEW, international external partner)
2. BMBF collaborative research consortium „OncoPATH“ (2013-2016), coordinator CS
3. BMBF German Consortium for Translational Cancer Research “Molecular Diagnostics of Colorectal Cancer“ (2012-2016), coordinator CS
4. BMBF collaborative research consortium „ColoNET“ (2009-2012), coordinator CS

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

- Built up a sequencing facility for targeted sequencing within Charité Pathology and has access to WGS via DKTG core facility.
- Own bioinformatic experience for sequencing data evaluation, establishing of panels and bioinformatics pipelines
- Experience in 3D organoid establishment, culturing and manipulation
- Member of the molecular tumor conference at the Charité Comprehensive Cancer Center and the DKTG Master Program for comprehensive molecular stratification of cancer patients

Any other supporting documents specified in the work programme for this call

Not applicable.

**Publications and grants with other consortium members

[Proposal number 754688] [Proposal acronym  **MESI-STRAT**] – Part B

[Page number 79]

Partner 11 – UDUR - Durham University, UK.

Date of termination: 01.02.2019; tasks are taken over by UiB due to move of SG from UDUR to UiB.

Description of the Institution

Durham University, founded in 1832, has an excellent worldwide reputation, and is ranked within the top 100 worldwide. The University is engaged in a full range of higher educational activities, including high-quality teaching and learning at undergraduate and postgraduate levels, advanced research and scholarship, partnerships with businesses and other private and public sector bodies, and partnerships and initiatives with community and voluntary sector organisations. It provides a stimulating environment to nourish and support the needs of a world-class academic community. Its academic teaching and research programmes are delivered through 25 academic departments contained within three faculties: Arts and Humanities, Science, and Social Sciences & Health as well as eight interdisciplinary Research Institutes.

Experience and role in the project

Durham University has a strong track record in EU supported research currently undertaking over 100 projects, across FP6, FP7, and Horizon 2020 awards. The organisation has been the coordinator in several FP projects including COFUND, COST, ERC, MCSA and across the H2020 funding landscape.

Main task undertaken in the consortium

UDUR will contribute to data management and deposition (**WP2**), and bioinformatics network analysis and analysis of RNAseq data (**WP5**).

CV of PI and other people involved

Dr. Sushma Grellscheid (F) [SG] has a strong track record in genomics research, especially focusing on next generation sequencing, genetics and RNA biology. She is the recipient of several fellowships and awards throughout her career, and is currently Lecturer in RNA Genomics at the School of Biological and Biomedical Sciences (SBBS) at Durham University. She is the academic lead for computational biology at SBBS, and chair of the computational infrastructure committee. She has several publications in international peer reviewed journals resulting from national and international collaborations. She is a visitor at EMBL-EBI where she is involved in large collaborative projects involving sequencing and data management.

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. Ghosh P, **Grellscheid SN***, Sowdhamini R. A tale of two paralogs: human Transformer2 proteins with differential RNA-binding affinities. *J Biomol Struct Dyn.* 2016 Sep;34(9):1979-86. PMID: 26414300.
2. Feracci M, Foot JN, **Grellscheid SN**, Danilenko M, Stehle R, Gonchar O, Kang HS, Dalgliesh C, Meyer NH, Liu Y, Lahat A, Sattler M, Eperon IC, Elliott DJ, Dominguez C. Structural basis of RNA recognition and dimerization by the STAR proteins T-STAR and Sam68. *Nat Commun.* 2016 Jan 13;7:10355. PMID: 26758068.
3. Lahat, A and **Grellscheid SN***. Book Chapter in Field Guidelines for Genetic Experimental Designs in High-Throughput Sequencing. Editors: Ana M. Aransay, José Luis Lavín Trueba. ISBN: 978-3-319-31348-1. 2016
4. **Heberle AM, Prentzell MT, van Eunen K, Bakker BM, **Grellscheid SN**, Thedieck K. Molecular mechanisms of mTOR regulation by stress. *Mol Cell Oncol.* 2014 Dec 3;2(2):e970489. doi: 10.4161/23723548.2014.970489. PMID: 27308421.

**Publications and grants with other consortium members

[Proposal number 754688] [Proposal acronym  MESI-STRAT] – Part B

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5. **Grellscheid S***, Dalglish C, Storbeck M, Best A, Liu Y, Jakubik M, Mende Y, Ehrmann I, Curk T, Rossbach K, Bourgeois CF, Stévenin J, Grellscheid D, Jackson MS, Wirth B, Elliott DJ. Identification of evolutionarily conserved exons as regulated targets for the splicing activator tra2 β in development. PLoS Genet. 2011 Dec; 7(12):e1002390. PMID: 22194695.

* Corresponding author.

5 relevant previous projects or activities, connected to the subject of this proposal

1. EMBL-EBI STFS fellow 2011-2012, continued and existing collaborations with Enright and Expression Atlas groups at EMBL-EBI.
2. Addison Wheeler fellowship at Durham University and collaboration with Newcastle University on BBSRC funded project on NGS gene expression profiling in Ageing.
3. Current scientific advisory board member of ISGSB and organiser of the 2014 International systems biology conference.
4. **Royal Society Travel Grant, UK: Translational control by mTOR and Stress Granules (2014-2015). Together with KT, UMCG
5. Large-scale NGS transcriptional profiling of alternative splicing switches in human ageing skin. Collaboration with Proctor and Gamble.

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

Durham University has made significant investment in high performance computing with the Hamilton cluster and in-house HPC support.

Any other supporting documents specified in the work programme for this call

Not applicable.

Partner 12 – NIN - Neuroimmun GmbH, Germany

Description of the Institution

Neuroimmun GmbH was founded in 2016 by Dr. Kellner. Since 2008 Dr. Kellner develops own markers in neurological, immunological and cardiovascular implications relating to the biochemistry of amino acids and biogenic amines, such as tryptophan, kynurenone, serotonin, histamine quinolinic acid and kynurenic acid (products see www.neuroimmun.com).

Experience

The main expertise of Dr. Kellner is the development of ELISAs. He owns a patent for kynurenone-ELISAs and is independent from third party licences which provides freedom to operate. Developed ELISAs are validated according to the criteria defined by ICH Q2. With a headcount of 5 employees, Neuroimmun GmbH is located in Karlsruhe, Germany. Worldwide distribution of Neuroimmun GmbH ELISAs is organised by Immundiagnostik AG.

Main tasks undertaken in the consortium

NIN contributes to **WP4** to assess Trp metabolites by quantitative measurements of enzyme concentrations (e.g., IDO1), and intracellular and extracellular metabolites by ELISA (e.g., kynurenone, Trp, serotonin, kynurenic acid, quinolinic acid). NIN will also develop multiplex assays for the before mentioned metabolites if they occur jointly in MESI marker panels for ER+BC subgroups for subsequent commercialization (**WP9**).

CV of PI and other people involved

Dr. Karl-Heinz Kellner (M) [KK], CEO of Neuroimmun GmbH will be primarily responsible for carrying out the proposed activities.

As a Doctor of Science with a diploma in biotechnology, Dr. Kellner has been managing research and development projects for 17 years (a) as a PhD, 1993-1997, (b) as a consultant, since 1998, (c) in his own biotech section, since 2004.

The main developments of Dr. Kellner are listed below:

- 1993-1997: Universität des Saarlandes, Saarbrücken: PhD thesis: Separation of derivatised amino acids using supported liquid membranes
- 1997-1998: Rudolf Spitzmüller technical consulting, junior project manager
- 7/1998: CEO of own company: Dr. Kellner technical consulting (currently 5 employees)
- 1/2004: CEO/CSO of Dr. Kellner biotechnological development – a section of Dr. Kellner technical consulting, development of ELISA for amino acid quantification in clinical chemistry.
- 5/2016: CEO/CSO of Neuroimmun GmbH –, development and production of ELISA for amino acid quantification in clinical chemistry

Intellectual Property:

1. Patent: Automatenfähiger Immunoassay für Biogene Amine (EP 11 797 208.3) Patent granted
2. Patent: In vitro diagnostic and prognosis of contrast induced nephropathy (Application N°: 10 2015 104 088.3). Patent filed

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. **Dyah L. Dewi, Soumya R. Mohapatra, Saioa Blanco Cabañes, Isabell Adam, Luis F. Somarribas Patterson, Bianca Berdel, Masroor Kahloon, Loreen Thürmann, Stefanie Loth, Katharina Heilmann, Dieter Weichenhan, Oliver Mücke, **Ines Heiland**, Pauline Wimberger, Jan Dominik Kuhlmann, **Karl-Heinz Kellner**, **Sarah Schott**, Christoph Plass, Michael Platten, Clarissa Gerhäuser, Saskia Trump & **Christiane A. Opitz** (2017). Suppression of indoleamine-2,3-dioxygenase 1 expression by promoter hypermethylation in ER-positive breast cancer. *OncoImmunology*, (February), 1–12. <http://doi.org/10.1080/2162402X.2016.1274477>

**Publications and grants with other consortium members

2. Christoph Rechetededer, ... **KH Kellner**, ... Berthold Hocher. (2016) Pre-Interventional Kynurene predicts Longterm Outcome after Contrast Media Exposure due to Coronary Angiography, ASN Kidney Week 2016 (Chicago), 8. JAHRESTAGUNG DER DEUTSCHEN GESELLSCHAFT FÜR NEPHROLOGIE 2016 (Berlin)
3. Fabian Heunisch, MD Lyubov Chaykovska, MD, Gina von Einem, MD Markus Alter, MD Thomas Dschietzig, MD Axel Kretschmer, MD **Karl-Heinz Kellner**, MD and Berthold Hocher, MD (2017). ADMA predicts major adverse renal events in patients with mild renal impairment and/or diabetes mellitus undergoing coronary angiography. Medicine (Baltimore). 2017 Feb; 96(6):e6065. doi: 10.1097/MD.00000000000006065.
4. 2014-2016: Development of a Sandwich-ELISA of Indolamin-2,3-Dioxygenase (**Product: IDO 1 ELISA**)
5. 2013-2015: Development of ELISA for products of L-typtophan metabolism (funded by German Federal Ministry of Economy: ZIM-EP130068,), **Products: L-Kynurene, Quinolinic acid and Kynurene acid ELISA**

Up to 5 relevant previous projects or activities, connected to the subject of this proposal:

1. Development of a Multiplex-Assay for tryptophan metabolites (Ministry of Economy: ZIM-KF ZF4257201 AJ6: 1/2016 – 8/2019); **Product: LC-MS/MS for all metabolites of tryptophan metabolism**
2. Development of a Sandwich-ELISA of Indolamin-2,3-Dioxygenase (funded by German Federal Ministry of Economy: ZIM-EP141714, 1/2015-12/2016), **Product: IDO 1 ELISA**
3. Development of ELISA for products of L-tryptophan metabolism (funded by German Federal Ministry of Economy: ZIM-EP130068, 1/2013-3/2015), **Products: L-Kynurene, Quinolinic acid and Kynurene acid ELISA**
4. Development of ELISA for Tryptophan-Depletion (funded by German Federal Ministry of Economy: ZIM-KF2105002FR0, 11/2010-10/2013) - **Product: L-Tryptophan, L-Phenylalanin, L-Tyrosin ELISA**

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

1. Fully equipped biochemical lab
2. Access to LC-MS/MS

Any other supporting documents specified in the work programme for this call

Not applicable.

Description of the Company

SysBioSim B.V. has been providing mathematical modelling and systems biology simulation services, since 2014, to pharmaceutical as well as health & food ingredient companies in order to improve the drug and active ingredient development process. The commercial services provided by SysBioSim include performing predictive analysis via writing mathematical models of signaling and metabolic pathways and running simulations. We develop specifically designed models and simulations for our clients to answer their research questions. The models are developed based on existing literature and proprietary client data to directly simulate the human organism. Through mathematical modeling, predictions can be made on the efficacy, efficiency, dosage, and adverse events of drug candidates. Thus, our services help our clients to reduce time and costs by better designing their R&D programs as well as animal and clinical studies.

Experience and role in the project

SysBioSim is an innovative start-up that **bridges science and scientific research with applicable business**. Our expertise is in providing systems biology services in a commercial setting. As a dynamic start-up offering services in a novel field, we have built a network as well as interest within the pharmaceutical and health & food ingredient industries. In order to build scientific excellence in modeling, our strategy is to specifically focus on developing strong expertise in signaling and metabolic pathway modeling while remaining diversified and flexible on the business end. Our expertise lays within utilizing experimental results from **both fundamental** as well as **translational sciences** to develop predictive models that can greatly improve the drug development process and thus hopefully the lives of patients and consumers. Our diverse team enables us to apply our expertise starting from idea development to delivering an end product/service to the market.

SysBioSim will contribute to the model development from both the scientific and business aspect. Scientific contribution will be via the assessment and development of signalling pathways based on the prior theoretical and practical work (confidential) done on tumorigenesis. SysBioSim will also guide the development of MESI-STRAT's models to ensure high commercial value and commercialize the end product. Furthermore, SysBioSim will play a major role in dissemination of the MESI-STRAT's models via interviews, scientific and business speeches as well as networking activities.

Main Tasks undertaken in the consortium

SBS is co-leader of **WP9** – Dissemination and communication. SBS will contribute to the integration of MESI models and network analyses and will run a pipeline for MESI model customization for pharma stakeholders (**WP5**).

CV of PI and other people involved

Mrs. Basak Tektemur Altay, MBA, MSc. – CEO (F), [BA]: Mrs. Tektemur Altay is the founder and the CEO of SysBioSim. She brings expertise in business and life sciences as well as network and communication skills. In addition to generating innovative ideas, she brings together the means to turn these ideas into a viable business. Having business degrees and expertise that are built on a scientific background, Tektemur Altay successfully commercializes emerging opportunities in science with an eye on the (positive) social impact. She has knowledge and expertise in all management aspects such as strategy, business development, finance and marketing.

Mrs. Tektemur Altay earned her Bachelor's degree from the Molecular Biology and Genetics program that has an equal density of experimental and bioinformatics education. After graduation, Tektemur Altay obtained an MBA and MSc. on International Business. She worked at an agro-biotechnology company in the business development department with the task to establish a new business branch for the company. Starting with market and business analyses, she built the business case, created a network with the majority of the players in the field and generated sales. She built a brand name for the company in a new field in less than 2 years and reached a position where sustainable sales could be obtained. She also acted as a strategy manager in the company, reporting directly to the management board on strategic issues about both scientific and business aspects. She gave advice to scientific teams on the business aspects of EU-funded projects.

She went on to establish a new entity in the Netherlands for a Dutch and a Chinese partnership in the field of laboratory equipment and instruments, generating sales within 6 months. She was responsible for EMEA market, directly reporting to the CEO.

Following this experience, she established her start-up in the Leiden Bio Science Park Hub. As a founder and owner of the company in the relatively new field of Systems Biology, she generated business and scientific strategy with the aim to support clients within the life sciences industry and forged collaborations with academia. In the short time of slightly more than two years, she managed to provide an organic growth for the company, generate investor interest and has gotten involved in EU projects.

Dr. A. Lisa Norte – Project Manager (F), [LN]: Dr. Norte brings seven years of experience in managing scientific research projects as well as working on and coordinating international collaborations. She earned her Ph.D. at the University of Southern California in Molecular and Computational Biology and has a multidisciplinary background that includes Microbiology, Biochemistry, and Biophysics. Dr. Norte is responsible for budget planning, time management and maintaining the scope of projects. She is the point of contact for ongoing projects at SysBioSim and is also involved in scientific writing as well as literature analysis to bridge modeling with biological reality.

In 2015 she received her Ph.D. in Molecular and Computational Biology from the University of Southern California. She was awarded ‘Extramural Paper of the Month’ by the National Institute of Environmental Health Sciences based on the important findings and potential impact on public health of her thesis work. During her Post-Doc at TU Delft, Dr. Norte was responsible for the coordination of a multidisciplinary international project funded by the Human Frontier in Science Program and was involved in merging biochemical techniques with nanotechnology. Presently, she is a project manager at SysBioSim and due to her multidisciplinary background has been involved in both the management and scientific aspects of projects.

Dr. Milan van Hoek – Scientific Consultant (M), [MH]: Dr. van Hoek works at SysBioSim on a project basis providing the company with his expertise in designing and implementing new and more efficient models and algorithms. He has a background in theoretical physics and mathematical modeling, specifically in the area of metabolic pathways. He completed his Ph.D. thesis -The Evolutionary Dynamics of Metabolic Adaptation- at Utrecht University and continued his research as a postdoc at CWI doing computational modeling of the gut microbial metabolism. He has expertise in software engineering in a commercial setting. Dr. van Hoek and SysBioSim have a mutual understanding that a full-time position will be open for him upon granting of the H2020 project. He will be responsible for leading a team of modelers and coders.

In 2008 he received his Ph.D. in Theoretical Biology/Bioinformatics from Utrecht University which mainly focused on modeling metabolic pathways. During his Post-Doc at CWI, Dr. van Hoek studied microbial metabolism, using a combination of linear programming techniques, genetic algorithms, and numerical simulations and was also involved in organizing biweekly modeling meetings with the Netherlands Consortium for Systems Biology. As a result of his postdoctoral research, Dr. van Hoek initiated a collaboration with TNO testing his model predictions with TNO's *in vitro* gut model. Presently, he is a Scientific Software Engineer at Alten Netherlands and a Scientific Consultant at SysBioSim.

Prospective Personnel Profile:

Post-Doc or Graduate (F/M) with metabolic modeling expertise: SysBioSim will hire a systems biologist with modeling capabilities to work with the team under the direct supervision of Dr. van Hoek.

List of up to 5 relevant publications/products/services/software/other achievements relevant to the call content:

1. Emergence of microbial diversity due to cross-feeding interactions in a spatial model of gut microbial metabolism. MJA Van Hoek, RMH Merks. bioRxiv, 059956. 2016.
2. Redox balance is key to explaining full vs. partial switching to low-yield metabolism. MJA van Hoek, RMH Merks. BMC systems biology 6 (1), 22. 2012
3. Metabolic adaptation after whole genome duplication. MJA van Hoek, P Hogeweg. Molecular Biology and Evolution 26 (11), 2441-2453. 2009.

List of up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. SysBioSim - CWI collaboration: Integration of existing cell-based models from CWI of cell-ECM interaction and MET with existing molecular-level and metabolic dynamic models of SysBioSim.
2. Literature Based Validation Study: effects of rapeseed oil on colon cancer via analyzing putative indicators
3. Modeling of Signaling Pathways in Hepatocellular Carcinoma: *In silico* analysis of the effects of an isothiocyanate on human health and hepatocellular carcinoma

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

SysBioSim is currently investing in following infrastructure:

The modelling and simulations on SysBioSim's end will require computing power, and storing of the output data and models will require storage space. We are building the following infrastructure with Apple computers since many bioinformatics and modeling tools work (and are maintained) better on Apple's operating system:

2 x MacPro 6 core + monitors, keyboards and other accessories
2 x iMac 27-inch + accessories
NAS: Synology DS1515+ with 10 TB - 20 TB

The aforementioned infrastructure has an estimated monetary value of €25000. SysBioSim will guarantee to use its own infrastructure for the execution of this project as an in-kind contribution without any guarantee that aforementioned configuration is the exact configuration. SysBioSim may decide to invest in the form of in-kind contribution in a separate storage unit if need be.

Any other supporting documents specified in the work programme for this call

Not applicable.

Description of the Institution

The Heidelberg Institute for Theoretical Studies is a private, non-profit research institute.

HITS conducts basic research in the natural sciences, mathematics and computer sciences with a focus on the processing, structuring, and analyzing of large amounts of complex data and the development of computational methods and software. The research fields range from molecular biology to astrophysics. HITS is organized as (currently) 13 independent research groups.

Experience and role in the project

HITS has successfully participated in numerous EU projects, ranging from language recognition to structural biology. The SDBV group has been part of numerous national, transnational and EU projects, with contribution to data and model management for systems biology, systems medicine, and drug design. The hallmark of their work is combining training, implementation, and service.

Main Tasks undertaken in the consortium

HITS leads MESI-SEEK setup and maintenance in **WP2**, and contributes to network analysis in **WP5**. The work will be focused on compliant, streamlined, simplified, integrated, and FAIR exchange between the users in MESI-STRAT and beyond the project. The SEEK extensions which HITS will build in the frame of MESI-STRAT will benefit the broader systems medicine community and will improve FAIR data management, standards, and curation, thereby furthering HITS business and contributing to **WP9**.

CV of PI and other people involved

PD Dr. Wolfgang Müller (M) [WM] heads the SDBV group at HITS. He is a trained physicist and computer scientist working in information retrieval and data management for the last 20 years. He has been coordinating the data management of the German Virtual Liver Network, is coordinating the NBI-SysBio node of de.NBI, the German Network for Bioinformatics Infrastructure, and been PI on other infrastructure projects, as described below. His interest lies in providing data that lends itself to improved retrieval, as well as providing data management that satisfy both research needs and privacy concerns.

Dr. Olga Krebs (F) [OK] is a wet-lab biologist and highly experienced biodata expert from HITS. In SysMO-DB I and II, as well as now in FAIRDOM, she has been working collecting user requirements and transferring them into scientific data management solutions, training, and advised experimentalist and modelers together. She has travelled extensively to projects and presented her respective projects in several international forums.

5 relevant publications/products/services/software/other achievements relevant to the call content:

1. Wolstencroft K, **Krebs O**, Snoep J, Stanford N, Bacall F, Golebiewski M, Kuzyakiv , Nguyen Q, Owen S, Soiland-Reyes S, Straszewski J, van Niekerk D, Williams A, Malmström L, Rinn B, **Müller W**, and Goble C. FAIRDOMHub: a repository and collaboration environment for sharing systems biology research (2016), Nucleic Acids Research, 2016, 1. DOI: 10.1093/nar/gkw1032
2. **Krebs O**, Wolstencroft K, Stanford N, Morrison N, Golebiewski M, Kuzyakiv R, Owen S, Nguyen Q, Snoep J, **Müller W**, Goble C. FAIRDOM approach for semantic interoperability of systems biology data and models (2016). Proceedings of the 7th Workshop on Ontologies and Data in Life Sciences, Vol. 16922016. ISSN 1613-0073
3. Wolstencroft K, Owen S, **Krebs O**, Nguyen Q, Stanford N, Golebiewski M, Weidemann A, Bittkowski M, An L, Shockley D, Snoep J, **Müller W**, and Goble C. SEEK: a systems biology data and model management platform (2015), BMC Systems Biology 2015:33. DOI: 10.1186/s12918-015-0174-y

4. Wolstencroft, K, Owen, S, Horridge, M, Jupp, S, **Krebs, O**, Snoep, J, du Preez, F, **Mueller, W**, Stevens, R, Goble, C. Stealthy annotation of experimental biology by spreadsheets (2013), Concurrency and Computation: Practice and Experience, Issue 25:4, pages 467 - 480, 2013, 10.1002/cpe.2941.

5. Wolstencroft K, Owen S, du Preez F, **Krebs O, Mueller W**, Goble CA, Snoep JL (2011) The SEEK: A Platform for Sharing Data and Models in Systems Biology, Methods in Enzymology, Volume 500: 629-655 PUBMED: 21943917

List of up to 5 relevant previous projects or activities, connected to the subject of this proposal

Müller group coordinated the data management in the BMBF-funded

- (1) **Virtual Liver Network**,
- (2) the current (2) **LiSyM** (liver systems medicine) network, the related SBEpo project.
- (3) It is now part of the transnational (3) **FAIRDOM** project that is dedicated to FAIR data management. As such it is part of (4) **ISBE**, the interim phase of the Infrastructure for Systems biology in Europe.

The group is part of standardisation initiatives, such as (5) **COMBINE**.

SDBV is coauthor of the SEEK software which will be the core of the data management.

Co-author of companion tools Rightfield and Exemplify.

Author, maintainer, curator of the SABIO-RK data base for reaction kinetics data for use in modelling.

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

HITS is hosting the FAIRDOM Hub as well as a number of openSEEK web application instances that serve as hub for other projects.

Any other supporting documents specified in the work programme for this call

Not applicable

Description of the Institution

The University Medical Center Groningen (UMCG) is one of the largest hospitals in the Netherlands and the largest employer in the Northern part of the Netherlands. More than 10,000 employees are working on providing patient care and on cutting-edge scientific research, focused on ‘healthy and active ageing’. Research at the UMCG is characterized by a combination of fundamental and patient-orientated clinical research. The interaction between these two stimulates the development of new clinical and research opportunities.

Experience and role in the project

Research in the **Section of Systems Medicine** (BMB) is focused on the (patho) physiology of mammalian metabolism, from cells to the entire body. Specific fields of interest are systems approaches to study metabolic disease, congenital disorders and cancer. The department of paediatrics, in which Section of Systems Medicine is embedded, has long standing expertise in research and diagnostics of metabolism by stable isotope-based fluxomics and mass spectrometry based metabolomics.

Oncological research at the UMCG is organized within the **Cancer Research Center Groningen (CRCG)**, in close collaboration between the Departments of Medical Oncology, Nuclear Medicine and Molecular Imaging, Surgical Oncology, Hospital Pharmacy, and Pathology (<https://www.umcg.nl/EN/Research/InstitutesProgrammes/CRCG/paginas/default.aspx>). One of the main aims of the CRCG is the realization of translational research. The goal of the **Department of Medical Oncology** is to improve the treatment of cancer patients. Main foci are the identification and characterization of novel therapeutic targets, the development of better imaging strategies and molecular biomarkers for tumour detection and patient monitoring, the increase of drug sensitivity of tumours, early clinical studies with novel therapeutics, investigation into palliative care in cancer patients, and work on the reduction of side effects of therapy in cancer survivors (healthy aging). The department has significant experience in the design and execution of both investigator driven and industry sponsored clinical trials. All staff are GCP trained and there is a dedicated protected website to ensure access to trial documents for relevant staff.

The Department of Medical Oncology has a particular focus on **breast cancer**, with regard to preclinical and clinical intervention strategies directed at invasion and metastases; as well as early clinical trials with novel anticancer agents and healthy survivorship after breast cancer. Furthermore, early translational trials are/have been performed with novel PET and SPECT tracers, developed at the UMCG, to allow in vivo visualization of molecular tumor specific targets including cancer drug targets. This environment, focused on highly translational studies, provides a fruitful basis for the MESI-STRAT project. The success of this collaboration is already evidenced by shared external grants and joint publications as well as several collaborations with research groups abroad. In this setting, expansion of translational projects towards clinical implementation is now the focus of multicenter national and international breast trials (such as the CTMM MAMMOTH and KWF/Alpe d’Huzes IMPACT project), initiated by the UMCG.

Main Tasks undertaken in the consortium

UMCG/BMB will contribute to measurements in **WP4** and related modeling in **WP5** (fluxomics). While being the coordinator, UMCG conducts project management (**WP8**), communication, dissemination and exploitation (**WP9**) tasks. For all other instances in which UMCG is mentioned in the DoA, UMCG has an advisory role without person-months.

Note in particular that the colleagues at the UMCG Oncology department are involved as advisors and offer access to four clinical trials out of 21 trials in task 7.4, without person-months. Details are given in the GA amendment request letter for the amendment as of 01 February 2019.

CV of PI and other people involved (including gender)

Prof. B.M. Bakker, PhD (F) [BMB] is a professor in medical systems biology. Bakker applies systems biology approaches to understand metabolic aberrations in inborn errors of metabolism, age-related metabolic diseases, parasites, and cancer, and exploit them for novel therapeutic options. Her group has developed specialized infrastructure to study energy metabolism, including a novel proteomics method for absolute quantification of mitochondrial proteins, stable-isotope-based fluxomics, and dynamic and

genome-scale models. Always combining computational modelling and quantitative experimentation, she has worked on different organisms and at different levels of regulation to elucidate fundamental principles of metabolic regulation. For her work on the identification of antiparasitic drug targets she received the award of the Netherlands Society for Biochemistry and Molecular Biology (NVBMB) and an NWO-'Vernieuwingsimpuls' grant. Her position as a leader in the field is acknowledged by her chairmanship of the International Study Group for Systems Biology, her membership of the board of BioSB (the Dutch research school for bioinformatics and systems biology) and the award of an NWO Centre for Systems Biology Research. Specific expertise includes: computational modeling, enzyme kinetics, metabolomics, flux analysis, metabolic control analysis, and bifurcation analysis. In the consortium she will have a bridging position between wet lab and computational modelling and she will contribute fluxomic measurements and support related metabolic modeling. She supervised 11 PhD students and 8 postdocs. She has published over 90 peer-reviewed international papers (h-index 29 in WoS, top papers with 100-380 citations).

Prof. E.G.E. de Vries MD, PhD (F) [EV] professor of Medical Oncology committed her entire career in making progress in the care for cancer patients. She actively promoted the view that a multidisciplinary approach with close interactions between the laboratory and clinic is crucial for improving prospects for cancer patients. She performs her research in parallel to her clinical duties, which enables her to translate questions emerging from clinical practice to basic research and *vice versa*. Her focus is on interdisciplinary, translational research, aiming for personalized medicine. Diagnosis and therapy of breast cancer, molecular imaging and early clinical trials are important main research interests. She has received and coordinated numerous grants, including grants from the EU, Dutch Cancer Society, Dutch public-private consortia TIPharma and CTMM. She is Academy Professor of the Royal Netherlands Academy of Arts and Sciences (KNAW), Fellow of the European Academy of Cancer Sciences and a Member of the Governing Body of the European Academy of Cancer Sciences. In 2009 she received the European Society of Medical Oncology (ESMO) award for her outstanding contribution to the development of oncology in Europe, and in 2014 she received the Professor Muntendam award from the Dutch Cancer Society. She supervised 106 PhD students and has published over 800 scientific papers.

C. Schröder MD, PhD (F) [CSC] is a medical oncologist, with a focus on breast cancer, at the department of Medical Oncology of the UMCG. She conducts large scale multi-center clinical breast cancer trials within the Netherlands, and has her own preclinical research line regarding the breast cancer microenvironment. Schröder's research focus is to explore novel rational treatment options to enhance therapeutic efficacy and personalized medicine, in interdisciplinary, translational research. This has led to breast cancer research regarding preclinical and clinical intervention strategies directed at the breast cancer microenvironment and metastases, early clinical trials with novel anticancer agents, as well as large scale registration- and translational trials for rare subgroups including inflammatory and **male breast cancer**. It has also led to preclinical and clinical molecular imaging studies, with regard to visualization of tumor specific targets including cancer drug targets. She has procured funding for her research efforts from several sources including the Clinical Research Award from the Dutch Cancer Society for her grant application: Molecular imaging to guide targeting the breast cancer microenvironment (2010). She is member of several institutional and (international) boards including the **Dutch Male Breast Cancer Consortium (chair)**, the **scientific advisory board of Dutch Cancer Society**, and the **Medical Ethical Committee of the UMCG**. She is involved in **national breast cancer guideline development**. Her research as PI is embedded in the CRCG, the Netherlands. She is currently supervising 10 PhD projects and has published over 60 papers in international peer-reviewed journals. She is involved in national and international collaboration networks, including Institute Jules Bordet, Brussels, Belgium and the Dana-Farber Cancer Institute, Boston, MA, U.S.A. She is a member of **international research consortia regarding male breast cancer and inflammatory breast cancer**.

Prof. S. de Jong PhD (M) [SJ], Professor of Preclinical and Translational Oncology. He coordinates several courses in Medical and Biomedical Sciences programs. He has given many lectures on platinum resistance and apoptosis being an internationally recognized expert in this field. He has published over 150 peer-reviewed papers (5200 citations and an h-index of 42). His research is focused on exploring signaling pathways to enhance therapeutic efficacy of cancer treatment using cell line models, xenograft models and ex-vivo patient samples. He has extensive expertise in establishing **human cancer models**

in mice and living ex-vivo patient tumors (PDX models) to test efficacy of novel signaling pathway targeted drugs. He is a program leader of the CRCG and board member of the **EurOPDX consortium**. He has been involved and managed several (inter)national projects from the EU, Ireland Enterprise, Dutch Cancer Society, TI Pharma, and pharmaceutical companies. He has supervised 29 (MD)PhD students. He is currently supervising 8 PhD students, 2 technicians and 1 postdoctoral researcher, supported with grants from the Dutch Cancer Society and (pharmaceutical) companies (Synthon, PerkinElmer, NanoFM and Roche). He is team member within the ERC Advanced grant OnQview.

M. Jalving MD, PhD (F) [HJ] is a medical oncologist, involved in patient care and teaching and with a strong research interest in understanding and targeting **metabolism in cancer**. She received a Dutch Cancer Society and a Cancer Research UK grant for a clinical research fellowship at the Weatherall Institute of Molecular medicine in Oxford in 2009. In 2010, she received an Msc from the University of Oxford on **experimental drug trial design** and specializes in **early phase clinical trials**. She supervises 4 PhD students and has published 16 scientific papers.

R.S.N. Fehrman MD, PhD (M) [RF], medical oncologist and bio-informatician at the department of Medical Oncology of the UMCG. In addition to his training as a medical doctor, he completed one full year of Mathematics and Computer Science, after which he continued to obtain his MSc degree in Cognitive Science and Engineering. He is a principal investigator at the CRCG. His research focusses on **integrative omics approaches** to identify driver genetic alterations, genes and biological pathways that are relevant for the pathophysiological behavior and treatment response of tumors and rapidly translate these findings to clinical practice. In 2017, he was selected for a Young Leader's Fellowship Grant from the European Cancer Organisation (ECCO). In 2015 he received a Veni grant form NWO/ZonMW (Netherlands Organization for Scientific Research. In 2013, he received a large personal Dutch Cancer Society grant that enabled him to build his own research group. Currently, he supervises 9 PhD students and has published 42 scientific papers. In addition, he is co-principal investigator within 2 large scale projects focusing on personalized medicine for immunotherapy in the oncological setting.

5 relevant publications/products/services/software/other achievements relevant to the call content: § denotes corresponding authorships

1. Martines, AMF, van Eunen, K, Reijngoud, DJ, & **Bakker, BM**. The promiscuous enzyme medium-chain 3-ketoacyl-CoA thiolase triggers a vicious cycle in fatty-acid beta-oxidation. PLOS Comput. Biol. 2017; 13(4), [e1005461]. (2017)doi: 10.1371/journal.pcbi.1005461
2. **Byrne AT, Alférez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, Budinská E, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, **de Jong S**, Jonkers J, Kemper K, Lanfrancone L, Mælandsmo GM, Marangoni E, Marine JC, Medico E, Norum JH, Palmer HG, Peper DS, Pelicci PG, **Piris-Gimenez A**, Roman-Roman S, Rueda OM, Seoane J, **Serra V**, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L. Interrogating open issues in cancer precision medicine with patient-derived xenografts. Nat Rev Cancer. 2017 Jan 20. doi: 10.1038/nrc.2016.140.
3. van Eunen, K, Volker-Touw, CML., Gerding, A, Bleeker, A, Wolters, JC, Rijt, van, W, ... **Bakker, BM**. Living on the edge: substrate competition explains loss of robustness in mitochondrial fatty-acid oxidation disorders. BMC Biology. 2016; 14(1), [107]. DOI: 10.1186/s12915-016-0327-5
4. Wolters, JC, Ciapaite, J, van Eunen, K, Niezen-Koning, KE, Matton, A, Porte, RJ, Horvatovich, P, **Bakker, BM**, Bischoff, R & Permentier, HP. Translational Targeted Proteomics Profiling of Mitochondrial Energy Metabolic Pathways in Mouse and Human Samples. J. Proteome Res.2016; 15(9), 3204-3213.

5. **Heberle, AM, Prentzell, MT, Van Eunen, K, **Bakker, BM**, Grellscheid, SN, & Thedieck, K. Molecular mechanisms of mTOR regulation by stress. Mol. Cell. Proteomics. 2015; 2(2), e970489. DOI: 10.4161/23723548.2014.970489

List of up to 5 relevant previous projects or activities, connected to the subject of this proposal

1. **BMB, KT and SG are elected members of the International Scientific Advisory Board of the **International Study Group for Systems Biology (ISGSB)**
2. BMB is board member and co-founder of BioSB, the **Dutch Research School for Bioinformatics and Systems Biology** (www.biosb.nl, 2013 - present)
3. CSC is a member of the **scientific advisory board of the Dutch Pink Ribbon Foundation**, initiator and **chair of the Dutch Male Breast Cancer Consortium**, steering board member of the **EORTC-BIG Male Breast Cancer Consortium**.
4. **Together with VHO/VIS, SJ is a **board member of the EurOPDX consortium**, and has obtained a grant from Synthon (2014- 2017): Efficacy of SYD985 in targeting TICs/CSCs in breast cancer cells with variable Her2 expression.

Description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work

- The framework for proteomic and metabolomic analyses which UMCG contributes to MESI-STRAT is offered by the **Interfaculty mass spectrometry center (IMSC)**, located in the same building as the labs of BMB, and the **Lab of Clinical Chemistry**/ Dept. of Pediatrics, hosting the MS instrumentation, infrastructure and expertise to smoothly conduct the tasks within MESI-STRAT.
- The **Systems Biology Centre for Energy Metabolism and Ageing (SBC-EMA**, co-founded by BMB) nucleates expertise on computational modeling strategies and ¹³C fluxomics, and has a strong collaboration with the IMSC (above). Hence, proteomics and metabolomics strategies and related modeling techniques are already tailored to the pathways relevant for MESI-STRAT.
- Embedded within the department of medical oncology is a clinical trial phase 1 unit with dedicated doctors, research nurses and data managers. Three staff members including dr M Jalving and prof. EGE de Vries are directly involved. All staff are GCP trained and there is a dedicated protected website to ensure access to trial documents for relevant staff. Extensive experience in sample collection and processing is available
- Strong collaboration with the **Genomics Coordination Centre** which has a team of ~25 project leaders, programmers, postdocs and PhD students on a mission to research, develop and support next-generation life sciences with database and analysis infrastructures. It provides bioinformatic services to research groups in the UMCG, University of Groningen (RUG)

Any other supporting documents specified in the work programme for this call
Not applicable.

4.2. Third parties involved in the project (including use of third party resources)

Not applicable for partners 1, and 3-14.

Partner 2 (PATH):

Does the participant plan to subcontract certain tasks (please note that core tasks of the project should not be sub-contracted)	Yes
<i>If yes, please describe and justify the tasks to be subcontracted</i> Partner 2 (PATH) will subcontract the collection of blood and urine samples of stable ER+BC patients as described in task 6.2 (WP6) and ER+BC patients before and after ending ET, as described in task 7.3 (WP7). The clinical centers obtaining these samples need to be fully certified BC centers and need to be in close proximity to the PATH cohort to ensure effective follow-up. The costs (113.300 Euros) arise for staff time and consumables to take, label and transport the samples to the PATH biobank. The subcontracting will be carried out ensuring the best value for money and avoiding any conflict of interests.	
Does the participant envisage that part of its work is performed by linked third parties ¹	No
<i>If yes, please describe the third party, the link of the participant to the third party, and describe and justify the foreseen tasks to be performed by the third party</i>	
Does the participant envisage the use of contributions in kind provided by third parties (Articles 11 and 12 of the General Model Grant Agreement)	No
<i>If yes, please describe the third party and their contributions</i>	

4.3. Financial support to third parties

See 4.2

Financial support in the form of a grant awarded after a call for proposals

Not applicable.

Financial support in the form of a prize

Not applicable.

¹ A third party that is an affiliated entity or has a legal link to a participant implying a collaboration not limited to the action. (Article 14 of the Model Grant Agreement).

Section 5: Ethics and Security

5.1 Ethics

Ethical considerations are essential for the success of MESI-STRAT. Not only regarding areas, such as human subjects protection and animal care, for which MESI-STRAT partners are obliged to file ethics committees/animal welfare proposals, but also more generally regarding topics such as honesty, objectivity, integrity, carefulness, openness, respect for intellectual property, responsible publication, responsible mentoring, non-discrimination, respect for colleagues and social responsibility. In our consortium and its boards we will strive to always promote and strengthen these ethical principles. More specifically, openness to the outside will be enabled by our data management plan and our DEC committee, open communication within MESI-STRAT will be promoted by our management plan (WP8) and the strategic board. Respect of intellectual property will be secured by our IP management plan and the DEC (WP8, WP9, section2, Impact). Social responsibility will be implemented through the patient organization PATH as co-coordinator of MESI-STRAT, the patient organization Europa Donna in our IAB as well as the German Cancer Information Service (KID) at DKFZ, which through the International Cancer Information Service Group (ICISG), closely interacts with other European colleagues delivering cancer information.

Below we will outline how we will deal with the ethical issues outlined in the ethical self-assessment:

5.1.1 Human embryos & fetuses

Not applicable, as no research on human embryos & fetuses will be carried out in MESI-STRAT

5.1.2 Human beings

The applicants will adhere to ethical principles, applicable international, EU and national law and country-specific ethics legislation.

Two of our clinical partners, Dr. Sarah Schott (SS) from UKL-HD and Dr. Carolien Schröder (CSC) from UMCG are members of the ethics committees of their institutions.

MESI-STRAT will perform clinical studies on ER+ BC patients.

The copies of the ethics approvals for these clinical studies are provided in the optional ethics supporting documents Annex 3.2.

For the convenience of the reviewers we reproduce here Table 2 from Section 1.3.b. Specifically, the MESI-STRAT trials will encompass the following studies:

MESI-STRAT clinical and preclinical trials. Trials without drug treatments are grouped into WP6, and trials with drug treatments into WP7. *The clinical study number corresponds to the numbers in the Annex for Essential Information on Clinical Studies, where all study details are provided. The trial numbers correspond to the task numbers in WPs 6 and 7.

Study category	Study type	Clinical Study N° & Trial #*	Short name	Study title	Study design
Trials without drug treatments: WP6	clinical	Study No 1 WP6: Trial 6.1	Risk Detection Trial	Identification and validation of MESI marker panels discriminating high risk vs. low risk ER+BC patient subgroups	Samples and clinical data from PATH biobank
		Study No 2 WP6: Trial 6.2	Relapse Detection Trial	Identification and validation of MESI marker panels detecting ER+BC patient subgroups with relapse	Samples and clinical data from PATH biobank and clinical trials associated with MESI-STRAT
		Study No 3 WP6: Trial 6.3	Relapse Prediction Trial	Retrospective identification and validation of MESI marker panels at diagnosis predicting patient subgroups with future relapse or stable disease	Samples and clinical data from PATH biobank
		Study No 4 WP6: Trial 6.4	Tissues for Preclinical Trials	Screening and collection of ER+BC tissues with subgroup specific MESI marker panels for preclinical models (PDX, bioreactor)	Samples obtained in the frame of ongoing clinical studies at VHIO and UKL-HD
Trials with drug treatments: WP7	preclinical	WP6: Task 6.5	Preclinical Model - Subgroup Assignment	Identification of primary cell and PDX models representing novel ER+BC subgroups defined by differential MESI marker expression	Samples and data from pre-clinical trials at VHIO, DKFZ and DDI
		WP7: Task 7.1	Preclinical Intervention Trials	Validation of predictive MESI marker panels in primary cell cultures, cultured primary tissues, and pre-clinical interventional trials in PDX models	Samples and data from pre-clinical trials at VHIO, DDI, DKFZ and UIBK
	clinical	Study No 5 WP7: Trial 7.2	WOO Trial	Prospective window of opportunity trial 2 weeks neoadjuvant Anastrozole in post-menopausal women with ER+BC	Interventional clinical trial performed at UKL-HD
		Study No 6 WP7: Trial 7.3	ET Termination Trial	Analysis of longitudinally collected serum and urine from ER+BC patients before and after termination of ET	Prospective clinical trial by PATH, collecting samples/clinical data from patients on and off ET
		Study No 7 WP7: Trial 7.4	Intervention Validation Trials	Clinically validate predictive MESI-models and marker panels for targeted drug interventions	21 clinical trials by partners and collaborators; incl. 3 male cohorts
		WP7: Task 7.5	IIT / Umbrella Trial Design	Design own IIT and umbrella trials, in which ER+BC patients will be stratified to different therapies by MESI-marker panels	For future impact, UKL-HD, UMCG, VHIO will design and initiate IIT & umbrella trials

The numbering of the clinical studies is according to the Annex “Essential information for clinical studies”.

Clinical studies No. 1 and 3

Risk Detection Trial:

Identification and validation of MESI marker panels discriminating high risk vs. low risk ER+BC patient subgroups (Trial 6.1, WP6)

and

Relapse Prediction Trial:

Retrospective identification and validation of MESI marker panels at diagnosis predicting patient subgroups with future relapse or stable disease (Trial 6.3, WP6)

Approval from the ethics committee of the University of Bonn, Germany (225/06, see Annex 3.2.1) has been obtained by PATH for the collection and analysis of tumor tissue and serum at diagnosis. This study analyses biological samples that are present at PATH and for which informed consent for the planned analyses has been obtained.

As an example, the informed consent and patient information document from PATH is provided in Annex 3.3a.

If necessary, samples from the GEKKO study can be used to complement the PATH cohort samples at diagnosis. GEKKO encompasses 190 samples from BC patients and is willing to share these samples for the measurement of MESI marker panels (see letter). Approval from the ethics committee of the University of Heidelberg, Germany (S-392/2015, see Annex 3.2.1) has been obtained for the collection, storage and analysis of biological fluids, including serum at diagnosis

Clinical Study No. 2

Relapse Detection Trial:

Identification and validation of MESI marker panels detecting ER+BC patient subgroups with relapse (Trial 6.2, WP6)

Prospectively collected sera of stable patients from the PATH cohort sera collected from matched ER+ BC patients at relapse/distant metastasis in the frame of studies (appropriate baseline samples from the IMPACT, PRAEGNANT or Everolimus/Exemestane studies) will be employed. An approval from the ethics committee of the University of Heidelberg (S-496/2014, see Annex 3.2.2) is in place for the collection of biological fluids and the analysis of tumor tissue.

As an example, the informed consent and patient information document is provided in Annex 3.3b.

An application for an ethics approval for the prospective collection of blood and urine for patients from the PATH cohort is currently being prepared by PATH. Ethics votes for the IMPACT study (METc 2013/146, see Annex 3.2.3), the Everolimus /Exemestane study (2013.406, see Annex 3.2.4) and the PRAEGNANT (S-391/2014, see Annex 3.2.5) study are in place.

For the sera collection, the amount of blood per donation will not exceed national and local regulations or the amount specified in the informed consent leaflets.

Clinical study No. 4

Tissues for Preclinical Trials:

Screening and collection of ER+BC tissues with subgroup specific MESI marker panels for preclinical models (PDX, bioreactor) (Trial 6.4, WP6),

See also **5.1.3 Human cells and tissues** in this document.

In the frame of ongoing clinical studies at VHIO and UKL-HD, ER+ BC cells and tissues will be collected for preclinical models.

Specifically,

- *Primary cells established from ER+ BC patient tissues*

If necessary primary ER+ BC from fresh BC tissue will be established in the course of MESI-STRAT this will only be done after an appropriate ethics approval is in place and after free and fully informed consent of the donors.

- *Primary ER+ BC tissues cultured in perfusion-based bioreactors*

Primary ER+ BC tissues will be cultured in perfusion-based bioreactors for the testing of targeted therapies after appropriate ethics approvals are in place and after free and fully informed consent of the donors. This is covered by the ethics approval S-496/2014, see Annex 3.2.2 for the collection of biological fluids and tumor tissue for biomarker discovery (DNA, RNA, proteins and metabolites in cells, tissues, serum, plasma, urine, CSF and saliva of healthy controls and cancer patients).

- *Use of human ER+ BC cells and tissues for preclinical trials*

Human ER+BC tissue will be used for the generation of PDX models at VHIO, this is covered by the ethics approval PR(IR)53/2010, see Annex 3.2.11, which allows the investigation of the “Tumorigenesis and study drug sensitivity in xenoimplant models derived from breast cancer biopsies from patients in active treatment”

Clinical study No. 5

WOO trial:

Prospective Window of opportunity trial 2 weeks neoadjuvant Anastrozole in Postmenopausal Women with ER+ BC. (Trial 7.2, WP7)

This interventional clinical trial will be a single center, open-label, non-randomized prospective investigator driven Window of opportunity study performed at UKL-HD.

The administered drug Anastrozole is a standard of care therapy for postmenopausal women. For ethical reasons only women that will receive an aromatase inhibitor after surgery will be included in the WOO trial. Therefore only the sequence of aromatase inhibitor application will be altered as Anastrozole will be given for 2 weeks before routine surgery as opposed to its regular adjuvant application after surgery. The trial medication Anastrozole is a standard of care therapy for postmenopausal women. For ethical reasons only women that would receive an aromatase inhibitor after surgery will be included in the WOO trial. Anastrozole is well known and approved by German regulatory authorities for the treatment of postmenopausal ER+ BC patients. Due to its safety profile we expect only few serious adverse events (SAEs) to occur. All relevant safety information can be found in the Summary of Product Characteristics (SmPC). Prof. Dr. Andreas Schneeweiss from UKL-HD is experienced in neoadjuvant administration of Anastrozole, as Anastrozole is already administered in the frame of the neoMONARCH study for two weeks in a neoadjuvant setting in combination with Abemaciclib.

For the sera collection, the amount of blood per donation will not exceed national and local regulations or the amount specified in the informed consent leaflets.

Dr. Sarah Schott and Prof. Dr. Andreas Schneeweiss from UKL-HD together with the clinical research organisation (CRO) KKS, which belongs to UKL-HD, will apply for regulatory and ethical approvals - ensuring that all

regulatory and ethical requirements will have been met before the clinical trial is initiated (i.e. approval by the regulatory authority, the independent ethics committee, and other appropriate authorities (data protection, etc.), and registration in clinical databases (National Regulatory Agencies, EudraCT and clinicaltrials.gov).

The patient information leaflet, informed consent and full study protocol will be developed in accordance with the guidelines and recommendations of Good Clinical Practice (GCP) and the Declaration of Helsinki, guiding physicians in biomedical research involving human subjects. For the design, patient information brochure and ethical aspects we will in addition work closely together with trained specialized patient advocates and ethicists. The informed consent form will be signed, witnessed and dated in duplicate. We will retain an original signed informed consent form in the investigator file of the study.

The clinical trial will be a single center, investigator driven study at UKL-HD. Therefore UKL-HD will be the sponsor and will take care of the insurance for the participating patients. Dedicated MDs will take care of these patients. The PI and all other MDs involved will have completed the specific GCP training for clinical scientists, which covers rules and organization for clinical research.

UKL-HD will be responsible for (i) study monitoring, (ii) communication with regulatory/health authorities and ethics committees, and (iii) monitoring and declaring of (S)AEs. The CRO KKS that belongs to and supports UKL-HD will conduct the data management.

Monitoring:

The study's quality assurance management is based on a risk-based approach. According to ICH/GCP guidelines, the sponsor will ensure that the trial is adequately monitored. Data monitoring will protect the rights and well-being of patients, ensure that reported trial data are accurate, complete, and verifiable from source documents, and that the trial is being conducted in compliance with the currently approved protocol/amendment(s), GCP, and the applicable regulatory requirements.

On-site and remote monitoring will be performed by UKL-HD. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

Safety assessment and management:

Adverse events (AEs) will be ascertained by the investigators using non-leading questions, noted as spontaneously reported by the patients to the medical staff or observed during any measurements on all study days. The observation period begins with the first administration of the IMP (before the first administration of the IMP: medical history) and ends with the last study visit. AEs will be documented in the patient file and in the CRF. All subjects who present AEs, whether considered associated with the use of the trial medication or not, will be monitored by the responsible investigator to determine their outcome; this applies to withdrawals too.

AEs and SAEs that are on-going at the time of death are considered not resolved or resolving.

All SAEs and their relevance for the benefit/risk assessment of the study will be evaluated continuously during the study and for the final report. All SAEs will be documented in the "Serious Adverse Event" form.

All SAEs must be reported by the investigator Sponsor and the responsible Safety Officer at the KKS Heidelberg within 24 hours after the SAE becomes known using the "Serious Adverse Event" form. The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the trial medication.

SUSARs are to be reported to the responsible ethics committees, the competent authority and to all participating investigators. All SAEs will be subject to a second assessment by a designated person, who will be independent from the reporting investigator. The second assessor will fill out a 'Second Assessment Form' for each SAE and send it back per fax to the responsible person at the KKS Heidelberg within 48 hours.

Data management:

An eCRF will be developed in English for recording all the demographic and clinical data in the study centre online. The eCRF will be developed on a designated platform ensuring appropriate read and write access for the study centre. Patients will be identified by a study-specific subject number (pseudonymization). Entries will be checked for consistency by the system. Additionally, the data will be monitored regularly, in order to avoid missing data.

Sample management:

Sample management will be performed in collaboration with the NCT liquid biobank. As a biobank focused on high-quality sample handling and storage as well as management processes ensuring that samples are prepared and stored in consistent conditions, the NCT liquid biobank will provide the infrastructure and support for quality-

assured handling and storage of the samples collected in the frame of the WOO trial in the MESI-STRAT project (see letter).

As the sponsor UKL-HD will maintain close contact with regulatory authorities and the independent ethics committee throughout the duration of the clinical trial and until the end of the study.

Clinical study No. 6

ET Termination trial:

Analysis of longitudinally collected serum and urine from ER+ BC patients before and after termination of ET (Trial 7.3, WP7)

An approval from the ethics committee of the University of Bonn, Germany (225/06) has been obtained by PATH for the collection and analysis of tumor tissue and serum at diagnosis. An application for an ethics approval for the prospective collection of blood and urine for patients from the PATH cohort is currently being prepared by PATH.

For the sera collection, the amount of blood per donation will not exceed national and local regulations or the amount specified in the informed consent leaflets.

Clinical study No. 7

Intervention Validation Trials:

Clinically validate predictive MESI-models and marker panels for targeted drug interventions (Trial 7.4, WP7)

Clinical studies in ER+BC present several challenges including the long time to relapse, the low percentage of relapsing patients, and the risk for relapse remaining constant over two decades. Hence, trials with endpoints such as progression free survival are long-term efforts that cannot be carried out within the typical budget and duration of a H2020 project.

One of the ways how MESI-STRAT overcomes these limitations is by taking advantage of existing and ongoing trials and analyzing MESI-models and marker panels in patients receiving targeted drug interventions.

MESI-STRAT will investigate the effects of targeted drug interventions on MESI marker panels and their association with drug response in human ER+ BC patients using sera and urine obtained from clinical studies. If enough patients of a MESI-marker defined ER+BC subgroup predicted to respond to a specific drug intervention are available in a clinical trial, the predictive power of the MESI marker panel to stratify patients to the targeted drug intervention will be validated by analyzing if the patients of this subgroup respond better to this drug than the rest of the study population.

In the frame of translational analyses of samples obtained from clinical studies/standard of care drug treatments performed by our clinical partners and clinical collaborators (see letters) serum and urine will be analysed for MESI networks and marker panels in agreement with the PIs/board of these studies or in the case of standard drug treatments after informed consent and in the presence of an ethics vote for analysis of these markers in serum and urine from the patients (present e.g., for UKL-HD, S-496/2014). If the informed consent and ethics vote of a clinical study encompass our analyses, no further ethics approval for the analyses is necessary. If this is not the case an addendum to the ethics vote will be applied for at the responsible ethics committee and the MESI-STRAT analyses will be included in the informed consent form.

The ethics approvals of the studies are provided in Annex 3.

For the sera collection, the amount of blood per donation will not exceed national and local regulations or the amount specified in the informed consent leaflets.

Study	Patient/tumor characteristics	Treatment	Center	Ethics vote
PRAEGNANT	MBC or inoperable loco-regional disease	Non-specific SoC medications	UKL-HD	S-391/2014
Ribecca	HR+ HER2- locally advanced BC or MBC	Cdk 4/6 inhibitor Ribociclib in combination with Letrozole	UKL-HD	261_16Az
Parcifal	ER+ HER2- MBC	Fulvestrant + Cdk4/6 inhibitor Palbociclib vs Letrozole + Palbociclib	UKL-HD VHIO	AFmu-290/2015
DETECT V/ CHEVENDO	HR+ HER2+ MBC	Chemo vs. ET + Trastuzumab/Pertuzumab	UKL-HD	113/15
IMPACT	MBC	Non-specific SoC medications	UMCG	METc 2013/146
FDHT PET + Bi-calutamide	MBC	bicalutamide	UMCG	METc 2015/396
POSEIDON	HR+ HER2- MBC	Tamoxifen + Isoform selective Pi3K inhibitor GDC-0032 vs. Tamoxifen alone	VHIO	M14POS / POSEIDON
Everolimus /Ex-emestane	postmenopausal patients with advanced MBC who have progressed on Anastrozole or Letrozole	Everolimus + Exemestane	E. Boven; VUMC (NCT02109913)	2013.406
Lilly I3Y-MC-JPCG	previously treated HR+ HER2- MBC	Abemaciclib + Tamoxifen vs. Abemaciclib alone	VHIO	with Eli Lilly
GEICAM 2015-07 (C31006) TAKEDA	ER+ HER2- advanced or MBC that has progressed during or after Aromatase Inhibitor therapy	FIIMLN0128 (A TORC1/2 Inhibitor) + Fulvestrant	VHIO	with Takeda
D3610C00001	advanced solid malignancies	Akt inhibitor AZD5363	VHIO	with Astra-Zeneca
Bayer 16298	HER2- MBC subjects with bone metastases treated with Hormonal Treatment background therapy	Placebo-controlled trial of Radium-223 Dichloride vs. Placebo	VHIO	with Bayer
Bayer 17096	HER2- MBC subjects with bone metastases treated with Hormonal Treatment background therapy	Placebo-controlled trial of Radium-223 Dichloride + Exemestane and Everolimus vs. Placebo + Exemestane and Everolimus	VHIO	with Bayer
PUMA-NER-5201	solid tumors with activating HER2, HER3 or EGFR mutations or with EGFR gene amplification	Tyrosine kinase inhibitor Neratinib	VHIO	with PUMA Biotechnology
PMT4979g	HR+ locally advanced BC or MBC	isoform selective Pi3K inhibitor taselisib (GDC-0032)	VHIO	with Roche
Monaleesa-2	advanced BC	Cdk 4/6 inhibitor Ribociclib + Letrozole vs. Letrozole alone	samples supplied by Novartis (application initiated)	with Novartis
Padma	MBC	Palbociclib + ET vs. Chemo	UKL-HD, study in preparation	in preparation
Dutch CDK4/6 Trial	adjuvant treatment or at progression	Cdk4/6 Inhibitor + ET versus Cdk4/6 at progression	UMCG, VUMC in preparation	in preparation

In addition, we will validate whether MESI-models and marker panels predictive in female ER+ BC also apply to male ER+ BC. Using male ER+ BC samples from two clinical trials on male BC conducted at UMCG and samples of BRCA mutated male BC patients available in the NCT tissue bank of UKL-HD we will validate if MESI models and marker panels predictive in female ER+ BC also apply to male ER+ BC.

Study	Patient/tumor characteristics	Samples	Center	Ethics vote
Male breast cancer: prospective into perspective	male BC	200 serum/plasma samples and fresh frozen BC tissues prospectively collected from males	UMCG	METc 2013/291
MALE BREAST CANCER study	male BC	800 FFPE BC samples retrospectively collected from males	UMCG	MEC-2011-015
BRCA-mutated male BC cohort	BRCA-mutated male BC cohort	clinical data from 137 male BC patients with BRCA mutations	UKL-HD	samples in NCT tissue bank

Guidance documents

The applicants certify that they will adhere strictly to all existing ethical and safety provisions of the individual states and of the EU. The execution of the grant will conform to relevant EU and national legislation including:

- the Charter of **Fundamental Rights** of the EU.
- **Helsinki Declaration** as developed by the World Medical Association in its latest version.
- the **GCP Directive 2005/28/EC** of 8 April 2005 of the European Parliament and of the Council with principles and detailed guidelines for GCP with regard to conducting clinical trials of medicinal products for human use.
- the principles laid down in the **Oviedo Bioethics Convention**
- **EU Regulation No 536/2014** on clinical trials on medicinal products for human use

5.1.3 Human cells or tissues

MESI-STRAT will use human cells and tissues:

1) *Cell lines*

Cell lines such as MCF7, ZR-75-1, BT474 and T47D will be obtained from commercial sources such as ATCC.

2) *Primary cells established from ER+ BC patient tissues*

If necessary primary ER+ BC from fresh BC tissue will be established in the course of MESI-STRAT this will only be done after an appropriate ethics approval is in place and after free and fully informed consent of the donors.

3) *Primary ER+ BC tissues cultured in perfusion-based bioreactors*

Primary ER+ BC tissues will be cultured in perfusion-based bioreactors for the testing of targeted therapies after appropriate ethics approvals are in place and after free and fully informed consent of the donors.

4) *Use of human ER+ BC cells and tissues for preclinical studies*

Human ER+BC tissue will be used for the generation of PDX models at VHIO, this is covered by the ethics approval PR(IR)53/2010, see Annex 3.2.11, which allows the investigation of the “Tumorigenesis and study drug sensitivity in xenoimplant models derived from breast cancer biopsies from patients in active treatment”

5) *Analysis of ER+ BC tissues obtained from PATH biobank*

An approval from the ethics committee of the University of Bonn, Germany (225/06, see Annex 3.2.1) has been obtained by PATH for the collection and analysis of tumor tissue at diagnosis. This study will analyse tissues that are present at PATH and for which informed consent for the planned analyses has been obtained.

The applicants will keep track of the **origin** of the cells and tissues they use, produce or collect and obtain the necessary accreditation/designation/authorisation/licensing for using, producing or collecting the cells or tissues as well as the free and fully informed consent of the donors.

The applicants will adhere to ethical principles, applicable international, EU and national law. All analyses/experiments have to be performed under country-specific ethics legislation.

5.1.4 Personal data

The personal data relevant to MESI-STRAT is mostly clinical data.

The data will be pseudonymized, patient identity will be protected by study-specific, unique patient codes.

The MESI repository for clinical data will be set up at the central DataCenter of the IT Core Facility of the DKFZ, which complies with all regulations of data safety necessary for storage of personal data and the protection of confidentiality of individual records. The access to these rooms is protected by the use of an intrusion detection system, the protection of building trays, the use of an automatic access control system, the use of motion detectors and video control. As a supplementary organizational measure, there is a key regulation for the access to this DataCenter agreed with the data protection officer of the DKFZ. In December 2016, the DataCenter has been certified by TÜV-IT (Trusted Site Infrastructure Levels 1 and 2). The data is stored on hard disks and tapes of central file servers located in the central DataCenter of the DKFZ. The data is stored on self-encrypting data carriers. If a hard disk is removed from the storage system, the key for the hard disk is automatically destroyed after a short period of time. For backup and archiving data, the IT Core Facility runs a large robot system. Data stored on central file servers is automatically backed up and can be restored after a technical defect or accidental deletion within specified deadlines.

Only authorized users can access the data. The authorization is managed in the central Active Directory of the DKFZ. The assignment or modification of the access rights for the individual users takes place exclusively on written request, which is signed by the superior. Access attempts are logged, both successful and unsuccessful. Managing clinical data at the DKFZ is according to the law on the protection of personal data (Landesdatenschutzgesetz – LDSG-BW). Subsequently, for any patient related data (both clinical and experimentally generated) an additional data security application must be filed for every project (Verfahrensmeldung), for both in house and consortia projects.

The DKFZ PI applying must detail the following sections as clearly as possible:

1. All types of data that will be used in the course of the study (contact data of the collaborators as applicable, pseudonymised clinical data, generated data ...etc.)
2. A list of all participating individuals that will have access to this data and the level access assigned to each.
3. Proof of ethical approval to conduct this study by all participating partners.
4. Copies of informed consents that cover all forms of data acquisition and generation required for this study.
5. Required IT resources for data storage and processing.
6. Data type and required time for storage after the completion of the project.

Upon application submission, approval of the DKFZ ITCF department on the suggested technical requirements is needed, followed by the approval of the data security officers at DKFZ. Further monitoring and inspection of good conduct is carried out by the data security officers during the course of the project. DKFZ IT administrators ensure the security of the data as outlined above.

Guidance documents

The applicants will adhere to ethical principles, applicable international, EU (in particular, EU Directive 95/46/EC and the new General Data Protection Regulation No 2016/679, which will apply from 25 May 2018), national law and country-specific ethics legislation as well as the free and fully informed consent of the persons concerned ('data subjects').

5.1.5. Animals

Research on animals:

The project involves in vivo experiments in mice. **No** non-human primates, dogs, cats, guinea pigs, rabbits will be used. With regard to the small animal assays, all procedures will be cleared by local and national ethics committees and performed as authorised by the appropriate national laws and regulations, in compliance with EC Directive 86/609 and its implementation in national legislation. All institutional, national and EU regulations, guidelines and legal requirements are fully met with respect to animal protection. In accordance with the Amsterdam protocol on animal protection and welfare, animal experiments will be replaced with alternatives wherever possible and suffering of animals will be avoided or kept to a minimum.

The research on animals will be performed as part of WP6 (task 6.4) and WP7 (task 7.1) at VHIO and DDI.

The use of experimental animals is essential for the establishment of in vivo cancer xenograft models, which are needed for the propagation of tumor material and for the validation of therapeutic strategies. All proposed strategies to be tested in vivo will be preselected by thorough in vitro screening using cell culture systems and other assays as far as is possible. Selection meetings with all participants will ensure that the expertise of the whole consortium certifies that only the most promising strategies are further tested in vivo.

Reduction/Replacement/Refinement

The following principles will be respected:

- it is recognised that laboratory animals not only have an instrumental value, but also an intrinsic value in themselves, which must be respected. Animals must always be treated as sentient creatures.
- while accepting the need for animal use for the advancement of scientific knowledge and for human and animal health and well-being, the consortium strongly endorses the principles of the “Three Rs”. This means that exhaustive efforts will be made to replace the use of live animals by non-animal alternatives, to reduce the number of animals used in experiments to the minimum that is required for obtaining meaningful results and to refine procedures, so that the degree of suffering is minimised. Specifically, to limit the number of animals as much as possible without compromising scientific value, we will incorporate cultivation of primary 3D cell cultures and cultivation of freshly excised human ER+ BC tissue in perfusion-based bioreactors developed for tissue engineering purposes, which successfully maintain viable tumor, immune and stromal cells in ER+ BC tissues for up to 21 days.
- animal use is subject to independent expert review, for both scientific and animal welfare considerations.
- investigators assume that procedures that would cause pain in humans also cause pain in other vertebrates, unless there is evidence to the contrary. Procedures that may cause more than momentary or minimal pain or distress in animals are performed, where appropriate, with sedation, analgesia, anaesthesia or any other suitable mean to reduce pain or distress, in accordance with accepted veterinary practice.
- the best practical living conditions are maintained for animals kept for research purposes. The care and health monitoring of animals is under the supervision of veterinarians or specialists in the field of laboratory animal science; animals will be sacrificed at the end of the procedures.
- investigators and other personnel involved in the design and conduct of animal-based experiments are adequately educated and trained.

Animals are sacrificed by intraperitoneal injection of anaesthetic. Procedures are adopted to ensure that the amount of suffering to the animals is minimised and their welfare is protected as far as possible (e.g. improvements in technique, application of humane endpoints, environmental enrichment). Tumor bearing animals reach endpoints when tumour weight exceeds 10% of body weight, animals lose body weight >15% or show the first signs of suffering from systemic disease, i.e. hind limb paralysis or reduced food uptake.

VHIO and DDI have a licence to perform animal experiments in fully equipped central animal facilities. They adhere to the guidelines applicable to the care and the treatment of animals used in laboratory work as outlined by the Spanish and Belgian governments, respectively. A veterinarian or other expert supervises the well-being of experimental animals. At both VHIO and DDI, animal welfare officers are appointed. These officers give advice

on new applications, provide laboratory animal education, advise researchers on the design and performance of animal experiments, and coordinate the registration of laboratory animals, animal experiments, and persons involved in animal experiments. All scientists who are responsible for the design and conduct of animal experiments are educated in one of the biomedical sciences (biology, medicine, veterinary medicine, pharmacy, etc.), and are knowledgeable in laboratory animal science, encompassing welfare issues, ethical aspects and alternatives to animal experiments. Within MESI-STRAT, all scientists dealing with animal studies have extensive experience with conducting animal studies.

Animals will be housed in temperature-controlled rooms (23°C) with 12 h light cycling, and will receive standard mouse chow and water ad libitum. All mice will receive cage enrichment when they arrive at the animal facility. All procedures will be performed under general anesthesia and postoperative analgesia. Post-surgery, animals will be observed frequently until normal activity has resumed, and will be housed individually. After experiments, animals will be checked daily to ensure continuing good health. If any animal shows signs of distress such as pilo-erection, hunched appearance, persistent inactivity, significant weight loss of e.g. 15%, or with normal eating and drinking activity not resumed after 48 h from the end of the procedure, animals will be sacrificed.

Violeta Serra (VS) from VHO will investigate immune-deficient PDX models. An animal license for the investigation of the efficacy of Akt inhibition in combination with Paclitaxel in tumors from patients with Her2+ BC implanted subcutaneously in mice is in place at VHO (see Document 8763, Annex 3.1.1). Animal licenses for further treatments will be applied for.

Benoit van den Eynde (BE) from DDI will investigate immune-competent PDX models. BE has animal licenses for the investigation of i) novel mechanisms that allow tumors to resist or escape immune-mediated rejection and to optimize vaccine treatments using mice as model organisms (see 2015/UCL/MD/14, Annex 3.1.2) as well as ii) the role of hypoxia in the immunosuppressive tumoral microenvironment and the immune response (see document 2015/UCL/MD/15, Annex 3.1.3). If necessary, further licenses will be applied for.

Guidance documents

The applicants will adhere to ethical principles, applicable international, EU (in particular, Directives 2003/65/EC, 86/609/EEC and EU Directive 2010/63/EU) and national law as well as country-specific ethics legislation. In addition, the ARRIVE Guidelines will be followed.

5.1.6 Non-EU countries

Not applicable

5.1.7 Health & safety

Utmost attention will be given to the health & safety of the researchers involved. Infectious biological samples are the most likely source of hazard. It will be secured that the work with biological material will be performed under adequate precautions and in appropriate laboratories.

Wherever possible, biological materials will be tested for infectious agents.

The applicants will adhere to ethical principles, applicable international, EU and national law as well as country-specific legislation.

5.1.8 Dual use

Not applicable

5.1.9 Exclusive focus on civil applications

Not applicable

5.1.10 Potential misuse of research results

Not applicable

5.2 Security²

Please indicate if your project will involve:

- activities or results raising security issues: (NO)
- 'EU-classified information' as background or results: (NO)

² See article 37 of the [Model Grant Agreement](#)

5.3 Ethics Requirements

Identified Ethic Issues

The ethical issues in this project are: involvement of human participants (both patients and healthy volunteers as control group), physical intervention, invasive techniques, collection of biological samples (DNA, RNA, cells, tissues, serum, plasma, urine, saliva), collection of data, use of secondary data, data from biobank, processing of genetic information, tracking/observation of participants, use of animals (vertebrates, genetically modified), non-EU countries and cross-border transfer of data and tissue samples, work safety.

Ethics Recommendations

None

Ethics Opinion

Conditional ethics clearance (i.e. clearance is subject to conditions, i.e. ethics requirements. The requirements must either be fulfilled before grant signature or become part of the grant agreement)

5.3.1 Pre-Grant Requirements

Environmental protection and safety

1. If relevant, copies of facilities authorisations must be provided (e.g. security classification of laboratory, GMO authorisation).

We confirm that we have all the documents and met all requirements signalled by the Ethics reviewers as pre-grant requirements.

Specifically, the following partners will perform experiments that require security classification of the Laboratory and GMO authorization:

UNIVERSITAET INNSBRUCK (UIBK)

ACADEMISCH ZIEKENHUIS GRONINGEN (UMCG)

DEUTSCHES KREBSFORSCHUNGZENTRUM (DKFZ)

FUNDACION PRIVADA INSTITUT D'INVESTIGACIONES ONCOLOGICAS DE VALL-HEBRON (VHIO)

DE DUVE INSTITUTE (DDI)

UNIVERSITETET I BERGEN (UiB)

CHARITE - UNIVERSITAETS MEDIZIN BERLIN (CHAB)

We have collected the respective documents, as listed in the following:

Ethics related documents	Providing Partner name	reference document		description	Expiry date
		File name	date		
Pre-grant requirements					
copies of facilities authorisations (e.g. security classification of laboratory, GMO authorisation).	UIBK	UIBK_S1 Permit_2776_001	05.08.1996	The document specifies the security level (S1) and GMO activities declaration for the Institute for Biochemistry (HZ 5.032/1-Pr/4/96)	none
		The dieck contract UIBK page 12	28.05.2018	Excerpt from K. Thedieck's contract at UIBK (signed by the rector of Innsbruck University) confirming the space and budget to setup an S2 level lab at the Institute for Biochemistry. The S2 upgrade is ongoing and planned to be finalized at KT's start at UIBK. This list will be hence updated with the according S2 permit.	none
	UMCG	UMCG_Waarts_At testation_lab safety_MESISTRAT	20.9.2017	Document signed by institutional security officer documents that appropriate health and safety procedures conform-	none

				ing to relevant local/national guidelines/legislation are followed for staff involved in MESI-STRAT.	
	UMCG_FMW-2330-16927-2004	3.11.2005	Bijlage 1 for "UMCG_Waarts_Attestation_lab safety_MESI-STRAT": The document specifies the security levels (ML-I and ML-II) in building 3226 that hosts the labs in which the UMCG part of experimental work for MESI-STRAT will be conducted	none	
	UMCG_10.0291 melding 8.19 ADL 1 ERIBA ge-scande br en for-mulier	17.6.2010	update for document UMCG_FMW-2330-16927-2004 (belongs to bijlage 1)	none	
	UMCG_10.0404 besluit melding WmB. ADL1 ERIBA	5.8.2010	update for document UMCG_FMW-2330-16927-2004 (belongs to bijlage 1)	none	
	UMCG_3226.-.04	n.a.	Bijlage 2 for "UMCG_Waarts_Attestation_lab safety_MESI-STRAT": floor map of building 3226 specifying security levels of the different labs (ML-I, ML-II)	none	
	UMCG_Langelaar benoeming locatiebeheerder GGO	8.4.2015	The locatiebeheerder (LB) and the verantwoordelijk medewerker (VM) are the responsible GMO officers for before mentioned laboratories and are responsible that appropriate health and safety procedures conforming to relevant local/national guidelines/legislation are followed for all staff .	none	
	UMCG_The-dieck_benoeming verantwoordelijk medewerker GGO	11.9.2015		none	
DKFZ	DKFZ_201709071 04953655	23.03.2011	The document specifies the security level (S1) and GMO permit for lab facilities of partner Opitz at DKFZ (DKFZ.HD.01.01) approved by the federal Regierungspraesidium.	none	
VHIO	VHIO_Resolución A_ES_16_I-15 Actividades tipo 2	17.5.2017	Dr. Violeta's laboratory's GMO activities declaration (reference: A/ES/16/53 and A/ES/16/54) aproved by Spanish Ministry. This certification includes the security number classification GMO evaluated as number 2.	none	
DDI	DDI_Permis LABO 416507	14.6.2016	The document 'Octroi de permis d'utilisation confinée d'OGM et/ou pathogènes' details security level and GMO permit for DDI. The annex concerning more particularly the laboratories of MESI-STRAT partner B. van den Eynde is on page 54-58. The lab facilities for animal experimentation (on animals infected with defective recombinant viruses) are covered on pages 81-82.	14.6.2021	
	DDI_Dossier Technique Operation 2010Wol17	20.2.2010	In addition, the document for operation 2010/WOL/17 covers GMO animal experimentation from Permis n° 358259 (validity 10 years instead of 5 years).	20.12.2020	
	DDI_Xavier Havaux- Attestation wol56 DDUV	6.09.2017	The document „Attestation wol56“ signed by the institutional security officer documents that appropriate health and safety procedures conforming to relevant local/national guidelines/legislation are followed for staff involved in MESI-STRAT.	none	
	DDI_006-17 Rpt VLT LICR DDUV GECE 74+3	22.2.2017	Report of the latest laboratory security audit in our lab (Feb 15, 2017).	none	

		DDUV GECE et LICR 75 +3			
UiB	UiB_GMO-UiB-Godkjenning	20.3.2007	Document approving the GMO and HSE routines in the labs used for the project in Bergen. The work to be conducted in the framework of the MESI-STRAT project will be at the lowest security level. The approval is signed by the official government authorities of Norway.	none	
CHAB	Licence S1	11.7.1994	approval of S1 security level for laboratories in which MESI-STRAT staff works at CHAB	none	
	S1-update-20160706	6.7.2016	Update for Licence S1	none	
	Licence S2	19.6.1997	approval of S2 security level for laboratories in which MESI-STRAT staff works at CHAB	none	
	S2-update-20130115	15.1.2013	Update for Licence S2	none	
	Licence_project_leader_CSers	18.5.1998	license for work with GMO for laboratories in which MESI-STRAT staff works at CHAB (Prof. Sers)	none	
	Licence_project_leader_CSers-update 20160322	21.03.2016	Update GMO license (Prof. Sers)	none	
	Protocol_site_visit_lageso_2016	10.6.2016	Protocol of the last site visit by the relevant legal authority (LaGeSO)	none	

2. The applicant must ensure that appropriate health and safety procedures conforming to relevant local/national guidelines/legislation are followed for staff involved in this project.

All partners who perform laboratory work in GMO laboratories under the according security classification, listed above, supplied documents on security classification and related safety procedures, according to national and European legislation (see table above). This provides evidence that appropriate health and safety procedures conforming to relevant local/national guidelines/legislation are followed for staff involved in this project.

Neuroimmun (NIN) is a young startup SME, whose lab facilities for ELISA assays development became operational only in 2016. No GMO work is conducted in these labs, which is why S1/2 security classifications and GMO permits are not applicable. Audits of health and safety procedures with respect to relevant local/national guidelines/legislation are currently under way and are expected to be completed by April 2018. The documentation will be provided to the EC as soon as this procedure is completed.

Initial experimental work on assay development will be performed in collaboration with and by personnel at DKFZ, which has all relevant security documentation in place (see documents DKFZ). Only at a later stage in the project (after prognostic marker discovery and validation, i.e. at least one year after April 2018) will assay development be also implemented at the Neuroimmun lab. Lab security documentation will thus be provided to the EC before lab work at Neuroimmun starts.

This procedure has been agreed with the MESI-STRAT PO Adoracion Navarro-Torne on 12-09-2017 in Brussels.

5.3.2 Post-Grant Requirements

Third countries

- 1. The applicant must confirm that the ethics standards and guidelines of Horizon2020 will be rigorously applied, regardless of the country in which the research is carried out.**

The applicant confirms that the ethics standards and guidelines of Horizon2020 will be rigorously applied, regardless of the country in which the research is carried out.

- 2. The applicant must provide details on the material which will be imported to/exported from EU and provide the adequate authorisations.**

Samples will be exported to Norway for metabolic measurements performed by UiB in month 13 at the earliest. Therefore, the details on this material and permits for export of samples to Norway will be provided in the form of a deliverable in month 12 or later upon request. A material transfer agreement will be concluded between the respective parties accordingly taking into account ethics standards and guidelines of H2020 as well as national and EU data protection laws and regulations.

Protection of personal data

- 1. The applicants must devise a data management plan including detailed information on the procedures that will be implemented for data collection, storage, protection, retention, reuse and/or destruction. Compliance confirmation with current national and EU legislation must be included.**

The applicants will devise a data management plan including detailed information on the procedures that will be implemented for data collection, storage, protection, retention, reuse and/or destruction. Compliance confirmation with current national and EU legislation will be included.

The data management plan will be delivered in form of a deliverable in month 6.

- 2. The applicants must also include in the plan a policy making sure that the collected data is harvested on strict "need to know" and "need to use" basis. As such, but non-limitedly, the applicants must also include in the plan a privacy impact assessment.**

The applicants will include a policy making sure that the collected data is harvested on strict "need to know" and "need to use" basis. In other words, no data will be requested by MESI-STRAT that is irrelevant for our studies. To prevent any breaches of anonymity, the applicants will also include in the plan a privacy impact assessment addressing whether any meta-data could be garnered from the research, and/or, whether there is cross-referencing with other data bases.

- 3. Copies of current legal "paper trail evidence" by the competent Data Protection Authority/ "one stop shop" as applicable, must be collected and provided to the Commission, upon request, to ensure continuing compliance with ongoing legislation.**

Each beneficiary dealing with personal data will ensure for their own institution that legal paper trail evidence will be collected and kept and will provide them to the Commission upon request through the coordinator. Each applicant dealing with personal data protection has their own data protection officer.

- 4. If the position of a Data Protection Officer is established, their opinion/confirmation that all data collection and processing will be carried according to current EU and national legislation should be collected and submitted to the Commission upon request, as well as all administrative documents and permissions in relation to data import and export.**

As several beneficiaries deal with personal data, the Data Protection Officers of each of the respective institutions will give their opinion/confirmation that all data collection and processing will be carried out according to current EU and national legislation for the personal data handled by this partner, and the administrative documents and permissions in relation to data import and export will be collected as well, when necessary. The documents will be submitted upon request. Please also refer to the answer to question no. 3.

5. Applicants should provide detailed information on privacy/confidentiality and the procedures that will be implemented for data collection, storage, access, sharing policies especially when third party countries are concerned, protection, retention and destruction. Confirmation that they comply with national and EU legislation.

We will provide detailed information on privacy/confidentiality and the procedures that will be implemented for data collection, storage, access, sharing policies, and especially when third party countries are concerned, protection, retention and destruction. Only pseudonymized data will be shared with third party countries. All data management, curation and protection will be according to EU regulation and EU directive. In the case of MESI-STRAT this concerns Norway, and UK at the time when the Brexit will be implemented. We confirm that they will comply with national and EU legislation.

6. Templates of the informed consent forms and information sheet for data collection and processing must be submitted.

Templates of the informed consent forms and information sheet for data collection and processing will be submitted upon request by month 6 for Clinical Studies No. 1-6. For clinical study No 7 (Intervention Validation Trial), at least one (but not all) of the available clinical trials will be selected, based on MESI-STRAT results on targeted interventions at a later time in the project. At this time, templates of the informed consent forms and information sheet for data collection and processing will be submitted for the selected trial(s). An according update will be made to the DMP at that time.

[Note that "upon request" has been included in the wording of the above paragraph to reconcile the text with section "Humans", point 3 (see following paragraph)].

Humans

1. Details on incidental findings must be provided. The applicants must detail the three management pathways (right "not to know", "transmission of the collected information to the GP" and "direct information disclosure"). A policy must be devised and implemented.

We will provide details on the way we will handle incidental findings. This may differ in the different studies performed in the frame of MESI-STRAT. For retrospective studies and studies associated with MESI-STRAT (Clinical Study No 1-4, and 7) we will adhere to the previously chosen management path. For the Clinical Study No 6 (ET Termination Trial) we will follow the policy of participant 2 (PATH Biobank). For Clinical Study No 5 (WOO Trial) we will devise and implement a management pathway to deal with incidental findings after counseling with the clinicians involved and with our ethics advisor.

2. Details on the procedures and criteria that will be used to identify/recruit research participants must be provided.

We will provide details on the procedures and criteria that will be used to identify/recruit research participants and submit them with the respective ethics approvals.

3. Templates of the informed consent forms and information sheet must be submitted on request. Templates of the informed consent forms and information sheets will be submitted on request.

4. Copies of ethics approvals for the research with humans must be submitted for each of the studies listed in table 2, page 45 part B2.

Copies of ethics approvals for the research with humans will be submitted for Clinical Studies No. 1-6, listed in table 2, page 45 part B5. For clinical study No 7 (Intervention Validation Trial), at least one (but not all) of the available clinical trials will be selected at a later time, based on MESI-STRAT results on targeted interventions. At this time, ethics approvals will be submitted for the selected trial(s). An according update will be made to the DMP.

[Note: Table 2, page 45 does not exist in part B2 but in B5. Therefore, we corrected this reference.]

[Note that insurance cover applies in MESI-STRAT only to Clinical Study No. 5 (WOO Trial). Therefore, this was specified accordingly.]

5. Detailed information must be provided on the informed consent procedures studies that will be or have been implemented for the participation of humans, i.e. each of the studies listed in table 2, page 45 part B2.

For Info, Specifically:

Participants must have the right:

- To know that participation is voluntary
- To ask questions and receive understandable answers before making a decision
- To know the degree of risk and burden involved in participation
- To know who will benefit from participation
- To know the procedures that will be implemented in the case of incidental findings
- To receive assurances that appropriate insurance cover is in place
- To know how their data will be collected, protected during the project and either destroyed or reused at the end of the research, if plans to reuse the data exist, participants should be duly informed, and consented also for this further usage,
- To withdraw themselves and their data and samples from the project at any time
- To know of any potential commercial exploitation of the research.

Detailed information will be provided on the informed consent procedures that will be or have been implemented for the participation of humans, i.e. for Clinical Studies No. 1-6, listed in table 2, page 45 part B5. For clinical study No 7 (Intervention Validation Trial), at least one (but not all) of the available clinical trials will be selected at a later time, based on MESI-STRAT results on targeted interventions. At this time, detailed information on the informed consent procedures will be provided for the selected trial(s). An according update will be made to the DMP.

Specifically:

Participants will have the right

- To know that participation is voluntary
- To ask questions and receive understandable answers before making a decision
- To know the degree of risk and burden involved in participation
- To know who will benefit from participation
- To know the procedures that will be implemented in the case of incidental findings
- To receive assurances that appropriate insurance cover is in place (only applicable to Clinical Study No. 5)
- To know how their data will be collected, protected during the project and either destroyed or reused at the end of the research, if plans to reuse the data exist, participants will be duly informed, and consented also for this further usage,
- To withdraw themselves and their data and samples from the project at any time
- To know of any potential commercial exploitation of the research.

[Note: Table 2, page 45 does not exist in part B2 but in B5. Therefore, we corrected this reference.]

6. The applicant must clarify whether adults unable to give informed consent will be involved and, if so, justification for their participation must be provided.

Only adults that are able to give informed consent will be included into the studies.

7. The applicant must clarify how consent/assent will be ensured in case adults unable to give informed consent are involved.

Not applicable as only adults that are able to give informed consent will be included into the studies.

8. The applicant must clarify whether vulnerable individuals/groups will be involved. Details must be provided about the measures taken to prevent the risk of enhancing vulnerability/stigmatisation of individuals/groups, e.g. in the case of male breast cancer.

We will obtain the data and samples in pseudomized form and hence we will not be able to trace the samples back to the donating human beings. Therefore, there is no risk of enhancing vulnerability/stigmatisation of individuals or groups.

Human cells/tissues

1. In case of use of human cells/tissues available commercially, details on cells/tissues type and provider must be submitted.

In case of use of human cells/tissues available commercially, details on cells/tissues type and provider will be submitted according to the project plan at this time. This information will be updated in case other human cells/tissues are to be included into the project later on, due to scientific considerations.

2. In case human cells/tissues are obtained within the project, details on cells/tissues type and ethics approval must be provided.

In case human cells/tissues are obtained within the project, details on cells/tissues type and ethics approval will be provided according to the project plan at this time. This information will be updated in case other human cells/tissues are to be included into the project later on, due to scientific considerations.

3. In case human cells/tissues are obtained within another project, details on cells/tissues type and authorisation by primary owner of data (including references to ethics approval) must be provided

In case human cells/tissues are obtained within another project, details on cells/tissues type and authorisation by primary owner of data (including references to ethics approval) will be provided at a later time, according to the project plan. This information will be updated in case other human cells/tissues are to be included into the project later on, due to scientific considerations.

[Note: this concerns Clinical Study No 7, for which the appropriate studies and samples will only be chosen later in the project, and ethical approval will be presented at that time (see also clarifications for D10.2, D10.3, D10.4).

4. In case of human cells/tissues stored in a biobank, details on cells/tissues type must be provided, as well as details on the biobank and access to it.

In case of human cells/tissues stored in a biobank, details on cells/tissues type will be provided, as well as details on the biobank and access to it according to the project plan at month 6. This information will be updated in case other human cells/tissues are to be included into the project later on, due to scientific considerations.

5. Clarification is required as to whether informed consent is in place for the use and re-use, i.e. the propagation, of patient derived human breast cancer tissues in the PDX mouse models. Informed consent forms and information sheets must be provided.

Informed consent and information sheets for the use and re-use, i.e. the propagation, of patient derived human breast cancer tissues in the PDX mouse models are in place and have been provided (see Optional Annex 3: Ethics, Supporting Documents, Annex 3.3.c)).

The informed consent and information sheet clarifies that the tissues will be propagated for "use and re-use": Specifically, the informed consent and information sheet states that "The obtained samples will be implanted into immunosuppressed mice with the aim of obtaining sufficient tumour to carry out subsequent studies." (...) These samples, as previously informed, will be used for the purpose of carrying out this study, as well as to be able to participate in future studies of this research group or those of other groups dedicated to oncological research (...)."

6. Regarding liquid biopsies at DKFZ and UKL-HD, Heidelberg, the informed consent information sheet and the clinical study protocol must be revised to allow withdrawal of both data and samples from the biobank and from the study.

We will revise the informed consent form and the clinical study protocol regarding liquid biopsies at DKFZ and UKL-HD to allow withdrawal of both data and samples from the biobank and from the study and submit this in month 6.

Animals

1. In case research protocols are not defined, general information must be kept by the beneficiary in the project files on the nature of the experiments, the procedures to ensure the welfare of the animals, and how the Principle of the Three Rs will be applied. This information must be provided upon request.

This point is not applicable to our project. No animal experiment will be conducted without defined research protocols, approved by the legal authorities.

2. When submitting the application for scrutiny to the competent local/national ethics boards/bodies for authorization, detailed information should be provided on why living animals have to be used and why that species has been chosen. In addition, information should be given on the numbers of animals to be used in experiments, the nature of the experiments, the procedures that will be carried out and their anticipated impact (e.g. potential for pain, suffering, stress) and how that has been minimised. Furthermore, details should be provided on what procedures have been implemented to ensure the welfare of the animals during their lives (e.g. husbandry, minimising harms, criteria for humane endpoints, inspection protocols). The applicant should provide evidence of awareness of relevant European legislation and regulations covering animal experimentation and that the Principle of the Three Rs will be rigorously applied.

We will comply with point 2. Animal permits, entailing the requested information, for existing experiments and samples will be provided at month 6. For animal experiments designed based on data gained during the MESI-STRAT project, the related animal permits will be applied for and will be submitted later during the course of the project.

3. Copies of relevant authorisations (for breeders, suppliers, users, and facilities) for animal experiments must be submitted. These must cover the work with genetically modified animals where applicable.

We will submit in month 6 copies of relevant authorisations (for breeders, suppliers, users, and facilities) for animal experiments, which cover the work with genetically modified animals where applicable.

4. Copies of ethical approvals by the competent local/national ethical/legal bodies, together with copies of relevant authorizations for animal experiments must be forwarded to the European Commission prior to the commencement of the research. These must cover the work with genetically modified animals where applicable.

We will forward copies of ethical approvals by the competent local/national ethical/legal bodies, together with copies of relevant authorizations for animal experiments, to the European Commission prior to the commencement of the research via the EC participant portal. These will cover the work with genetically modified animals where applicable.

We will submit in month 6 the documents for existing experiments, whereas those for experiments designed based on project results will be submitted later. Hence these documents will be continuously updated.

5. Copies of training certificates/personal licenses of the staff involved in animal experiments must be provided.

We will provide copies of training certificates/personal licenses of the staff involved in animal experiments according to our planning in month 6. These will be updated as applicable as the project progresses.

General

- 1. Due to the severity of the ethics issues raised by the proposed research work, it is required that an independent Ethics Advisor is appointed to oversee the implementation the ethical concerns involved in this research. A report by the ethics Advisor must be submitted to the Agency/Commission/ERC with the financial reports.**

We will appoint an independent Ethics Advisor to oversee the implementation the ethical concerns involved in this research. A report will be submitted to the Agency/Commission/ERC with the financial reports.

Ethics Checks

Because of the significant ethical issues involved in this project including a large number of patient data and tissue samples, unresolved issues regarding data management and protection and open issues regarding therapeutically relevant incidental findings and the potentially significant new ethical challenges that might arise from this research, Follow Up/Audit of this project would be prudent.

When there is an audit, the documents and ethics compliance of the project will be provided for analysis to the EC.

5.4 Ethics deliverables

The due dates for all ethics deliverables are presented below.

For some of the ethics deliverables, the text preset by the EC does not comply with the MESI-STRAT project content. Therefore, we make the following amendments/clarifications:

D10.1 NEC - Requirement No. 1

due date: month 12

1. The applicant must confirm that the ethics standards and guidelines of Horizon2020 will be rigorously applied, regardless of the country in which the research is carried out.
2. The applicant must provide details on the material which will be imported to/exported from EU and provide the adequate authorisations.

Ad 2. We clarify as follows:

Unlike the statement in the ethics report, we do NOT import samples/material from non-EU countries. We only export samples to Norway for metabolite measurements. The applicant will therefore provide details on the material which will be exported from (but not imported to) EU and provide the adequate authorisations.

D10.2 POPD - Requirement No. 2

due date: month 6

1. The applicants must devise a data management plan including detailed information on the procedures that will be implemented for data collection, storage, protection, retention, reuse and/or destruction. Compliance confirmation with current national and EU legislation must be included.
2. The applicants must also include in the plan a policy making sure that the collected data is harvested on strict "need to know" and "need to use" basis. As such, but non-limitedly, the applicants must also include in the plan a privacy impact assessment.
3. Copies of current legal "paper trail evidence" by the competent Data Protection Authority/ "one stop shop" as applicable, must be collected and provided to the Commission, upon request, to ensure continuing compliance with ongoing legislation.
4. If the position of a Data Protection Officer is established, their opinion/confirmation that all data collection and processing will be carried according to current EU and national legislation should be collected and submitted to the Commission upon request, as well as all administrative documents and permissions in relation to data import and export.
5. Applicants should provide detailed information on privacy/confidentiality and the procedures that will be implemented for data collection, storage, access, sharing policies especially when third party countries are concerned, protection, retention and destruction. Confirmation that they comply with national and EU legislation.
6. Templates of the informed consent forms and information sheet for data collection and processing must be submitted.

Ad 6. We clarify as follows:

Templates of the informed consent forms and information sheet for data collection and processing must be submitted upon request for Clinical Studies No. 1-6. For clinical study No 7 (Intervention Validation Trial), at least one (but not all) of the available clinical trials will be selected, based on MESI-STRAT results on targeted interventions at a later time in the project. At this time, templates of the informed consent forms and information sheet for data collection and processing will be submitted for the selected trial(s). An according update will be made to the DMP at that time.

Explanation:

Clinical Study No 7 will not start in the beginning of the project, and not all studies available (listed in part B5, pp. 117-118) will be used to ultimately conduct Clinical Study No 7. We will only be able to decide later in the project, based on our results, which of the available targeted interventions (listed in B5, pp. 117-118) are relevant to be analysed in our project. We will then select accordingly, from which clinical trial(s) we need to obtain samples. This is described in detail in part B1-3 and the ethical annex (part B5). Only for the relevant trials will we provide information sheets and ethical approvals, before performing any analysis. The data management plan will be updated for clinical studies starting later during the course of the project.
To reconcile the text with D10.3, point 3 (below), "upon request" has been included in the wording.

D10.3 H - Requirement No. 3due date: **month 6**

1. Details on incidental findings must be provided. The applicants must detail the three management pathways (right "not to know", "transmission of the collected information to the GP" and "direct information disclosure"). A policy must be devised and implemented.
2. Details on the procedures and criteria that will be used to identify/recruit research participants must be provided.
3. Templates of the informed consent forms and information sheet must be submitted on request.
4. Copies of ethics approvals for the research with humans must be submitted for each of the studies listed in table 2, page 45 part B2.
5. Detailed information must be provided on the informed consent procedures studies that will be or have been implemented for the participation of humans, i.e. each of the studies listed in table 2, page 45 part B2.

For Info, Specifically:**Participants must have the right:**

- To know that participation is voluntary
- To ask questions and receive understandable answers before making a decision
- To know the degree of risk and burden involved in participation
- To know who will benefit from participation
- To know the procedures that will be implemented in the case of incidental findings
- To receive assurances that appropriate insurance cover is in place
- To know how their data will be collected, protected during the project and either destroyed or reused at the end of the research, if plans to reuse the data exist, participants should be duly informed, and consented also for this further usage,
- To withdraw themselves and their data and samples from the project at any time
- To know of any potential commercial exploitation of the research.

Ad 3.

This point notes that "Templates of the informed consent forms and information sheet must be submitted on request." We have added "on request" above to D10.2 point 6, in order to reconcile these two requirements.

Ad 4-5. We clarify as follows:

"4. Copies of ethics approvals for the research with humans must be submitted for Clinical Studies No. 1-6, listed in table 2, page 45 part B5. For clinical study No 7 (Intervention Validation Trial), at least one (but not all) of the available clinical trials will be selected at a later time, based on MESI-STRAT results on targeted interventions. At this time, ethics approvals will be submitted for the selected trial(s). An according update will be made to the DMP."

5. Detailed information must be provided on the informed consent procedures that will be or have been implemented for the participation of humans, i.e. for Clinical Studies No. 1-6, listed in table 2, page 45 part B5. For clinical study No 7 (Intervention Validation Trial), at least one (but not all) of the available clinical trials will be selected at a later time, based on MESI-STRAT results on targeted interventions. At this time, detailed information on the informed consent procedures will be provided for the selected trial(s). An according update will be made to the DMP."

Explanations:

- See above, explanation for D10.2, point 6.
- "Table 2, page 45 part B2" mentioned in the EC text does not exist in part B2 but only in B5. Therefore, this must be corrected throughout to read "table 2, page 45 part B5".

Ad 5. We clarify as follows:

"Participants must have the right: (...)

- to receive assurances that appropriate insurance cover is in place (only applicable to Clinical Study No. 5) (...)"

Explanation:

Insurance cover applies in MESI-STRAT only to Clinical Study No. 5 (WOO Trial). Therefore, this was specified accordingly.

D10.4 H - HCT - Requirement No. 4 due date: month 6

1. In case of use of human cells/tissues available commercially, details on cells/tissues type and provider must be submitted.
2. In case human cells/tissues are obtained within the project, details on cells/tissues type and ethics approval must be provided.
3. In case human cells/tissues are obtained within another project, details on cells/tissues type and authorisation by primary owner of data (including references to ethics approval) must be provided
4. In case of human cells/tissues stored in a biobank, details on cells/tissues type must be provided, as well as details on the biobank and access to it.
5. Clarification is required as to whether informed consent is in place for the use and re-use, i.e. the propagation, of patient derived human breast cancer tissues in the 6. PDX mouse models. Informed consent forms and information sheets must be provided.
7. Regarding liquid biopsies at DKFZ and UKL-HD, Heidelberg, the informed consent information sheet and the clinical study protocol must be revised to allow withdrawal of both data and samples from the biobank and from the study.

Ad 1. We clarify as follows:

"1. In case of use of human cells/tissues available commercially, details on cells/tissues type and provider must be submitted according to the project plan at this time. This information will be updated in case other human cells/tissues are to be included into the project later on, due to scientific considerations."

Ad 2. We clarify as follows:

"2. In case human cells/tissues are obtained within the project, details on cells/tissues type and ethics approval must be provided according to the project plan at this time. This information will be updated in case other human cells/tissues are to be included into the project later on, due to scientific considerations."

Ad 3. We clarify as follows:

"In case human cells/tissues are obtained within another project, details on cells/tissues type and authorisation by primary owner of data (including references to ethics approval) must be provided at a later time, according to the project plan. This information will be updated in case other human cells/tissues are to be included into the project later on, due to scientific considerations."

Note: Point 3 cannot be provided at month 6, as this concerns Clinical Study No 7, for which the appropriate studies and samples will only be chosen later in the project, and ethical approval will be presented at that time (see also clarifications for D10.2 and D10.3).

Ad 4. We clarify as follows:

"4. In case of human cells/tissues stored in a biobank, details on cells/tissues type must be provided, as well as details on the biobank and access to it according to the project plan at this time. This information will be updated in case other human cells/tissues are to be included into the project later on, due to scientific considerations."

D10.5 A - Requirement No. 5 due date: month 6

1. In case research protocols are not defined, general information must be kept by the beneficiary in the project files on the nature of the experiments, the procedures to ensure the welfare of the animals, and how the Principle of the Three Rs will be applied. This information must be provided upon request.
2. When submitting the application for scrutiny to the competent local/national ethics boards/bodies for authorization, detailed information should be provided on why living animals have to be used and why that species has been chosen. In addition, information should be given on the numbers of animals to be used in experiments, the nature of the experiments, the procedures that will be carried out and their anticipated impact (e.g. potential for pain, suffering, stress) and how that has been minimised. Furthermore, details should be provided on what procedures have been implemented to ensure the welfare of the animals during their lives (e.g. husbandry, minimising harms, criteria for humane endpoints, inspection protocols). The applicant should provide evidence of awareness of relevant European legislation and regulations covering animal experimentation and that the Principle of the Three Rs will be rigorously applied.
3. Copies of relevant authorisations (for breeders, suppliers, users, and facilities) for animal experiments must be submitted. These must cover the work with genetically modified animals where applicable.
4. Copies of ethical approvals by the competent local/national ethical/legal bodies, together with copies of relevant authorizations for animal experiments must be forwarded to the European Commission prior to the commencement of the research. These must cover the work with genetically modified animals where applicable.
5. Copies of training certificates/personal licenses of the staff involved in animal experiments must be provided.

Ad 1. We clarify as follows:

Point 1 is not applicable to the MESI-STRAT project. No animal experiment will be conducted without defined research protocols, approved by the legal authorities. Therefore, no general document is required as a deliverable.

Ad 2. We clarify as follows:

Animal permits, entailing the requested information, for existing experiments and samples will be submitted by month 6, observing the mentioned criteria. For animal experiments designed based on data gained during the MESI-STRAT project, the related animal permits will be applied for later during the course of the project.

D10.6 GEN - Requirement No. 7 due date: month 3

1. Due to the severity of the ethics issues raised by the proposed research work, it is required that an independent Ethics Advisor is appointed to oversee the implementation the ethical concerns involved in this research. A report by the ethics Advisor must be submitted to the Agency/Commission/ERC with the financial reports.

D10.7 H - Requirement No. 8 due date: month 3

6. The applicant must clarify whether adults unable to give informed consent will be involved and, if so, justification for their participation must be provided.
7. The applicant must clarify how consent/assent will be ensured in case adults unable to give informed consent are involved.
8. The applicant must clarify whether vulnerable individuals/groups will be involved. Details must be provided about the measures taken to prevent the risk of enhancing vulnerability/stigmatisation of individuals/groups, e.g. in the case of male breast cancer.



Systems Medicine of Metabolic-Signaling networks -
A New Concept for Breast Cancer Patient Stratification

Essential information to be provided for proposals including clinical trials/studies/investigations/cohorts

This template only concerns you if your proposal contains a clinical trial/study/investigation! In the following, clinical trials/studies/investigations/cohorts are collectively referred to as 'clinical studies'¹ Clinical studies have a number of methodological and regulatory specificities. Information on these issues is crucial for evaluators to assess the scientific quality of the proposal. The following guidance should help applicants to provide this essential information on clinical studies in a standardised format.

For each clinical study performed within the scope of the proposal, information on the issues listed below should be provided, compiled into one single document per proposal based on this template². Each section must be shortly and concisely described. In case one or more issues do not apply to a particular study, please briefly explain/justify.

When the requested information is currently not available (e.g. a clinical study is planned for a later stage of the project and will be based on data from prior studies) the source of this data and/or the applied methodology should be described.

Information provided in this template does not need to be repeated elsewhere in the proposal, but can be referred to.

There are no page limitations for this template, but explanations should be as concise as possible.

Information outside the scope of this template will not be taken in account in the proposal evaluation. No other chapters or annexes (containing e.g. complete study protocols) can be added to this template. Section headings should not be changed.

Ethics considerations have to be addressed in the appropriate section of the proposal. Similarly, risks and contingency plans have to be addressed in the respective section of the proposal (part B.3.2 and table 3.2.a) (not in this template!). If contingency plans are not outlined in the proposal (and the grant agreement), your grant agreement might be terminated and/or the EU/IMI2 JU contribution significantly reduced should a study not proceed as planned.

*Three **mandatory deliverables** have to be implemented in the proposal for each clinical study included in the proposal. Further information on the mandatory deliverables can be found in Annex 2.*

¹ A 'clinical study' is defined for the purpose of this template as any clinical research involving a substantial amount of work related to the observation of, data collection from, or diagnostic or therapeutic intervention on multiple or individual patients. It includes but is not limited to clinical trials in the sense of the EU Clinical Trials Directive (2001/20/EC)

² If the proposal contains more than one clinical study, each study should be described in its own main chapter (1.1, 1.2, 1.3...; 2.1, 2.2...; 3.1... etc.) as indicated in the example below.

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1 Overview: MESI-STRAT trials

For the convenience of the reviewers we reproduce here Table 2 from Section 1.3.b.

The MESI-STRAT trials will encompass the following studies:

MESI-STRAT clinical and preclinical trials. Trials without drug treatments are grouped into WP6, and trials with drug treatments into WP7. *The clinical study number corresponds to the numbers in this document. The trial numbers correspond to the task numbers in WPs 6 and 7.

Study category	Study type	Clinical Study Nº & Trial #*	Short name	Study title	Study design
Trials without drug treatments: WP6	clinical	Study No 1 WP6: Trial 6.1	Risk Detection Trial	Identification and validation of MESI marker panels discriminating high risk vs. low risk ER+BC patient subgroups	Samples and clinical data from PATH biobank
		Study No 2 WP6: Trial 6.2	Relapse Detection Trial	Identification and validation of MESI marker panels detecting ER+BC patient subgroups with relapse	Samples and clinical data from PATH biobank and clinical trials associated with MESI-STRAT
		Study No 3 WP6: Trial 6.3	Relapse Prediction Trial	Retrospective identification and validation of MESI marker panels at diagnosis predicting patient subgroups with future relapse or stable disease	Samples and clinical data from PATH biobank
		Study No 4 WP6: Trial 6.4	Tissues for Preclinical Trials	Screening and collection of ER+BC tissues with subgroup specific MESI marker panels for preclinical models (PDX, bioreactor)	Samples obtained in the frame of ongoing clinical studies at VHIO and UKL-HD
Trials with drug treatments: WP7	preclinical	WP6: Task 6.5	Preclinical Model Subgroup Assignment	Identification of primary cell and PDX models representing novel ER+BC subgroups defined by differential MESI marker expression	Samples and data from preclinical trials at VHIO, DKFZ and DDI
		WP7: Task 7.1	Preclinical Intervention Trials	Validation of predictive MESI marker panels in primary cell cultures, cultured primary tissues, and pre-clinical interventional trials in PDX models	Samples and data from preclinical trials at VHIO, DDI, DKFZ and UIBK
	clinical	Study No 5 WP7: Trial 7.2	WOO Trial	Prospective window of opportunity trial 2 weeks neoadjuvant Anastrozole in postmenopausal women with ER+BC	Interventional clinical trial performed at UKL-HD
		Study No 6 WP7: Trial 7.3	ET Termination Trial	Analysis of longitudinally collected serum and urine from ER+BC patients before and after termination of ET	Prospective clinical trial by PATH, collecting samples/ clinical data from patients on and off ET
		Study No 7 WP7: Trial 7.4	Intervention Validation Trials	Clinically validate predictive MESI-models and marker panels for targeted drug interventions	21 clinical trials by partners and collaborators; incl. 3 male cohorts
	WP7: Task 7.5	IIT / Umbrella Trial Design		Design own IIT and umbrella trials, in which ER+BC patients will be stratified to different therapies by MESI-marker panels	For future impact, UKL-HD, UMCG, VHIO will design and initiate IIT & umbrella trials

2 Clinical study No. 1

2.1 Identifier

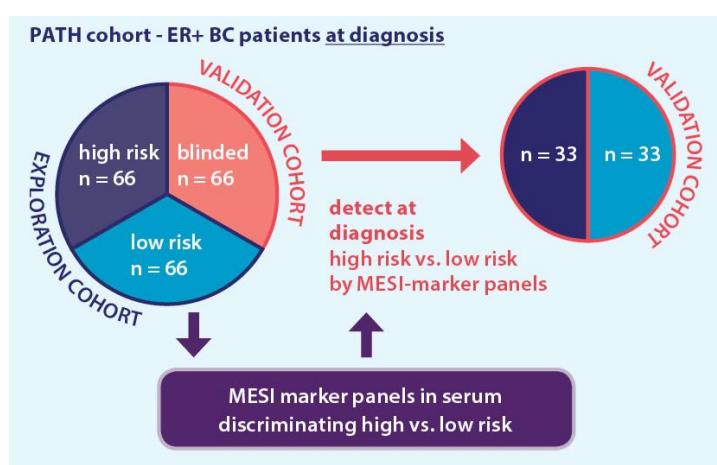
Risk Detection Trial:

Identification and validation of MESI marker panels discriminating high risk vs. low risk ER+BC patient subgroups (Trial 6.1, WP6)

2.2 Study design and endpoints

2.2.1 Study design

Cross-sectional and validation study



Analysis of 66 sera from the PATH cohort collected at diagnosis from women with high and low risk ER+ BC, respectively, for signalling pathways and metabolites will allow identification of MESI marker panels detecting high/low risk in ER+ BC patients. To validate if the identified markers indeed discriminate between high and low risk patients, 66 sera of women with high and low risk ER+ BC, respectively will be analysed in a blinded fashion and assigned to high

and low risk groups according to their MESI marker panels. Comparison with the known clinical characteristics will allow validation of the discriminatory power of the identified MESI markers between low and high risk BC patients. In addition, selected tumor tissues representative for specific MESI markers signatures will be analysed in detail regarding their signaling and metabolic networks to gain a better understanding of the molecular mechanisms underlying the MESI marker panels discriminating high and low risk patients. The samples will be provided by MESI-STRAT partners.

2.2.2 Primary and secondary endpoint(s)

Primary endpoint:

Identification of MESI marker panels detecting high/low risk in ER+ BC patients.

2.2.3 Relevant guidance documents

(a) International guidelines:

- [ICH Guideline for Good Clinical Practice E6\(R1\)](#);
- [Declaration of Helsinki](#);
- OECD Guidelines on Human Biobanks and Genetic Research Databases <https://www.oecd.org/sti/biotech/44054609.pdf>.

(b) National guidelines

The PATH biobank is subject to German law. Samples and data stemm from German sites only.

- The maintenance of a biomaterial bank touches on two essential laws of the German basic law (Grundgesetz): the right to informational self-determination (Art. 2 paragraph 1 Grundgesetz). According to which the person concerned can decide to whom he/she is disclosing which type of personal information. As well as the fundamental right to freedom of research, Art. 5 paragraph 3 Grundgesetz;
- The German Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG);
- 2010 opinion of the German Ethics Council (Deutscher Ethikrat, DER) on biobanking;

(c) Institutional/ local guidelines and Standard Operating Procedures

- SOP No. 0210-G Processing of tissue for the Tumorbank of the foundation PATH.

2.3 Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees

Approval from the ethics committee of the University of Bonn, Germany (225/06) has been obtained by PATH for the collection and analysis of tumor tissue and serum at diagnosis. This approval includes the use of the data and samples for breast cancer research, including this use in MESI STRAT.

2.4 Subjects/population(s)

Samples from the following patients will be included:

- Patients with histologically documented ER+ breast cancer in the PATH cohort;
- Age > 18 yrs;
- signed informed consent form;
- invasive carcinoma of no special type (NST) or invasive lobular carcinoma;
- necessary biological material and clinical follow-up data available.

Tissue and serum samples are provided by the non-profit organization Patients' Tumor Bank of Hope (PATH Biobank, Augsburg, Germany: <http://www.path-biobank.org/index.php/en/about-path/>) as standardized fresh frozen tissue and blood serum specimens. Patients provided written, informed consent for the storage of samples and data, follow-up contact, and further use of samples and data for research purposes.

High risk and low risk ER+ BC patients will be selected according to the criteria below. 50 sera of each pre- and postmenopausal high and low risk ER+ BC patients will be provided (200 sera in total) and corresponding BC tissues of approx. 5 patients per group (20 BC tissues in total).

Selection of ER+ BC patients

Low risk	High risk
Tumor size less than 2 cm in diameter (pT1)	premenopausal: tumor size more than 2 cm in diameter (\geq pT2-3) postmenopausal: tumor size more than 5 cm in diameter (\geq pT3)
No cancer cells in any nearby lymph nodes (pN0)	Cancer cells have spread to 4 to 9 axillary lymph nodes, or have enlarged the internal mammary lymph nodes (\geq pN2)
Well differentiated, slower growing cells (G1)	Less differentiated, faster growing cells (G 2-3)
No metastasis (M0)	No metastasis (M0)

To harmonize the collectives we will include the following most common histopathological tumor types: Invasive carcinoma of no special type (NST, also known as invasive ductal carcinoma) and invasive lobular carcinoma.

Definition of sub-populations if subgroup analysis is intended.

Analysis of pre- and postmenopausal low and high risk ER+ BC patients.

2.5 Statistic analysis plan(ning) and power calculation

Statistic analysis will be done using univariable and multivariable logistic regression models. The possible sample size in our trials is limited by practical realities such as the feasibility of comprehensive metabolic analyses of all of the samples. However, it is still possible to assess what can be achieved with the available sample size: Based on our own data, we expect standard deviations for the primary marker candidates of TRP and KYN of 15 resp. 0.8 units. Given the available sample size of 66, this will allow us to be able to detect differences between groups of about 60% of the standard deviations for both tasks (corresponding to about 9 units for TRP and 0.5 units for KYN), which we consider to be realistic differences. The power for the logistic regression models was approximated using a two-sided two-sample t-test (alpha=5%, Power=90%). Validation will be performed in groups half this size.

2.6 Cumulative safety and efficacy information

2.6.1 Cumulative safety information

Not applicable, as this study is performed on samples already stored in the PATH biobank and does not involve any interventions.

2.6.2 Cumulative efficacy information

Not applicable, as this study is performed on samples already stored in the PATH biobank and does not involve any interventions.

2.7 Conduct

2.7.1 Schedule for study conduct including timelines for key study milestones³

The mandatory milestones for clinical trials incl. “First Patient, First Visit (FPFV)”, “Last Patient, First Visit (LPFV)” and “Last Patient, Last Visit (LPLV)” and the mandatory deliverables for clinical trials incl. “First study subject approvals package”, “Midterm recruitment report” and “Report on status of posting results” are provided for clinical trials, in which MESI-STRAT recruits patients (WOO trial, ET Termination trial, see table 2 in section 1). This trial relies on existing cohorts. Therefore, no patients will actively be recruited by MESI-STRAT and the mandatory milestones and deliverables are not applicable.

2.7.2 Description of recruitment strategy

Not applicable, as all samples are available in the PATH biobank, so that the feasibility of this study is not dependent on actual subject recruitment.

2.7.3 Description and assignment of intervention

Not applicable as no interventions are planned in this study.

2.7.4 Study management, study monitoring, data and sample management

PATH Biobank has longstanding expertise in biobanking and contributes to the European BIOBANKING AND BIOMOLECULAR RESOURCES RESEARCH INFRASTRUCTURE - EUROPEAN REASEARCH INFRASTRUCTURE CONSORTIUM (BBMRI-ERIC) initiative.

PATH was founded by BC survivors and is intended for the sole purpose of supporting BC research. PATH stores breast cancer tumor tissues, normal adjacent tissue samples and blood serum aliquots in fresh frozen quality from more than **9,200 BC patients** (out of which >7,400 ER+). For the storage of the samples PATH has established a decentralized biorepository. The samples are processed and stored according to strict SOPs, which is critical for our study as immediate freezing and storage at ultralow temperatures are essential for metabolite and protein measurements. Every patient has signed informed consent, and detailed clinical and therapeutic data sets annotate the samples. Follow-up information is available. To annotate the samples PATH runs a centralized database using Oracle® software and a LIMS Software developed in-house. Data sets comprise standardized clinical data as well as follow-up data.

Data collection and management

- Extensive annotating data sets provided by PATH;
- Centralized data base and project management in Munich, Germany;
- High data security of the MESI-STRAT REPOSITORY (for details, see section 5.1.4 Personal Data), which provides a comprehensive overview of all the patient samples available in MESI-STRAT.

³ Key study milestones will be scrutinised during the time course of the project. Significantly delayed key study milestones (e.g. FPFV) might lead to the termination of the grant agreement.

Sample management

- Uniform SOPs;
- Fresh frozen quality, storage in the gas phase of liquid nitrogen at minus 160° Celsius.

2.7.5 Sponsor, coordinating centre(s) and committees

The patient organisation Biobank PATH will coordinate this study. Sample and data management is performed by PATH following their existing biobanking SOPs and procedures. The MESI-STRAT Repository is run by DKFZ.

2.7.6 Study medication

Not applicable as no study specific medication will be administered in this study.

2.7.7 Clinical centres

PATH will carry out this study with its existing samples.

The samples of the PATH cohort have been collected in 7 certified breast cancer centers in Germany

1. Bonn: Evangelische Kliniken Bonn gGmbH, Johanniter-Krankenhaus; Universitäts-Frauenklinik Bonn;
2. Dortmund: St. Johannes-Hospital Dortmund, Brustzentrum;
3. Bochum/Herne: Universitäts-Frauenklinik Marienhospital Herne, Kooperatives Brustzentrum Bochum/Herne; St. Annahospital, Kooperatives Brustzentrum Bochum/Herne;
4. Kassel: Klinikum Kassel GmbH, IBZ- Interdisziplinäres Brustzentrum;
5. Marburg: Klinik für Gynäkologie, gynäkologische Endokrinologie und Onkologie, Universitätsklinikum Gießen und Marburg GmbH, Standort Marburg, Brustzentrum Regio;
6. Offenbach: Klinik für Gynäkologie und Geburtshilfe, Klinikum Offenbach GmbH;
7. Regensburg: Klinik für Frauenheilkunde und Geburtshilfe der Universität Regensburg am Caritas-Krankenhaus St. Josef.

2.8 Orphan designation

Not applicable.

2.9 'Unit costs per patient' for clinical trials / studies / investigations

Not applicable.

3 Clinical study No.2

3.1 Identifier

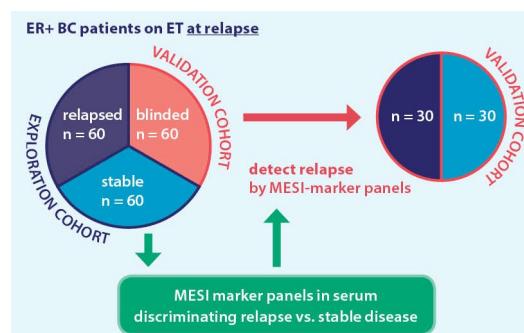
Relapse Detection Trial:

Identification and validation of MESI marker panels detecting ER+BC patient subgroups with relapse (Trial 6.2, WP6)

3.2 Study design and endpoints

3.2.1 Study design

Prospective case control study



Due to the long time to relapse, the low percentage of relapsing patients, and the risk for relapse remaining constant over two decades, ER+BC clinical trials with endpoints such as progression free survival are long-term efforts that cannot be carried out within the typical budget and duration of a H2020 project. MESI-STRAT overcomes this limitation by taking advantage of existing cohorts and trials to analyse MESI marker panels in patients at relapse.

60 prospectively collected sera of stable patients from the PATH cohort matched to 60 sera collected from ER+ BC patients at relapse/distant metastasis in the frame of studies (appropriate baseline samples from the PRAEGNANT or Everolimus Combined With Exemestane studies) will be employed.

Analysis of signalling pathways and metabolites in these sera will allow identification of MESI marker panels detecting relapse in ER+ BC patients. To validate if the identified markers indeed detect relapse, 60 sera of matched stable or relapsed women, respectively will be analysed in a blinded fashion and assigned to relapsed vs stable groups according to their MESI marker panels. Comparison with the known clinical characteristics of the tumors will allow validation of the discriminatory power of the identified MESI markers to distinguish between stable and relapsed patients.

3.2.2 Primary and secondary endpoint(s)

Primary Endpoint

Analysis of signalling pathways and metabolites to identify MESI marker panels detecting relapse in ER+ BC patients.

3.2.3 Relevant guidance documents

(a) International guidelines:

- [ICH Guideline for Good Clinical Practice E6\(R1\)](#);
- [Declaration of Helsinki](#);
- OECD Guidelines on Human Biobanks and Genetic Research Databases <https://www.oecd.org/sti/biotech/44054609.pdf>.
- EU Privacy Directive 95/46/EC and from the date the General Data Protection Regulation (EU) 2016/679 becomes effective (expected May 2018), this regulation shall apply to the extent applicable to the ongoing data collection

(b) National guidelines

Germany

- The maintenance of a biomaterial bank touches on two essential laws of the German basic law (Grundgesetz): the right to informational self-determination (Art. 2 paragraph 1 Grundgesetz). According to which the person concerned can decide himself to whom he / she is disclosing which personal information. As well as the fundamental right to freedom of research, Art. 5 paragraph 3 Grundgesetz;
- The German Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG);
- 2010 opinion of the German Ethics Council (Deutscher Ethikrat, DER) on biobanking;
- National Data Protection Act of Baden-Württemberg, Germany - LDSG-BW (for DKFZ and UKL-HD).

Netherlands

- Dutch Personal Data Protection Act (Wet Bescherming Persoonsgegevens ,WBP).

(c) Institutional/ local guidelines and Standard Operating Procedures

- SOP No. 0210-G Processing of tissue for the Tumorbank of the foundation PATH.

3.3 Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees

Approval from the ethics committee of the University of Heidelberg (S-496/2014) is in place for the collection and analysis of biological fluids and tumor tissue. An application for an ethics approval for the prospective collection of blood and urine for patients from the PATH cohort is currently being prepared by PATH. Ethics approvals for the IMPACT study (METc 2013/146), the Everolimus/Exemestane study (2013.406) and the PRAEGNANT study (S-391/2014) are in place.

3.4 Subjects/population(s)

Samples from the following patients will be included:

Histologically documented ER+ BC

Age > 18 yrs

Definition of sub-populations if subgroup analysis is intended.

Not intended

3.5 Statistic analysis plan(ning) and power calculation

Statistic analysis will be done using univariable and multivariable logistic regression models. The possible sample size in our trials is limited by practical realities such as the feasibility of comprehensive metabolic analyses of all of the samples. However, it is still possible to assess what can be achieved with the available sample size: Based on our own data, we expect standard deviations for the primary marker candidates of TRP and KYN of 15 resp. 0.8 units. Given the available sample size of 60, this will allow us to be able to detect differences between groups of about 60% of the standard deviations for both tasks (corresponding to about 9 units for TRP and 0.5 units for KYN), which we consider to be realistic differences. The power for the logistic regression models was approximated using a two-sided two-sample t-test (alpha=5%, Power=90%). Validation will be performed in groups half this size.

3.6 Cumulative safety and efficacy information

3.6.1 Cumulative safety information

Participation in trial 6.2 of MESI-STRAT does not introduce significant additional risk to participating patients. For the stable controls there will only be an additional blood draw and donation of urine. The amount of blood donation will not exceed national and local regulations or the amount specified in the informed consent leaflets. The collection of urine does not pose any risk. Finally, at each step throughout the sample collection, patients will have the option to opt out of any sample collection procedure at any time with no negative consequence to them or their medical care.

3.6.2 Cumulative efficacy information

Not applicable. Interventions such as drug treatments, for which efficacy information exist are not performed in this study.

3.7 **Conduct**

3.7.1 Schedule for study conduct including timelines for key study milestones⁴

The mandatory milestones for clinical trials incl. “First Patient, First Visit (FPFV)”, “Last Patient, First Visit (LPFV)” and “Last Patient, Last Visit (LPLV)” and the mandatory deliverables for clinical trials incl. “First study subject approvals package”, “Midterm recruitment report” and “Report on status of posting results” are provided for clinical trials, in which MESI-STRAT recruits patients (WOO trial, ET Termination trial, see table 2 in section 1). This trial relies on existing cohorts. Therefore, no patients will actively be recruited by MESI-STRAT and the mandatory milestones and deliverables are not applicable.

3.7.2 Description of recruitment strategy

First the available appropriate baseline samples (from the IMPACT, PRAEGNANT or Everolimus/Exemestane studies) will be identified using the MESI-respository (WP1), then the samples will be matched with patients from the PATH cohort, that will be invited to donate blood at clinical centers that will be subcontracted by PATH for the prospective collection of biological fluids. As the PATH biobank cohort consists of > 7800 ER+ BC patients with up to 10 years of follow-up, identification of matched stable patients from the PATH cohort will be easily achievable. As the PATH cohort patients have donated their BC tissue and serum specifically to support BC research, they have a genuine interest in promoting BC research. We therefore expect recall and willingness to donate blood and urine to be high.

3.7.3 Description and assignment of intervention

Not applicable as interventions such as drug treatments for which efficacy information exist are not performed in this trial.

3.7.4 Study management, study monitoring, data and sample management

The management of the studies, from which samples at relapse will be obtained is arranged for in their respective protocols and approved by the required ethics committees.

PATH will invite matched stable patients from the PATH cohort, that will be invited to donate blood at clinical centers that will be subcontracted by PATH for the prospective collection of biological fluids.

- The MESI-STRAT REPOSITORY (WP1) will allow a comprehensive overview of all the patient samples available in MESI-STRAT;
- Extensive annotating data sets provided in the frame of clinical trials or treating physicians at partner centers;
- High data security of the MESI-STRAT REPOSITORY (for details, see section 5.1.4 Personal Data).

⁴ Key study milestones will be scrutinised during the time course of the project. Significantly delayed key study milestones (e.g. FPFV) might lead to the termination of the grant agreement.

3.7.5 Sponsor, coordinating centre(s) and committees

This study will be coordinated by DKFZ.

3.7.6 Study medication

The medications are administered either in the frame of clinical trials independent from but associated to MESI-STRAT or in standard clinical care, MESI-STRAT will not influence or alter medications, but will only analyse samples from patients obtaining medications outside of MESI-STRAT.

3.7.7 Clinical centres

UKL-HD, UMCG and VHHIO

Samples will be also obtained from PRAEGNANT (partner UKL-HD).

3.8 *Orphan designation*

Not applicable.

3.9 '*Unit costs per patient*' for clinical trials / studies / investigations

Not applicable.

4 Clinical study No. 3

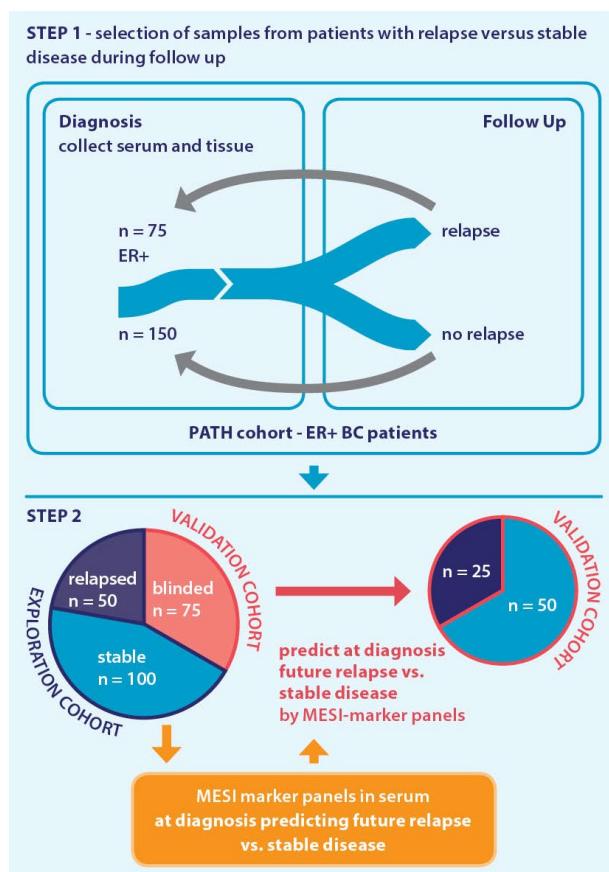
4.1 Identifier

Relapse Prediction Trial:

Retrospective identification and validation of MESI marker panels at diagnosis predicting patient subgroups with future relapse or stable disease (Trial 6.3, WP6)

4.2 Study design

Nested case control and validation study



Analysis of 50 sera obtained at diagnosis from patients from the PATH cohort that developed relapse/distant metastasis during follow-up compared to 100 sera from patients that remained stable for > 5 years for signalling pathways and metabolites to identify MESI marker panels predictive for future relapse/distant metastasis. To validate if the identified markers indeed are able to predict future relapse/distant metastasis, 75 sera will be analysed in a blinded fashion and assigned to deriving either from stable or relapsed patients according to their MESI marker signatures. Comparison with the known clinical characteristics of the patients will allow validation of the predictive power of the identified MESI marker panels for future relapse/distant metastasis. In addition, selected tumor tissues representative for specific MESI markers signatures of patients that remained stable and relapsed during follow-up will be analysed in detail regarding their signaling and metabolic networks to investigate the molecular mechanisms underlying the MESI marker panels predictive for future relapse.

4.2.1 Primary and secondary endpoint(s)

Primary Endpoint

Analysis of signalling pathways and metabolites to identify MESI marker panels predicting future relapse/development of distant metastasis in ER+ BC patients.

4.2.2 Relevant guidance documents

(a) International guidelines:

- [ICH Guideline for Good Clinical Practice E6\(R1\);](#)
- [Declaration of Helsinki](#);
- OECD Guidelines on Human Biobanks and Genetic Research Databases
<https://www.oecd.org/sti/biotech/44054609.pdf>.

(b) *National guidelines*

The PATH biobank is subject to German law. Samples and data stemm from German sites only.

- The maintenance of a biomaterial bank touches on two essential laws of the German basic law (Grundgesetz): the right to informational self-determination (Art. 2 paragraph 1 Grundgesetz). According to which the person concerned can decide himself to whom he / she is disclosing which personal information. As well as the fundamental right to freedom of research, Art. 5 paragraph 3 Grundgesetz;
- The German Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG);
- 2010 opinion of the German Ethics Council (Deutscher Ethikrat, DER) on biobanking;
- National Data Protection Act of Baden-Württemberg, Germany - LDSG-BW (for DKFZ).

(c) *Institutional/ local guidelines and Standard Operating Procedures*

- SOP No. 0210-G Processing of tissue for the Tumorbank of the foundation PATH.

4.3 Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees

Approval from the ethics committee of the University of Bonn, Germany (225/06) has been obtained by PATH for the collection, storage and analysis of tumor tissue and serum at diagnosis.

4.4 Subjects/population(s)

Samples from the following patients will be included:

- Patients with histologically documented ER+ breast cancer in the PATH cohort;
- Age > 18 yrs;
- Signed informed consent form;
- Necessary biological material and clinical follow-up data available.

Tissue and serum samples are provided by the non-profit organization Patients' Tumor Bank of Hope (PATH Biobank, Augsburg, Germany: <http://www.path-biobank.org/index.php/en/about-path/>) as standardized fresh frozen tissue and blood serum specimens. Patients provided written, informed consent for the storage of samples and data, follow-up contact, and further use of samples and data for research purposes.

The PATH data base currently contains 106 cases with distant metastasis during follow-up. Of these 75 will randomly be selected for this study. As controls 150 cases that were stable for more than 5 years from the PATH cohort will be selected from 1847 available cases.

Definition of sub-populations if subgroup analysis is intended.

Not intended.

4.5 Statistic analysis plan(ning) and power calculation

Statistic analysis will be done using univariable and multivariable logistic regression models. The possible sample size in our trials is limited by practical realities such as the feasibility of comprehensive metabolic analysis of all of the samples. However, it is still possible to assess what can be achieved with the available sample size: Based on our own data, we expect standard deviations for the primary marker candidates of TRP and KYN of 15 resp. 0.8 units. The expected numbers of 50 patients with relapses and 100 patients without relapses will allow detection of differences of roughly 60% of the standard deviation (corresponding to approx.. 9 units for TRP and 0.5 units for KYN), which we consider to be realistic differences. The power for the logistic regression models was approximated using a two-sided two-sample t-test (alpha=5%, Power=90%). Validation will be performed in groups half this size.

4.6 Cumulative safety and efficacy information

4.6.1 Cumulative safety information

Not applicable, as this study is performed on samples already stored in the PATH biobank and does not involve any interventions.

4.6.2 Cumulative efficacy information

Not applicable, as this study is performed on samples already stored in the PATH biobank and does not involve any interventions.

4.7 Conduct

4.7.1 Schedule for study conduct including timelines for key study milestones⁵

The mandatory milestones for clinical trials incl. “First Patient, First Visit (FPFV)”, “Last Patient, First Visit (LPFV)” and “Last Patient, Last Visit (LPLV)” and the mandatory deliverables for clinical trials incl. “First study subject approvals package”, “Midterm recruitment report” and “Report on status of posting results” are provided for clinical trials, in which MESI-STRAT recruits patients (WOO trial, ET Termination trial, see table 2 in section 1). This trial relies on existing cohorts. Therefore, no patients will actively be recruited by MESI-STRAT and the mandatory milestones and deliverables are not applicable.

4.7.2 Description of recruitment strategy

Not applicable, as all samples are available in the PATH biobank, so that the feasibility of this study is not dependent on actual subject recruitment.

4.7.3 Description and assignment of intervention

Not applicable as no interventions are planned in this study.

4.7.4 Study management, study monitoring, data and sample management

Data collection and management (including mechanisms to ensure data quality, completeness and integrity)

PATH Biobank has longstanding expertise in biobanking and contributes to the European BIOBANKING AND BIOMOLECULAR RESOURCES RESEARCH INFRASTRUCTURE - EUROPEAN REASEARCH INFRASTRUCTURE CONSORTIUM (BBMRI-ERIC) initiative.

PATH was founded by BC survivors and is intended for the sole purpose of supporting BC research. PATH stores breast cancer tumor tissues, normal adjacent tissue samples and blood serum aliquots in fresh frozen quality from more than **9,200 BC patients** (out of which >7,400 ER+). For the storage of the samples PATH has established a decentralized biorepository. The samples are processed and stored according to strict SOPs, which is critical for our study as immediate freezing and storage at ultralow temperatures are essential for metabolite and protein measurements. Every patient has signed informed consent, and detailed clinical and therapeutic data sets annotate the samples. Follow-up information is available. To annotate the samples PATH runs a centralized database using Oracle® software and a LIMS Software developed in-house. Data sets comprise standardized clinical data as well as follow-up data.

- The MESI-STRAT REPOSITORY will allow a comprehensive overview of all the patient samples available in MESI-STRAT;
- Extensive annotating data sets provided by PATH;
- Centralized data base and project management in Munich, Germany;

⁵ Key study milestones will be scrutinised during the time course of the project. Significantly delayed key study milestones (e.g. FPFV) might lead to the termination of the grant agreement.

- High data security of the MESI-STRAT REPOSITORY (for details, see section 5.1.4 Personal Data).

Sample management

- Uniform SOPs;
- Fresh frozen quality, storage in the gas phase of liquid nitrogen at minus 160° Celsius.

4.7.5 Sponsor, coordinating centre(s) and committees

The patient organisation Biobank PATH will coordinate this study. Sample management is done by PATH following their existing biobanking SOPs and procedures. Data management is done by DKFZ and PATH following highest security standards.

4.7.6 Study medication

Not applicable as no study specific medication will be administered in this study.

4.7.7 Clinical centres

PATH will carry out this study with its existing samples.

The samples of the PATH cohort have been collected in 7 certified breast cancer centers in Germany.

1. Bonn: Evangelische Kliniken Bonn gGmbH, Johanniter-Krankenhaus; Universitäts-Frauenklinik Bonn;
2. Dortmund: St. Johannes-Hospital Dortmund, Brustzentrum;
3. Bochum/Herne: Universitäts-Frauenklinik Marienhospital Herne, Kooperatives Brustzentrum Bochum/Herne; St. Annahospital, Kooperatives Brustzentrum Bochum/Herne;
4. Kassel: Klinikum Kassel GmbH, IBZ- Interdisziplinäres Brustzentrum;
5. Marburg: Klinik für Gynäkologie, gynäkologische Endokrinologie und Onkologie, Universitätsklinikum Gießen und Marburg GmbH, Standort Marburg, Brustzentrum Regio;
6. Offenbach: Klinik für Gynäkologie und Geburtshilfe, Klinikum Offenbach GmbH;
7. Regensburg: Klinik für Frauenheilkunde und Geburtshilfe der Universität Regensburg am Caritas-Krankenhaus St. Josef.

4.8 Orphan designation

Not applicable.

4.9 'Unit costs per patient' for clinical trials / studies / investigations

Not applicable.

5 Clinical study No. 4

5.1 Identifier

Tissues for Preclinical Trials:

Screening and collection of ER+BC tissues with subgroup specific MESI marker panels for preclinical models (PDX, bioreactor) (Trial 6.4, WP6)

5.2 Study design

Collection of fresh human ER+BC tissue for cultivation in perfusion-based bioreactors and the generation of PDX-models in ongoing clinical studies at VHIO and UKL-HD.

5.2.1 Primary and secondary endpoint(s)

Not applicable

Collection of ER+ BC tissue

5.2.2 Relevant guidance documents

(a) International guidelines:

- [ICH Guideline for Good Clinical Practice E6\(R1\);](#)
- [Declaration of Helsinki](#);
- OECD Guidelines on Human Biobanks and Genetic Research Databases
<https://www.oecd.org/sti/biotech/44054609.pdf>.

(b) National guidelines

Germany:

- The maintenance of a biomaterial bank touches on two essential laws of the German basic law (Grundgesetz): the right to informational self-determination (Art. 2 paragraph 1 Grundgesetz). According to which the person concerned can decide himself to whom he / she is disclosing which personal information. As well as the fundamental right to freedom of research, Art. 5 paragraph 3 Grundgesetz;
- The German Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG);
- 2010 opinion of the German Ethics Council (Deutscher Ethikrat, DER) on biobanking;
- National Data Protection Act of Baden-Württemberg, Germany - LDSG-BW (for DKFZ).

Spain:

Data Protection Legislation

Ley 41/2002, de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.

5.3 Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees

Approval from the ethics committee of the University of Heidelberg (S-496/2014) is in place for the collection of biological fluids and tumor tissue. Human ER+BC tissue will be used for the generation of PDX models at VHIO, this is covered by the ethics approval PR(IR)53/2010, see Annex 3.2.11, which allows the investigation of the “Tumorgeneity and study drug sensitivity in xenoimplant models derived from breast cancer biopsies from patients in active treatment”

5.4 Subjects/population(s)

The following patients will be included:

- Patients with histologically documented ER+ breast cancer
- Age > 18 yrs
- signed informed consent form

Definition of sub-populations if subgroup analysis is intended.

Not intended.

5.5 Statistic analysis plan(ning) and power calculation

Not applicable

5.6 Cumulative safety and efficacy information

5.6.1 Cumulative safety information

Not applicable, as this study does not involve any interventions.

5.6.2 Cumulative efficacy information

Not applicable, as this study does not involve any interventions.

5.7 *Conduct*

5.7.1 Schedule for study conduct including timelines for key study milestones⁶

The mandatory milestones for clinical trials incl. “First Patient, First Visit (FPFV)”, “Last Patient, First Visit (LPFV)” and “Last Patient, Last Visit (LPLV)” and the mandatory deliverables for clinical trials incl. “First study subject approvals package”, “Midterm recruitment report” and “Report on status of posting results” are provided for clinical trials, in which MESI-STRAT recruits patients (WOO trial, ET Termination trial, see table 2 in section 1). This trial is part of ongoing trials at VHIO and UKL-HD. Therefore, no patients will actively be recruited by MESI-STRAT and the mandatory milestones and deliverables are not applicable. Ethics votes are in place.

5.7.2 Description of recruitment strategy

This trial is part of ongoing trials at VHIO and UKL-HD. Therefore, no patients will actively be recruited by MESI-STRAT.

5.7.3 Description and assignment of intervention

Not applicable as no interventions are planned in this trial.

5.7.4 Study management, study monitoring, data and sample management

Data management

- The MESI-STRAT REPOSITORY will allow a comprehensive overview of all the patient samples available in MESI-STRAT;
- High data security (for details, see section 5.1.4 Personal Data).

Sample management

- Uniform SOPs;
- Immediate transfer of the samples to the laboratory

5.7.5 Sponsor, coordinating centre(s) and committees

VHIO will coordinate this study.

5.7.6 Study medication

Not applicable as no study specific medication will be administered in this trial.

⁶ Key study milestones will be scrutinised during the time course of the project. Significantly delayed key study milestones (e.g. FPFV) might lead to the termination of the grant agreement.

5.7.7 Clinical centres

VHIO, UKL-HD

5.8 *Orphan designation*

Not applicable.

5.9 '*Unit costs per patient*' for clinical trials / studies / investigations

Not applicable.

6 Clinical study No. 5

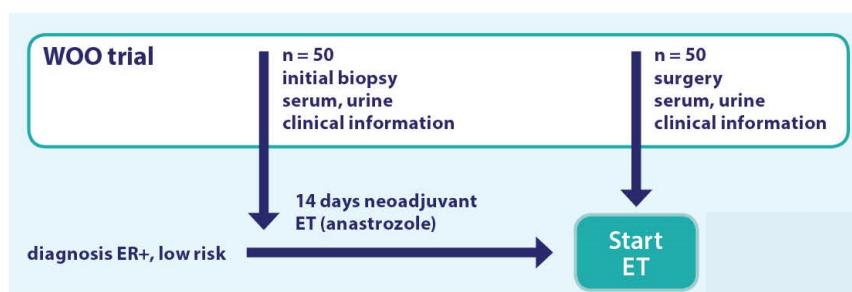
6.1 Identifier

WOO trial:

Prospective Window of opportunity trial 2 weeks neoadjuvant Anastrozole in Postmenopausal Women with ER+ BC. (Trial 7.2, WP7)

6.2 Study design and endpoints

6.2.1 Study design



This interventional clinical trial will be a single center, open-label, non-randomized prospective investigator driven Window of Opportunity study performed at UKL-HD.

The objectives of the WOO

study are to investigate the biological effects of Anastrozole monotherapy in serum, urine and tumor tissue of ER+ BC patients by assessing the percentage change from the baseline value in Ki67 expression after 2 weeks of therapy and analyzing gene expression, protein expression and metabolites in the tumor tissue (before and after Anastrozole treatment) as well as analyzing metabolite and signaling (MESI) panels in the sera and urine of the patients. The primary objective is to assess the association between biomarkers and biological/pathological outcome(s).

6.2.2 Primary and secondary endpoint(s)

The following primary endpoint will be assessed:

- association of MESI networks & MESI marker panels with biological/pathological responses.

The following secondary endpoints will be assessed:

- percent change in Ki67 expression from baseline to the core biopsy 2 weeks after the start of treatment;
- pCR defined as absence of invasive cancer in the breast and sampled regional lymph nodes;
- clinical response of the breast tumor to therapy as assessed by histopathology;
- radiologic response of the breast tumor as assessed by radiologic or ultrasound assessment.

6.2.3 Relevant guidance documents

The trial will be conducted in Germany according to the principles laid down in the following guidance documents:

- Declaration of Helsinki from October 2013
- Guideline for good clinical practice E6(R2), EMA/CHMP/ICH/135/1995
- The EU Clinical Trial Directive 2001/20/EC
- The new Clinical Trials Regulation (CTR) EU No 536/2014 (as soon as it become applicable)
- Note for guidance on statistical principals for clinical trials (CPMP/ICH/363/96)

- EU Privacy Directive 95/46/EC and from the date the General Data Protection Regulation (EU) 2016/679 becomes effective (expected May 2018), this regulation shall apply to the extent applicable to the ongoing data collection
- The German Drug Law (AMG, Arzneimittelgesetz) in its current version.
- The German Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG);
- National Data Protection Act of Baden-Württemberg, Germany - LDSG-BW

6.3 Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees

UKL-HD together with its clinical research organisation (CRO) KKS will deal with regulatory and ethical approvals - ensuring that all regulatory and ethical requirements will have been met before the clinical trial is initiated (i.e. approval by the regulatory authority, the independent ethics committee, and other appropriate authorities (data protection, etc.), and registration in clinical trial databases (National Regulatory Agencies, EudraCT and clinicaltrials.gov). The sponsor UKL-HD will maintain close contact with regulatory authorities and the independent ethics committee throughout the duration of the clinical trial and until the end of the study.

6.4 Subjects/population(s)

The inclusion criteria are as follows:

- Postmenopausal women;
- early-stage ER+ breast cancer;
- tumor size >1 cm;
- signed informed consent form.

The exclusion criteria are as follows:

- prior therapy for breast cancer;
- inflammatory cancers;
- Pregnancy;
- Any medical condition (e.g. substance abuse) that may, in the clinical judgement of the investigator, independently influence the subject's outcome during this study;
- Participation in another interventional clinical trial within the last four weeks.

Definition of sub-populations if subgroup analysis is intended.

Not intended.

6.5 Statistic analysis plan(ning) and power calculation

The statistical analysis will be done using an intra-individual comparison between measurements before and after 14 days of neoadjuvant ET therapy. Based on our previous measurements all relevant variables show an approximately normal distribution, therefore comparisons will be done using paired, two-sided t-tests (alpha=5%). We do not yet have access to longitudinal data regarding our potential markers. However, we expect intra-individual standard deviations to be smaller than standard deviations between different patients, and thus a sample size of 50 patients will be sufficient to find differences between groups of about 60% of the standard deviations for both tasks (corresponding to about 9 units for TRP and 0.5 units for KYN), which we consider to be relevant.

6.6 Cumulative safety and efficacy information

6.6.1 Cumulative safety information

The trial medication Anastrozole is a standard of care therapy for postmenopausal women. For ethical reasons only women that would receive an aromatase inhibitor after surgery will be included in the WOO trial. Therefore only the sequence of aromatase inhibitor application will be altered as Anastrozole will be given for 2 weeks before routine surgery as opposed to its regular adjuvant application. Anastrozole is well known and approved by German regulatory authorities for the treatment of postmenopausal ER+ BC patients. Due to its safety profile we expect only few serious adverse events (SAEs) to occur. All relevant safety information can be found in the Summary of Product Characteristics (SmPC). As at UKL-HD is experienced in neoadjuvant administration of Anastrozole, as Anastrozole has already been administered in the frame of the neoMONARCH study for two weeks in a neoadjuvant setting in combination with Abemaciclib.

6.6.2 Cumulative efficacy information

Anastrozole is approved by German regulatory authorities for the treatment of postmenopausal ER+ BC patients. All relevant efficacy information can be found in the Summary of Product Characteristics (SmPC).

6.7 Conduct

6.7.1 Schedule for study conduct including timelines for key study milestones⁷

In this section, include a (realistic!) planning of the schedule for the study conduct, including provisions and timelines for ethics and other administrative approvals. As a minimum, include realistic planning and timing for the key study milestones below. Dates for key study milestones are defined relative to the starting date of the project (i.e. month 1, month 6 etc.):

- First Patient (or study subject), First Visit (FPFV):
- Last Patient (or study subject), First Visit:
- Last Patient (or study subject), Last Visit:
- End of Study (including follow-up and data analysis):

Mile-stone #	Milestone name	Related WPs	Due date (month)	Means of verification
MS1	WOO Trial First Patient, First Visit (FPFV)	7	12	Informed consent signed
MS6	WOO Trial Last Patient First Visit (LPFV)	7	51	Informed consent signed
MS7	WOO Trial Last Patient Last Visit (LPLV)	7	54	Samples in NCT tissue bank (UKL-HD)
MS8	WOO Trial End of Study	7	57	Data analysis complete

Deliverable #	Deliverable name	WP #	Lead Partner	Type	Dissemination level	Delivery (months)
D7.1	WOO trial: First study subject approvals package	7	UKL-HD	R	CO	6
D7.3	WOO trial: Midterm recruitment report	7	UKL-HD	R	CO	24
D7.5	WOO trial: Report on status of posting results	7	UKL-HD	R	PU	57

6.7.2 Description of recruitment strategy

We will recruit the patients for the WOO trial at initial diagnosis, which is an overwhelming and devastating experience for them. We therefore expect significant dropout to occur. To overcome this problem, we plan to recruit 70 patients for this trial, although only 50 patients are required for the measurements. The recruitment strategy will be based on the participation of the expert centre UKL-HD specialised in breast cancer treatment. Our experience indicates that we will be able to recruit at least 25 patients per year.

6.7.3 Description and assignment of intervention

Study procedures and timelines

⁷ Key study milestones will be scrutinised during the time course of the project. Significantly delayed key study milestones (e.g. FPFV) might lead to the termination of the grant agreement.

SE Visit 1	day 1 until day 14	Day 14	V2
blood draw	treatment	blood draw	
urine collection		urine collection	
EORTC 30	Anastrozole will be supplied as tablets administered orally, 1 mg daily	EORTC 30	
vital signs		vital signs	
standard of care diagnostics		ultra sound	
screening: inclusion criteria/exclusion criteria			
biopsy (routine)			surgery (routine)
fresh frozen tissue			fresh frozen tissue

6.7.4 Study management, study monitoring, data and sample management

Study Management:

The trial sponsor will be UKL-HD. It is estimated that 6 months will be needed to set up the study and obtain the final ethics and regulatory approvals (first study subject approval package). A total of max. 70 patients will be enrolled within 45 months. The remaining 12 months will be dedicated to data analysis and the results of the trial will be published.

UKL-HD will be responsible for (i) study monitoring, (ii) communication with regulatory/health authorities and ethics committees, and (iii) monitoring and declaring of (S)AEs. The CRO KKS that belongs to and supports UKL-HD will conduct the data management.

Monitoring:

The study's quality assurance management is based on a risk-based approach. According to ICH/GCP guidelines, the sponsor will ensure that the trial is adequately monitored. Data monitoring will protect the rights and well-being of patients, ensure that reported trial data are accurate, complete, and verifiable from source documents, and that the trial is being conducted in compliance with the currently approved protocol/amendment(s), GCP, and the applicable regulatory requirements.

On-site and remote monitoring will be performed by KKS. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

Safety Assessment and Management:

Adverse events (AEs) will be ascertained by the investigators using non-leading questions, noted as spontaneously reported by the patients to the medical staff or observed during any measurements on all study days. The observation period begins with the first administration of the IMP (before the first administration of the IMP: medical history) and ends with the last study visit. AEs will be documented in the patient file and in the CRF. All subjects who present AEs, whether considered associated with the use of the trial medication or not, will be monitored by the responsible investigator to determine their outcome; this applies to withdrawals too.

AEs and SAEs that are on-going at the time of death are considered not resolved or resolving.

All SAEs and their relevance for the benefit/risk assessment of the study will be evaluated continuously during the study and for the final report. All SAEs will be documented in the "Serious Adverse Event" form.

All SAEs must be reported by the investigator to the sponsor and the responsible Safety Officer at KKS Heidelberg within 24 hours after the SAE becomes known using the "Serious Adverse Event"

form. The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the trial medication.

SUSARs are to be reported to the responsible ethics committees, the competent authority and to all participating investigators. All SAEs will be subject to a second assessment by a designated person, who will be independent from the reporting investigator. The second assessor will fill out a ‘Second Assessment Form’ for each SAE and send it back per fax to the responsible person at KKS Heidelberg within 48 hours.

Data management:

An eCRF will be developed in English for recording all the demographic and clinical data in the study centre online. The eCRF will be developed on a designated platform ensuring appropriate read and write access for the -study centre. Patients will be identified by a study-specific subject number (pseudonymization). Entries will be checked for consistency by the system. Additionally, the data will be monitored regularly, in order to avoid missing data.

Sample management:

Sample management will be performed in collaboration with the NCT liquid biobank, which is part of UKL-HD . As a biobank focused on high-quality sample handling and storage as well as management processes ensuring that samples are prepared and stored in consistent conditions, the NCT liquid biobank will provide the infrastructure and support for quality-assured handling and storage of the samples collected in the frame of the WOO trial in the MESI-STRAT project.

6.7.5 Sponsor, coordinating centre(s) and committees

UKL-HD will be the trial sponsor. It is planned to include patients at one site, UKL-HD, only.

6.7.6 Study medication

The study medication Anastrozole will be used within its market authorization. Therefore, no trial specific manufacturing or labelling procedure is necessary.

6.7.7 Clinical centres

Universtiy Hospital Heidelberg, UKL-HD

6.8 Orphan designation

Not applicable

6.9 'Unit costs per patient' for clinical trials / studies / investigations

Not applicable.

7 Clinical study No. 6

7.1 Identifier

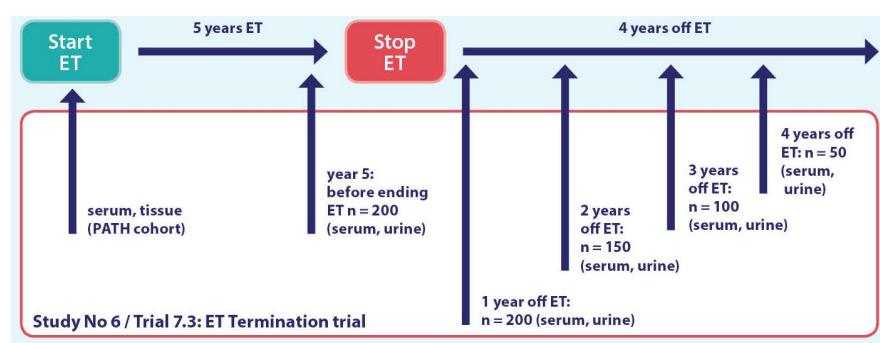
ET Termination trial:

Analysis of longitudinally collected serum and urine from ER+ BC patients before and after termination of ET (Trial 7.3, WP7)

7.2 Study design and endpoints

7.2.1 Study design

Prospective cohort study and validation study



PATH will coordinate the collection of longitudinal sera and urine from PATH cohort patients. ER+ PATH patients in the last year of endocrine treatment as well as in the following years without endocrine therapy will be invited to donate serum and urine once a year. This will allow us to obtain serum and urine in the presence and absence of ET. Analysis of serum/urine from patients before and after termination of ET and comparison to clinical follow-up may allow identification of MESI marker alterations predictive of recurrence after termination of ET. Patients with these markers might benefit from prolonged treatment beyond the current standard of 5 years.

7.2.2 Primary and secondary endpoint(s)

Primary endpoint:

Identification of MESI marker panel alterations in serum and urine in the presence and absence of ET

Secondary endpoint:

Analysis of serum/urine from patients before and after termination of ET and comparison to clinical follow-up may allow identification of MESI marker alterations predictive of recurrence after termination of ET.

7.2.3 Relevant guidance documents

(a) *International guidelines:*

- [ICH Guideline for Good Clinical Practice E6\(R1\)](#)
- [Declaration of Helsinki](#)
- Statistical principles for clinical trials ([CPMP/ICH/363/96](#))
- OECD Guidelines on Human Biobanks and Genetic Research Databases
<https://www.oecd.org/sti/biotech/44054609.pdf>

(b) *National guidelines*

- The maintenance of a biomaterial bank touches on two essential laws of the German basic law (Grundgesetz): the right to informational self-determination (Art. 2 paragraph 1 Grundgesetz). According to which the person concerned can decide himself to whom he / she is disclosing which personal information. As well as the fundamental right to freedom of research, Art. 5 paragraph 3 Grundgesetz.
- The German Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG)
- 2010 opinion of the German Ethics Council (Deutscher Ethikrat, DER) on biobanking

(c) *Institutional/ local guidelines and Standard Operating Procedures*

- SOP Nr. 0210-G Processing of tissue for the Tumorbank of the foundation PATH

7.3 Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees

An approval from the ethics committee of the University of Bonn, Germany (225/06) has been obtained by PATH for the collection and analysis of tumor tissue and serum at diagnosis. An approval from the the ethics committee of the Bavarian State chamber of Physicians for the prospective collection of biological fluids from the PATH cohort is currently being applied for by PATH.

7.4 Subjects/population(s)

The inclusion criteria are as follows:

- Patients with histologically documented ER+ breast cancer in the PATH cohort in their final year of receiving ET, willing to donate blood and urine once a year when they are off ET.
- Age > 18 yrs
- signed informed consent form

The exclusion criteria are as follows:

- other therapy for BC than ET ongoing
- inflammatory cancers
- Pregnancy
- Any medical condition (e.g. substance abuse) that may, in the clinical judgement of the investigator, independently influence the subject's outcome during this study
- Participation in another interventional clinical trial within the last four weeks

Definition of sub-populations if subgroup analysis is intended.

Not intended

7.5 Statistic analysis plan(ning) and power calculation

Statistic analysis will be done using univariable and multivariable logistic regression models. In this trial we will analyse more samples than in the ones above as we also want to investigate a possible association between MESI marker panel alterations after termination of ET and relapse/development of distant metastasis. Based on our own data, we expect standard deviations for the primary marker candidates of TRP and KYN of 15 resp. 0.8 units. Given the available sample size of 200, this will allow us to be able to detect differences between groups corresponding to about 5 units for TRP and 0.3 units for KYN, which we consider to be relevant differences. The power for the logistic regression models was approximated using a two-sided two-sample t-test (alpha=5%, Power=90%).

Based on the clinical follow-up data of the PATH cohort, we expect approx. 5 patients per year to develop metastasis. We therefore estimate that of the 200 patients studied on and off ET in this trial, approx. 20 will relapse during the 4 years of the study. These samples may allow the identification of MESI marker alterations predictive of recurrence after termination of ET.

7.6 Cumulative safety and efficacy information

7.6.1 Cumulative safety information

Participation in this trial does not introduce significant additional risk to participating patients. There will be one additional blood draw and urine collection per year for patients from the PATH cohort in their final year of ET and during subsequent years (max. 4 years). The amount of blood donation will not exceed national and local regulations or the amount specified in the informed consent leaflets. The collection of urine does not pose any risk. Finally, at each step throughout the sample collection, patients will have the option to opt out of any sample collection procedure at any time with no negative consequence to them or their medical care.

7.6.2 Cumulative efficacy information

Not applicable as no interventions such as drug treatments, for which efficacy information exists are performed in this trial.

7.7 Conduct

7.7.1 Schedule for study conduct including timelines for key study milestones⁸

In this section, include a (realistic!) planning of the schedule for the study conduct, including provisions and timelines for ethics and other administrative approvals. As a minimum, include realistic planning and timing for the key study milestones below. Dates for key study milestones are defined relative to the starting date of the project (i.e. month 1, month 6 etc.):

- First Patient (or study subject), First Visit (FPFV):
- Last Patient (or study subject), First Visit:
- Last Patient (or study subject), Last Visit:
- End of Study (including follow-up and data analysis):

Mile-stone #	Milestone name	Related WPs	Due date (month)	Means of verification
MS2	ET Termination Trial First Patient, First Visit (FPFV)	7	18	Informed consent signed
MS5	ET Termination Trial Last Patient First Visit (LPFV)	7	45	Informed consent signed
MS9	ET Termination Trial Last Patient Last Visit (LPLV)	7	57	Samples in PATH biobank
MS10	ET Termination Trial End of Study	7	57	Data analysis complete

Deliverable #	Deliverable name	WP #	Lead Partner	Type	Dissemination level	Delivery (months)
D7.2	ET termination trial: First study subject approvals package	7	PATH	R	CO	6
D7.4	ET termination trial: Midterm recruitment report	7	PATH	R	CO	30
D7.6	ET termination trial: Report on status of posting results	7	PATH	R	PU	57

7.7.2 Description of recruitment strategy

PATH will invite PATH cohort patients in their final year of ET to donate longitudinal sera and urine (one a year) at clinical BC centers, which will be subcontracted by PATH. 451 ER+ BC PATH patients in the last year of ET will be available throughout the first 48 months of the MESI-STRAT project period. From these patients tissue and serum at diagnosis is present in the PATH biobank. The patients have been in regular contact with PATH and clinical follow-up as well as up-to-date contact information is available. As the PATH cohort patients have donated their BC tissue and serum specifically to support BC research, they have a genuine interest in promoting BC research. We therefore expect recall and willingness to donate blood and urine to be high. We plan to recruit 200 of the 451 eligible ER+ PATH patients (44%) in the course of MESI-STRAT.

⁸ Key study milestones will be scrutinised during the time course of the project. Significantly delayed key study milestones (e.g. FPFV) might lead to the termination of the grant agreement.

7.7.3 Description and assignment of intervention

Not applicable as no interventions are tested in this trial.

The patients receive standard of care treatment (ET followed by no therapy) and blood and urine is analysed every year.

7.7.4 Study management, study monitoring, data and sample management

PATH Biobank has longstanding expertise in biobanking and contributes to the European BIOBANKING AND BIOMOLECULAR RESOURCES RESEARCH INFRASTRUCTURE – EUROPEAN REASEARCH INFRASTRUCTURE CONSORTIUM (BBMRI-ERIC) initiative.

PATH was founded by BC survivors and is intended for the sole purpose of supporting BC research. PATH stores breast cancer tumor tissues, normal adjacent tissue samples and blood serum aliquots in fresh frozen quality from more than **9,200 BC patients** (out of which >7,400 ER+). For the storage of the samples PATH has established a decentralized biorepository. The samples are processed and stored according to strict SOPs, which is critical for our study as immediate freezing and storage at ultralow temperatures are essential for metabolite and protein measurements. Every patient has signed informed consent, and detailed clinical and therapeutic data sets annotate the samples. Follow-up information is available. To annotate the samples PATH runs a centralized database using Oracle® software and a LIMS Software developed in-house. Data sets comprise standardized clinical data as well as follow-up data. PATH is in continuous contact with the patients that donated tissues and sera and therefore will be able to coordinate longitudinal collection of serum and urine.

Data collection and management

- Extensive annotating data sets provided by PATH;
- Centralized data base and project management in Munich, Germany;
- High data security (for details, see section 5.1.4 Personal Data).
- The MESI-STRAT Repository provides a comprehensive overview of all the patient samples available in MESI-STRAT.

Sample management

- Uniform SOPs;
- Fresh frozen quality, storage in the gas phase of liquid nitrogen at minus 160° Celsius.

7.7.5 Sponsor, coordinating centre(s) and committees

PATH biobank will coordinate this trial. Sample and data management is done by PATH following their existing biobanking SOPs and procedures.

7.7.6 Study medication

Not applicable as no study specific medication will be administered in trial 7.3.

7.7.7 Clinical centres

PATH will subcontract breast cancer centres for the collection of serum and urine.

7.8 *Orphan designation*

Not applicable

7.9 *'Unit costs per patient' for clinical trials / studies / investigations*

Not applicable.

8 Clinical study No. 7

8.1 Identifier

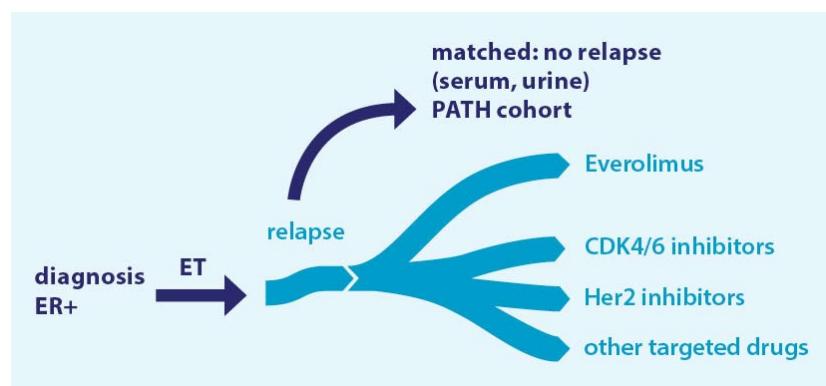
Intervention Validation Trials:

Clinically validate predictive MESI-models and marker panels for targeted drug interventions (Trial 7.4, WP7)

8.2 Study design and endpoints

8.2.1 Study design

Cross-sectional and validation study



Clinical studies in ER+BC present several challenges including the long time to relapse, the low percentage of relapsing patients, and the risk for relapse remaining constant over two decades. Hence, trials with endpoints such as progression free survival are long-term efforts that cannot

be carried out within the typical budget and duration of a H2020 project. One of the ways how MESI-STRAT overcomes these limitations is by taking advantage of existing and ongoing trials and analysing MESI-models and marker panels in patients receiving targeted drug interventions. MESI-STRAT will investigate the effects of targeted drug interventions on MESI marker panels and their association with drug response in human ER+ BC patients using sera and urine obtained from clinical studies (see WP1 for available material). If enough patients of a MESI-marker defined ER+BC subgroup predicted to respond to the investigated drug intervention are available in a clinical trial, the predictive power of the MESI marker panel to stratify patients to the targeted drug intervention will be validated by analysing if the patients of this subgroup respond better to this drug than the rest of the study population.

In addition, we will validate whether MESI-models and marker panels predictive in female ER+ BC also apply to male ER+ BC. Using male ER+ BC samples from two clinical trials on male BC conducted at UMCG and samples of BRCA mutated male BC patients available in the NCT tissue bank of UKL-HD we will validate if MESI models and marker panels predictive in female ER+ BC also apply to male ER+ BC.

8.2.2 Primary and secondary endpoint(s)

Primary endpoints:

- Identification of effects of targeted drug interventions on MESI marker panels
- Investigation of association of MESI marker panels with clinical response

Secondary endpoint:

- Validation of predictive MESI-models and marker panels for targeted drug interventions

8.2.3 Relevant guidance documents

(a) *International guidelines:*

- [ICH Guideline for Good Clinical Practice E6\(R1\)](#)
- European Union (EU) clinical-trial legislation ([Directive 2001/20/EC](#))
- [Declaration of Helsinki](#)
- Statistical principles for clinical trials ([CPMP/ICH/363/96](#))
- OECD Guidelines on Human Biobanks and Genetic Research Databases
<https://www.oecd.org/sti/biotech/44054609.pdf>

(b) *National guidelines*

Germany

- The maintenance of a biomaterial bank touches on two essential laws of the German basic law (Grundgesetz): the right to informational self-determination (Art. 2 paragraph 1 Grundgesetz). According to which the person concerned can decide himself to whom he / she is disclosing which personal information. As well as the fundamental right to freedom of research, Art. 5 paragraph 3 Grundgesetz.
- The German Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG)
- 2010 opinion of the German Ethics Council (Deutscher Ethikrat, DER) on biobanking
- National Data Protection Act of Baden-Württemberg, Germany - LDSG-BW (for DKFZ and UKL-HD)

Netherlands

- Dutch Personal Data Protection Act (Wet Bescherming Persoonsgegevens, WBP).

Spain:

Data Protection Legislation

Ley 41/2002, de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.

8.3 Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees

In the frame of translational analyses of samples obtained from clinical studies/standard of care drug treatments performed by our clinical partners and clinical collaborators (see letters) serum and urine will be analysed for MESI networks and marker panels in agreement with the PIs/board of these studies or in the case of standard drug treatments after informed consent and in the presence of an ethics approval for analysis of these markers in serum and urine from the patients (present e.g. for

UKL-HD, S-496/2014). If the informed consent and ethics approval of a clinical studies encompass our analyses, no further ethics approval for the analyses is necessary. If this is not the case an addendum to the ethics approval will be applied for at the responsible ethics committee and the MESI-STRAT analyses will be included in the informed consent form.

8.4 Subjects/population(s)

Study	Patient/tumor characteristics	Treatment	Center	Ethics approval
PRAEGNANT	MBC or inoperable loco-regional disease	Non-specific SoC medications	UKL-HD	S-391/2014
Ribeca	HR+ HER2- locally advanced BC or MBC	Cdk 4/6 inhibitor Ribociclib in combination with Letrozole	UKL-HD	261_16Az
Parsifal	ER+ HER2- MBC	Fulvestrant + Cdk4/6 inhibitor Palbociclib vs Letrozole + Palbociclib	UKL-HD VHIO	AFmu-290/2015
DETECT V/ CHEVENDO	HR+ HER2+ MBC	Chemo vs. ET + Trastuzumab/Pertuzumab	UKL-HD	113/15
IMPACT	MBC	Non-specific SoC medications	UMCG	METc 2013/146
FDHT PET + Bicalutamide	MBC	bicalutamide	UMCG	METc 2015/396
POSEIDON	HR+ HER2- MBC	Tamoxifen + Isoform selective Pi3K inhibitor GDC-0032 (taselisib) vs. Tamoxifen alone	VHIO	M14POS / POSEIDON
Everolimus /Exemestane	postmenopausal patients with advanced MBC who have progressed on Anastrozole or Letrozole	Everolimus + Exemestane	E. Boven; VUMC (NCT02109 913)	2013.406
Lilly I3Y-MC-JPCG	previously treated HR+ HER2- MBC	Abemaciclib + Tamoxifen vs. Abemaciclib alone	VHIO	with Eli Lilly
GEICAM 2015-07 (C31006) TAKEDA	ER+ HER2- advanced or MBC that has progressed during or after Aromatase Inhibitor therapy	FIIMLN0128 (A TORC1/2 Inhibitor) + Fulvestrant	VHIO	with Takeda
D3610C00001	advanced solid malignancies	Akt inhibitor AZD5363	VHIO	with AstraZeneca
Bayer 16298	HER2- MBC subjects with bone metastases treated with Hormonal Treatment background therapy	Placebo-controlled trial of Radium-223 Dichloride vs. Placebo	VHIO	with Bayer
Bayer 17096	HER2- MBC subjects with bone metastases treated with Hormonal Treatment background therapy	Placebo-controlled trial of Radium-223 Dichloride + Exemestane and Everolimus vs. Placebo + Exemestane and Everolimus	VHIO	with Bayer
PUMA-NER-5201	solid tumors with activating HER2, HER3 or EGFR mutations or with EGFR gene amplification	Tyrosine kinase inhibitor Neratinib	VHIO	with PUMA Biotechnology
PMT4979g	HR+ locally advanced BC or MBC	isoform selective Pi3K inhibitor taselisib (GDC-0032)	VHIO	with Roche
Monaleesa-2	advanced BC	Cdk 4/6 inhibitor Ribociclib + Letrozole vs. Letrozole alone	samples supplied by Novartis	with Novartis

			(application initiated)	
Padma	MBC	Palbociclib + ET vs. Chemo	UKL-HD, study in preparation	in preparation
Dutch CDK4/6 Trial	adjuvant treatment or at progression	Cdk4/6 Inhibitor + ET versus Cdk4/6 at progression	UMCG, VUMC in preparation	in preparation

Male breast cancer cohorts

Study	Patient/tumor characteristics	Samples	Center	Ethics approval
Male breast cancer: prospective into perspective	male BC	200 serum/plasma samples and fresh frozen BC tissues prospectively collected from males	UMCG	METc 2013/291
MALE BREAST CANCER study	male BC	800 FFPE BC samples retrospectively collected from males	UMCG	MEC-2011-015
BRCA-mutated male BC cohort	BRCA-mutated male BC cohort	clinical data from 137 male BC patients with BRCA mutations	UKL-HD	samples in NCT tissue bank

- Patients treated in clinical trials with drugs relevant for MESI-STRAT performed by our clinical partners and clinical collaborators
- Patients treated with standard of care drug treatments (ET: Tamoxifen, Fulvestrant, Letrozole, Anastrozole, Exemestane; targeted therapies: Everolimus, etc.)

Definition of sub-populations if subgroup analysis is intended.

If enough patients of a MESI-marker defined ER+BC subgroup predicted to respond to the investigated drug intervention are available in a clinical trial, the predictive power of the MESI marker panel to stratify patients to the targeted drug intervention will be validated by analysing if the patients of this subgroup respond better to this drug than the rest of the study population.

8.5 Statistic analysis plan(ning) and power calculation

The studies have been calculated based upon different endpoint than MESI marker panels. Based on the predictive power of the MESI marker panels that will be investigated for specific interventions and in specific subgroups predicted to respond to certain interventions, the sample size required for MESI marker panel analysis will be calculated.

8.6 Cumulative safety and efficacy information

8.6.1 Cumulative safety information

Participation in this trial does not introduce significant additional risk to participating patients. If at all, there will only be a serum vial of blood drawn in addition at blood draws performed in the frame of standard clinical care or in the study. The amount of blood donation will not exceed national and local regulations or the amount specified in the informed consent leaflets. The collection of urine does not pose any risk. Finally, at each step throughout the sample collection, patients will have the option to opt out of any sample collection procedure at any time with no negative consequence to them or their medical care.

8.6.2 Cumulative efficacy information

Not applicable as interventions such as drug treatments for which efficacy information exist are performed in the frame of the clinical studies performed outside MESI-STRAT or in the frame of standard clinical care and will not be altered by addition of serum and urine analyses for MESI marker panels.

8.7 Conduct

8.7.1 Schedule for study conduct including timelines for key study milestones⁹

The mandatory milestones for clinical trials incl. “First Patient, First Visit (FPFV)”, “Last Patient, First Visit (LPFV)” and “Last Patient, Last Visit (LPLV)” and the mandatory deliverables for clinical trials incl. “First study subject approvals package”, “Midterm recruitment report” and “Report on status of posting results” are provided for clinical trials, in which MESI-STRAT recruits patients (WOO trial, ET Termination trial, see table 2 in section 1). These trials are part of ongoing trials by our partners and collaborators. Therefore, no patients will actively be recruited by MESI-STRAT and the mandatory milestones and deliverables are not applicable.

⁹ Key study milestones will be scrutinised during the time course of the project. Significantly delayed key study milestones (e.g. FPFV) might lead to the termination of the grant agreement.

8.7.2 Description of recruitment strategy

- If samples from clinical trials for which ethics approvals and consent forms covering the analysis of MESI marker panels exist, they will be used for analysis, the recruitment of patients will be performed in the frame of these clinical trials and will not be performed by MESI-STRAT.

As the clinical trials MESI-STRAT is associated with are well planned and conducted by every experienced centers it is expected that recruitment will go smoothly.

- If serum and urine is collected from patients under standard clinical care treatments, the patients will be informed by the treating physician and after informed consent will be asked to donate a serum and urine sample. As the clinical centers partnering MESI-STRAT are state of the art BC centers of excellence that treat extremely high numbers of BC patients, it is expected that recruitment of patients under standard clinical care treatment will be easily achievable.

8.7.3 Description and assignment of intervention

Not applicable as interventions such as drug treatments for which efficacy information exist are performed in the frame of the clinical studies that are performed outside MESI-STRAT or in the frame of standard clinical care and will not be altered by additional serum and urine analyses for MESI marker panels.

8.7.4 Study management, study monitoring, data and sample management

In this trial MESI-STRAT will analyse samples from clinical studies conducted by partners and collaborators or collected from patients treated by standard clinical care. Therefore, MESI-STRAT will not conduct the studies, but only select appropriate studies, in which MESI marker panels can be validated. After ethical approval for the analysis of the samples/collection of the samples, provision of the samples and the relevant pseudonymized clinical data, the predictive power of the MESI marker panel to stratify patients to the targeted drug intervention will be validated by analysing if the patients of this subgroup respond better to this drug than the rest of the study population.

- The MESI-STRAT REPOSITORY (WP1) will allow a comprehensive overview of all the patient samples available in MESI-STRAT.
- Extensive annotating data sets
- High data security (for details, see section 5.1.4 Personal Data).

Sample management

- Uniform SOPs
- Fresh frozen quality, storage in the gas phase of liquid nitrogen at minus 160° Celsius

8.7.5 Sponsor, coordinating centre(s) and committees

UKL-HD will coordinate this trial.

8.7.6 Study medication

Not applicable as no study specific medication will be administered in this trial.

8.7.7 Clinical centres

UKL-HD, UMCG, VHHIO, and associated partners.

8.8 *Orphan designation*

Not applicable

8.9 '*Unit costs per patient*' for clinical trials / studies / investigations

Not applicable.



MESI-STRAT

Systems Medicine of Metabolic-Signaling networks -
A New Concept for Breast Cancer Patient Stratification

Acronym: MESI-STRAT

Optional Annex 3: Ethics Supporting Documents

Annex 3.1: Copies of licenses for animal experiments

Note: Short English summaries are provided below in the list of documents.

1. **Document 8763:** License for the investigation of the efficacy of Akt inhibition in combination with Paclitaxel in tumors from patients with Her2- BC implanted subcutaneously in mice.
2. **Document 2015/UCL/MD/14:** License for the study of novel mechanisms that allow tumors to resist or escape immune-mediated rejection and to optimize vaccine treatments using mice as model organisms.
and
Document 2015/UCL/MD/15: License for the study of the role of hypoxia in the immunosuppressive tumoral microenvironment and the immune response.

Annex 3.2: Copies of ethics approvals for clinical studies

Note: Short English summaries are provided below in the list of documents.

1. **Document 225/06:** Ethics approval of PATH for the collection and analysis of tumor tissue and serum at diagnosis, for WP6, tasks 6.1 and 6.3 (University of Bonn, Germany).
2. **Document S-496/2014:** Ethics approval from the ethics committee of UKL-HD for the collection of biological fluids and tumor tissue for biomarker discovery (DNA, RNA, proteins and metabolites in cells, tissues, serum, plasma, urine, CSF and saliva of healthy controls and cancer patients).

3. **Document METc 2013/146:** Ethics approval from the ethics committee of UMCG for the IMPACT study, a multicenter prospective observational cohort study in non-rapidly progressive MBC patients eligible for first-line systemic therapy undergoing molecular imaging.
4. **Document 2013.406:** Ethics approval from the ethics committee of VUMC, Amsterdam for the Everolimus/Exemestane study performed by E. Boven, investigating the PI3K pathway in tumor tissue and circulating DNA to obtain further insight in the efficacy of everolimus when combined with exemestane
5. **Document S-391/2014:** Ethics approval from the ethics committee of UKL-HD for the PRAEGNANT study, investigating biomarkers in patients with MBC
6. **Document 261_16Az:** Ethics approval for the Ribecca study, investigating the Cdk4/6 inhibitor Ribociclib in combination with Letrozole in locally advanced BC or MBC.
7. **Document AFmu-290/2015:** Ethics approval for the PARSIFAL study, investigating Fulvestrant in combination with the Cdk4/6 inhibitor Palbociclib versus Letrozole in combination with Palbociclib in ER+ HER2- MBC
8. **Document 113/15:** Ethics approval for the CHEVENDO study, investigating chemotherapy versus ET + Trastuzumab/Pertuzumab in HR+ HER2+ MBC
9. **Document METc 2015/396:** Ethics approval for the FDHT PET + Bicalutamide study, investigating if 18F-fluorodihydrotestosterone positron emission tomography (FDHT-PET) can be used to predict (early) treatment response to, and optimal dosing of the anti-androgen bicalutamide.
10. **Document M14POS / POSEIDON:** Ethics approval for the POSEIDON study, investigating Tamoxifen in combination with the isoform selective Pi3K inhibitor taselisib (GDC-0032) versus Tamoxifen alone in HR+ HER2- MBC
11. **Document PR(IR)53/2010:** Ethics approval to investigate the “tumorigenesis and study drug sensitivity in xenoimplant models derived from breast cancer biopsies from patients in active treatment”
12. **Document S-392/2015:** Ethics approval for the GEKKO study, a data- and liquid biobank for early cancer detection focusing on the detection and evaluation of novel biomarkers or biomarker signatures for the detection of cancer.
13. **Document METc 2013.291:** Ethics approval for the prospective collection and analysis of serum/plasma samples and fresh frozen BC tissues from male patients
14. **Document MEC-2011-015:** Ethics approval for the collection and analysis of FFPE BC tissues from male patients

Annex 3.3: Examples of patient information documents and informed consent forms

- a) PATH informed consent document and patient information for the collection and analysis of tumor tissue and serum at diagnosis.
- b) Informed consent form and patient information from DKFZ and UKL-HD for the collection of biological fluids and tumor tissue for biomarker discovery.
- c) Information sheet and informed consent form of the study “Tumorigenicity and analysis of drug sensitivity in biopsies from patients with cancer in active treatment implanted in immunosuppressed mice.”

Annex 3.4: Letters of Intent and Support

Annex 3.4.1 International Advisory Board

- Dr. Eric Hoedemaker, Medical Director Oncology, Novartis, NL
- Prof. Epie Boven, VU Medical Center Amsterdam, NL
- Prof. Gerburg Wulf, Dana-Farber Harvard Cancer Center, US;
- Prof. emerita A.-L. Borresen-Dale, The Norwegian Radium Hospital, NO;
- Susan Knox, CEO, EUROPA DONNA – The European Breast Cancer Coalition, IT;
- Doris Schmitt, PATH co-chair, executive board member of the European patient academy EUPATI, DE;
- Dr. Andreas Raue, Lead early stage immune-oncology development and biomarker discovery, Merrimack Pharmaceuticals, US;
- ITN EpiPredict, Dr P.J. Verschure, Coordinator, University of Amsterdam, NL and Prof. H. V. Westerhoff, Director of Manchester Centre for Integrative Systems Biology (MCISB), UK

Annex 3.4.2 Collaborating scientists and companies

- Dr. Eric Hoedemaker, Medical Director Oncology, Novartis, NL
- Dr. Sandra Orchard, Team Leader Molecular Interactions, EMBL-EBI, Hinxton, Cambridge, UK
- Dr. Robert Petryszak, Team Leader Gene Expression, EMBL-EBI, Hinxton, Cambridge, UK
- Dr. Sam Whitehouse, PhD MRSC, Chief Operating Officer, QuantuMDx Group Ltd, UK
- Dr. Werner M. Enz, President of the Board of Directors, CELLEC BIOTEK, Basel, CH

Annex 3.4.3 Collaborating clinical trials and biobanks

- Prof. E. Boven, Everolimus/Exemestane trial, VU Medical Center Amsterdam, NL
(see above, combined with letter for International Advisory Board)
- Dr. Romy Kirsten, NCT Liquid Biobank, UKL-HD, Heidelberg, DE
- Prof. Dr. Hermann Brenner, Gekko Study, DKFZ, Heidelberg, DE

- Dr. Inge Konings, VU Medical Center Amsterdam, NL
- Prof. Wallwiener, Prof. Tesch, Prof. Fasching, Prof. Brucker, PRAEGNANT multicenter study, DE

Annex 3.4.4 Institutional commitments

- Dr. Susanne Weg-Remers, German Cancer Information Service (KID), DKFZ, Heidelberg, DE
- Dr. Anja Dietzel, KKS clinical trials competence centre (CRO), UKL-HD, Heidelberg, DE
- Dr. Sikkema, Director, Tech Transfer Office, CSI-BGG, Groningen, NL
- Dr. Herzog, Director, Tech Transfer Office DKFZ, Heidelberg, DE

 Generalitat de Catalunya
Departament d'Agricultura,
Ramaderia, Pesca i Alimentació
Serveis Territorials a Barcelona
Secció de Biodiversitat i Activitats Cinegètiques

Generalitat de Catalunya
Serveis Territorials d'Agricultura,
Ramaderia, Pesca i Alimentació a
Barcelona

Número: 00065/1572/2016
Data: 08/02/2016 10:47:38

Registre de sortida

VALL D'HEBRON INSTITUT DE RECERCA

Sra. Montserrat Molano i Flores
Edifici Mediterrània - Estabulari
Pg. Vall d'Hebron, 119-129
08035 Barcelona

Assumpte : Comunicació prèvia de procediments d'experimentació
(expedient B-NPP-010/16)

Senyora,

Hem rebut la comunicació prèvia del procediment d'experimentació:

Títol: "Estudio de la eficacia de la inhibición de Akt para sensibilizar al tratamiento con paclitaxel los tumores derivados de pacientes con cáncer de mama Her2-negativo implantados subcutáneamente en modelos de ratón"

Investigador/a responsable: Albert Gris Oliver

Aquest procediment té assignat el número d'ordre DARP: **8763**.

D'acord amb l'article 32 del Decret 214/1997 de 30 de juliol sobre protecció dels animals utilitzats per a experimentació i altres finalitats científiques, aquest procediment té una validesa fins el **20 de gener de 2018**, sempre i quan no existeixi cap modificació del procediment.

Atentament,

El Cap de la Secció de Biodiversitat
i Activitats Cinegètiques


Josep Maria López Martín

Barcelona, 1 de febrer de 2016
ilp

Avinguda Meridiana, 38
08018 Barcelona
Tf. 93 409 20 90
Fax 93 552 48 83

PS /246



Comité d'Ethique pour l'Expérimentation Animale
Secteur des Sciences de la Santé
Université catholique de Louvain



Président :

Prof. P. Cani : Pharmacie

Membres :

Dr Y. Achouri : Transgenèse

Prof J.P. Beaufays : Bio-éthique

Prof. J.P. Dehoux : Vétérinaire UCL, Secrétaire

Prof. M.N Derèse : Juriste

Prof. D. Lison : Toxicologie

Prof. J. Maisin : Radiothérapie

Prof. A. Robert : Bio-statistiques

Ir V. Rosseels : Cellule Bien-Être Animal

Dr. G. Warnier : Vétérinaire LICR

Louvain en Woluwe, le 2 juin 2015

Professeur Van den Eynde
Laboratoire LICR

Professeur,

Vos deux projets intitulés :

(i) Projet intitulé : «Recherches et études de nouveaux mécanismes qui permettent aux tumeurs de résister ou d'échapper au rejet immunitaire et perfectionnement des traitements vaccinaux thérapeutiques en utilisant la souris comme modèle» a été accepté par le comité d'éthique de la faculté pour l'expérimentation animale sous la référence 2015/UCL/MD/14 (20000 souris sur 4 ans, sévérité tous les niveaux de douleur et anesthésie sans réveil). Les maîtres d'expérience responsables sont :

- CANE Stefania
- LAMY Juliette
- PILOTTE Luc
- RIBEIRO Floriane
- SCHRAMME Florence
- UYTENHOVE Catherine
- van der BRUGGEN Pierre
- Van den EYNDE Benoît
- ZHU Jingjing

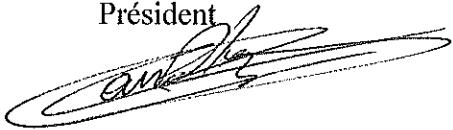
Nous vous rappelons, qu'en tant que directeur de laboratoire, vous êtes responsable du personnel travaillant avec des animaux et vous devez pouvoir justifier leur formation réglementaire quant à la législation sur le bien-être des animaux d'expérience.

(ii) Projet intitulé : « Rôle de l'hypoxie dans le micro-environnement tumoral immunosuppressif et la réponse immunitaire» a été accepté par le comité d'éthique de la faculté pour l'expérimentation animale sous la référence 2015/UCL/MD/15 (4000 souris sur 4 ans, sévérité tous les niveaux de douleur et anesthésie sans réveil). Le maître d'expérience responsable est le prof Van den Eynde.

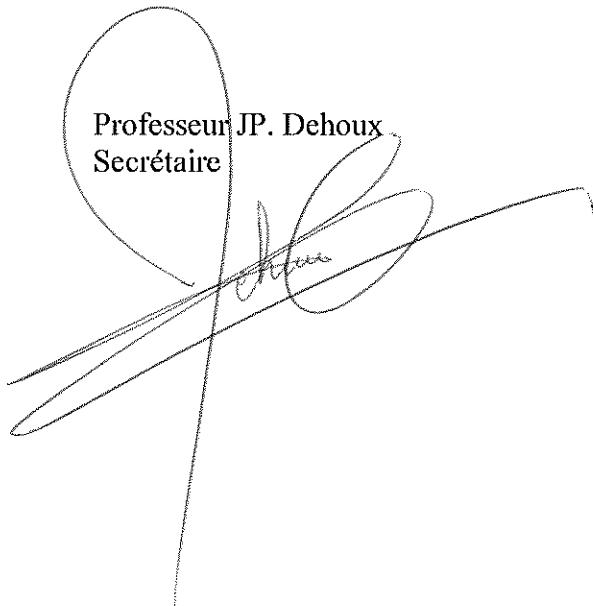
Nous vous rappelons, qu'en tant que directeur de laboratoire, vous êtes responsable du personnel travaillant avec des animaux et vous devez pouvoir justifier leur formation réglementaire quant à la législation sur le bien-être des animaux d'expérience.

Pour le Comité :

Professeur P. Cani
Président



Professeur JP. Dehoux
Secrétaire





Rheinische Friedrich-Wilhelms-Universität

Medizinische Fakultät

Ethik-Kommission

Ethik-Kommission - Medizinische Fakultät Bonn
Institut für Pharmakologie und Toxikologie, Reuterstr. 2 b, 53113 Bonn

persönlich / vertraulich

Herr

Prof. Dr. med. R. Büttner

Institut für Pathologie UK Bonn

Sigmund-Freud-Str. 25

53105 Bonn / durch Boten

53113 Bonn, 29.12.06

Reuterstr. 2 b

Durchwahl: 73 - 5415

Telefax: 73 - 4801

(Vorwahl national: 02 28-;

international: + 49 -2 28-)

e-mail: ethik@uni-bonn.de

Internet: <http://ethik.meb.uni-bonn.de>

Prof.Ra./br.

Lfd. Nr. 255/06

Bitte stets angeben!

Betr.: Ihr Antrag an die Ethik-Kommission

Studententitel: „Patienten-Tumorbank der Hoffnung“ der Stiftung PATH

Sponsor: Stiftung Path

- Checkliste
- Gutachterliche Stellungnahme
- Patienteninformation und Einverständniserklärung
- Broschüre zu PATH Patients Tumorbank of Hope

Sehr geehrter Herr Kollege Büttner,

Ihr obiger Antrag ging hier am 21.12.2006 ein und wird auf der nächsten Sitzung der Ethik-Kommission am 22. März 2006 beraten. Er wird hier unter der laufenden Nummer 255/06 geführt. Wir möchten Sie bitten, bei der künftigen Korrespondenz diese laufende Nummer stets anzugeben.

Mit freundlichen Grüßen

M. Braun
Prof. Dr. K. Racké
Vorsitzender der Ethik-Kommission
i.A. M. Braun / Sekr.



Rheinische Friedrich-Wilhelms-Universität

Medizinische Fakultät Ethik-Kommission

Ethik-Kommission - Medizinische Fakultät Bonn
Institut für Pharmakologie und Toxikologie, Reuterstr. 2 b, 53113 Bonn

persönlich / vertraulich

Herr

Prof. Dr. med. R. Büttner

Institut für Pathologie UK Bonn

Sigmund-Freud-Str. 25

53105 Bonn / durch Boten

53113 Bonn, 12.01.07

Reuterstr. 2 b

Durchwahl: 73 - 5415
Telefax: 73 - 4801
(Vorwahl national: 02 28-;
international: + 49 - 2 28 -)
e-mail: ethik@uni-bonn.de
Internet: http://ethik.meb.uni-bonn.de

Prof.Ra./br.

Herrn Prof. Dr. med. R. Büttner
bitte unterschreiben
R.W.

Lfd. Nr. 255/06

Bitte stets angeben!

Betr.: Ihr Antrag an die Ethik-Kommission
Studententitel: „Patienten-Tumorbank der Hoffnung“ der Stiftung PATH
Sponsor: Stiftung Path

- Checkliste
- Gutachterliche Stellungnahme
- Patienteninformation und Einverständniserklärung
- Broschüre zu PATH Patients Tumorbank of Hope

Sehr geehrter Herr Kollege Büttner,

die Ethik-Kommission für klinische Versuche am Menschen und epidemiologische Forschung mit personenbezogenen Daten der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn hat Ihren o.g. Antrag auf ihrer Sitzung am 11.01.2007 beraten. Sie ist aufgrund der vorgelegten Unterlagen zu dem Beschluss gekommen, gegen die geplante Studie keine grundsätzlichen berufsethischen oder berufsrechtlichen Bedenken zu erheben.

Die Ethik-Kommission weist allerdings noch auf folgende Punkte hin, die bei der Beratung aufgefallen sind, und berücksichtigt werden sollten:

- 1) In der Patienteninformation müsste klarer erläutert werden, dass die Krankheitsdaten von der Klinik ohne vorherige Pseudonymisierung an die Stiftung weitergeleitet werden, und dass dies in der Regel per Fax erfolgen soll. Die Probleme der Faxübertragung sowie die Maßnahmen für eine möglichst sichere Übertragung sollten erläutert werden. Eine Verpflichtung zur Einhaltung dieser Sicherheitsmaßnahmen sollte abgegeben werden.
- 2) Bei einem Widerruf der Einverständniserklärung muss den Patientinnen auch die Option eröffnet werden, dass bisher gesammelten Daten gelöscht werden (nicht nur nicht mehr verwendet werden)

Änderungen im Prüfplan müssen der Ethik-Kommission mitgeteilt werden und bedürfen der erneuten Beratung.

Des Weiteren müssen Änderungen bei den beteiligten Prüfärzten der Ethik-Kommission unverzüglich mitgeteilt werden.

Die ärztliche und juristische Verantwortung des Leiters der klinischen Prüfung und der an der Prüfung teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethik-Kommission durch unsere Stellungnahme unberührt.

Die Ethik-Kommission der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den ICH-GCP Richtlinien. Den Beratungen der Ethik-Kommission der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn liegt gemäß der gültigen Berufsordnung die maßgebende Deklaration des Weltärztekongresses von Helsinki in der letzten revidierten Fassung zugrunde.

Mit freundlichen Grüßen



Prof. Dr. K. Racké

Vorsitzender der Ethik-Kommission

Nachfolgend sind die Mitglieder der Ethik-Kommission aufgeführt, die in der Sitzung am 11.01.2007 den o. g. Antrag beraten haben:

Prof. Dr. K. Racké, Arzt für Pharmakologie und Toxikologie, Vorsitzender der Ethik-Kommission

Herr Prof. Dr. U. Bode, Arzt für Pädiatrie

Frau Mareille Warnken, Apothekerin

PD Dr. W. Bruchhausen, Medizinethiker

Prof. Dr. jur. M. Böse, Jurist

Dr. med. S. Stier, Arzt für Innere Medizin

Herr Matthias Grube, studentischer Vertreter

Frau Chr. Niedecken, Patientenvertreterin



Medizinische Fakultät Heidelberg

Ethikkommission der Med. Fak. HD | Alte Glockengießerei 11/1 | D-69115 Heidelberg

Frau Dr. med. Christiane Opitz
Deutsches Krebsforschungszentrum (DKFZ)
Im Neuenheimer Feld 280
69120 Heidelberg

—
08.10.2015
ts-cd

Berufsrechtliche Beratung

Unser Zeichen: **S-496/2014** (Bitte stets angeben)

Titel: Identifikation von Biomarkern in biologischen Flüssigkeiten und Geweben von Krebspatienten und Patienten mit entzündlichen Erkrankungen.
Kurztitel: Identifikation von Biomarkern.

Eingereichte Unterlagen:

- Ersteinreichung vom 17.09.2014:
Anschreiben vom 17.09.2014
Zusammenfassung
Checkliste Sonstige Studien
Formular für Erstantrag vom 17.09.2014
Probandeninformation Version 1 vom September 2014
Einwilligungserklärung (Probanden) (undatiert)
Patienteninformation Version 1 vom September 2014
Einwilligungserklärung (Patienten) (undatiert)
Studienprotokoll Version 1 vom 17.09.2014
CV Dr. med. Christiane Agnes Opitz
- Formelle Nachreichung vom 18.09.2014:
Formular für Erstantrag vom 18.09.2014
Probandeninformation Version 1 vom September 2014
Einwilligungserklärung (Probanden) (undatiert)
Patienteninformation Version 1 vom September 2014
Einwilligungserklärung (Patienten) (undatiert)
- Formelle Nachreichung vom 26.09.2014:
Anschreiben vom 17.09.2014
Anschreiben vom 26.09.2014 (E-Mail)
Zusammenfassung (mit Kliniklogo)
Formular für Erstantrag vom 18.09.2014
Probandeninformation Version 1 vom September 2014
Einwilligungserklärung (Probanden) Version 1 vom September 2014
Patienteninformation Version 1 vom September 2014
Einwilligungserklärung (Patienten) Version 1 vom September 2014
Studienprotokoll Version 1 vom 17.09.2014 (mit Kliniklogo)
- Inhaltliche Nachreichung vom 30.09.2015:
Probandeninformation Version 2 vom August 2015 (ohne Markierung der Änderungen)
Einwilligungserklärung (Probanden) (undatiert, ohne Markierung der Änderungen)
Patienteninformation Version 2 vom August 2015 (ohne Markierung der Änderungen)
Einwilligungserklärung (Patient) (undatiert, ohne Markierung der Änderungen)



Alte Glockengießerei 11/1
D-69115 Heidelberg

☎ +49 6221 338222 o (Empfang)
☎ +49 6221 3382222
✉ ethikkommission@med.uni-heidelberg.de

www.medizinische-fakultaet-hd.uni-heidelberg.de/ethikkommission

Vorsitz:
Prof. Dr. med. Thomas Strowitzki

Stellv. Vorsitz:
Prof. Dr. med. Johannes Schröder
Prof. Dr. med. Klaus Herfarth

Geschäftsleitung:
Dr. med. Verena Pfeilschifter

Sonstige Studien:
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☎ +49 6221 3382218
☎ +49 6221 3382222
✉ Sina.Bittar@med.uni-heidelberg.de

Christian Deisenroth, M.A.
☎ +49 6221 3382215
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✉ Christian.Deisenroth@med.uni-heidelberg.de



Bankverbindung:
Baden-Württembergische Bank Stuttgart
Konto-Nr.: 7421 500 429
BLZ: 600 501 01
SWIFT/BIC Code: SOLADEST
IBAN-Nr.: DE 64600501017421500429

Studienprotokoll Version 2 vom 27.08.2015 (ohne Markierung der Änderungen)

Antwortschreiben

Formelle Nachreicherung vom 30.09.2015:

Probandeninformation Version 2 vom September 2015 (mit Markierung der Änderungen)

Einwilligungserklärung (Probanden) Version 2 vom September 2015 (mit Markierung der Änderungen)

Patienteninformation Version 2 vom August 2015 (mit Markierung der Änderungen)

Einwilligungserklärung (Patient) Version 2 vom September 2015 (mit Markierung der Änderungen)

Studienprotokoll Version 2 vom 29.09.2015 (mit Markierung der Änderungen)

Antwortschreiben

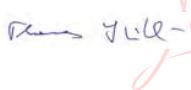
Sehr geehrte Frau Dr. Opitz,

die Ethikkommission hat Ihr Forschungsvorhaben in der Sitzung am 24.11.2014 beraten und hat **keine Bedenken gegen die Durchführung der Studie.**

Wir wünschen Ihnen bei der Durchführung der Studie viel Erfolg.

Bitte leiten Sie das Ergebnis der berufsrechtlichen Beratung und die studienrelevante Korrespondenz allen teilnehmenden Ärzten in unserem Zuständigkeitsbereich weiter.

Mit freundlichen Grüßen

Digital unterschrieben von
Dr. Strowitzki, Thomas
DN: c=DE, cn=Dr. Strowitzki,
Thomas, serialNumber=1
Datum: 2015.10.13 11:20:37
+02'00'

Prof. Dr. med. Thomas Strowitzki
Vorsitzender

Allgemeine Hinweise:

- Änderungen in Organisation und Ablauf der Studie sind der Kommission, zusammen mit einer Bewertung der Nutzen-Risiko-Relation, umgehend mitzuteilen. Sowohl die **Antragsnummer** als auch die **geänderten Passagen** sollten in den betreffenden Unterlagen **deutlich gekennzeichnet** sein, da anderenfalls keine zügige Bearbeitung möglich ist.
- Die Ethikkommission der Medizinischen Fakultät Heidelberg arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den ICH-GCP-Richtlinien. Ihren Beratungen liegt die Deklaration des Weltärztekongresses von Helsinki in der jeweils aktuellen Fassung zugrunde.
- Unabhängig vom Beratungsergebnis macht die Ethikkommission Sie darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung einer Studie beim Leiter der Studie und bei allen teilnehmenden Ärzten liegt.

Universitair Medisch Centrum Groningen**Medisch Ethische Toetsingscommissie**

Aan
 Dr. C.P. Schröder
 Medische Oncologie
DA11

Telefoon (050) 361 4204
 Fax (050) 361 4351

Bijlage(n)
 Kenmerk M13.141375

Datum	1 augustus 2013
Onderwerp	METc 2013/146
Titel onderzoek	Towards patient tailored cancer treatment supported by molecular imaging - IMPACT: IMaging PAtients for Cancer drug selecTion - Metastatic Breast Cancer.
ABR nr	NL43582.042.13
EudraCT	2013-000551041

De Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen (METc UMCG) heeft het onderzoeksprotocol met bovengenoemde titel beoordeeld in het kader van de Wet medisch-wetenschappelijk onderzoek met mensen (WMO).

De METc UMCG heeft geconstateerd dat het bovengenoemde onderzoeksprotocol voldoet aan de in art. 3 WMO gestelde voorwaarden en derhalve heeft de METc UMCG een **positief oordeel** uitgesproken wat betreft de uitvoering in het Universitair Medisch Centrum Groningen. Als verrichter wordt UMCG aangemerkt.

Het voornemen bestaat om het onderzoek, in Nederland, naast het Universitair Medisch Centrum Groningen, ook in andere instellingen uit te voeren.

- In de andere centra mag pas met het onderzoek worden begonnen als de METc UMCG hiertoe een nader (positief) oordeel heeft uitgesproken. De METc UMCG spreekt hierover een oordeel uit op grond van een zg. Onderzoeksverklaring van die centra.
- Ieder centrum draagt zelf zorg voor de verzekering van proefpersonen als bedoeld in de WMO die in dat centrum zullen worden geïncludeerd.

De commissie heeft de ingediende onderzoeksverklaring(en) bekeken. Zij heeft geconstateerd dat is voldaan aan de voorwaarden in artikel 3, onderdeel e en j, van de WMO. Derhalve geldt het positief oordeel voor:

- Universitair Medisch Centrum Groningen



- Vrije Universiteit Medisch Centrum
- Sint Radboud

Bij de beoordeling zijn o.a. de volgende documenten betrokken:

- Onderzoeksprotocol getiteld "*Towards patient tailored cancer treatment supported by molecular imaging IMPACT: IMaging PAtients for Cancer drug selecTion – Metastatic Breast Cancer*", versie 7, d.d. June 2013 en de daarbij behorende vragenlijsten
- Schriftelijke informatie voor proefpersonen, getiteld "*Op weg naar een op maat gesneden borstkankerbehandeling met behulp van moleculaire beeldvorming*", en het toestemmingsformulier voor gebruik in het UMCG, versie 6 d.d. 27-05-2013
- ABR-formulier NL43582.042.13 , versie 2 d.d. 18-06-2013
- Ontvangstbewijs EudraCT-nummer d.d 31-01-2013
- EudraCT application formulier 2013-000551041 gedateerd en ondertekend d.d. 27-03-2013
- Investigational Medicinal Product Dossier 89Zr-N-SucDf-trastuzumab, d.d. 01-02-2013
- Investigational Medicinal Product Dossier [18F]-FES,, d.d.03-01-2013
- CV van coördinerend onderzoeker en hoofdonderzoeker in UMCG, dr. C.P. Schröder
- CV van onafhankelijk arts in UMCG, prof. dr. E. Vellenga
- Onderzoeksverklaring Vrije Universiteit Medisch Centrum
- CV van de lokale (hoofd)onderzoeker VUMC, dr. C. W. Menke- van der Houven van Oordt
- Onderzoeksverklaring Sint Radboud
- CV van de lokale (hoofd)onderzoeker Sint Radboud, prof. dr. W.T.A. van der Graaf

Vast is komen te staan dat met de uitvoering van het bovengenoemde onderzoeksprotocol niet in strijd wordt gehandeld met de verboden als weergegeven in de artikelen 4, eerste lid, 5 en 6, eerste lid, van de WMO.

Gelet op het bepaalde in artikel 6, derde t/m negende lid, van de WMO is de METc UMCG Voorts van oordeel dat de proefpersonen op adequate, volledige en begrijpelijke wijze over het onderzoek worden geïnformeerd.

De METc UMCG heeft voorts vastgesteld dat op correcte wijze uitvoering is gegeven aan de verzekерingsplicht als neergelegd in artikel 7 van de WMO, zoals nader uitgewerkt in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen (Besluit van 23 juni 2003).

De commissie heeft geconstateerd dat een aansprakelijkheidsverzekering is afgesloten zoals bepaald in artikel 7, negende lid van de WMO.

Aan dit positieve oordeel zijn de volgende voorwaarden verbonden:

- Het onderzoek dient binnen één jaar na dagtekening van dit oordeel aan te vangen;
- De datum van aanvang van het onderzoek dient aan de METc UMCG te worden gemeld. Dit dient binnen vier weken na aanvang te gebeuren;
- De uitvoerder van het onderzoek is verplicht om, in geval het onderzoek een verloop neemt dat in noemenswaardige mate voor de proefpersoon ongunstiger is dan in het onderzoeksprotocol staat beschreven, de uitvoering van het onderzoek op te schorten en dit terstond aan de METc UMCG te melden met het verzoek om een nader oordeel;

- Wijzigingen in het onderzoeksprotocol mogen eerst worden geëffectueerd nadat de METc UMCG ook over deze wijzigingen een positief oordeel heeft uitgesproken;
- Jaarlijks dient een rapportage van de voortgang van het onderzoek aan de METc UMCG te worden overlegd. Hiervoor kan gebruik worden gemaakt van het formulier dat via de website van de METc kan worden gedownload. De METc UMCG ziet de eerste voortgangsrapportage uiterlijk één jaar na dagtekening van dit oordeel tegemoet;
- Beëindiging van het onderzoek dient, met opgaaf van redenen, aan de METc UMCG te worden gemeld. Dit dient binnen vier weken na beëindiging te gebeuren

Voorts wil de METc UMCG u wijzen op het volgende:

- Het door de METc UMCG uitgesproken oordeel is een oordeel als bedoeld in art. 3 WMO.
- Op grond van art. 23 WMO kan degene wiens belang rechtstreeks bij dit besluit is betrokken daartegen binnen zes weken na de dag waarop het besluit bekend is gemaakt administratief beroep aantekenen bij de Centrale Commissie Mensgebonden Onderzoek (CCMO), Parnassusplein 5, 2511 VX DEN HAAG (correspondentieadres: Postbus 16302, 2500 BH DEN HAAG).
- Een afschrift van dit oordeel wordt in ToetsingOnline verwerkt.

Met vriendelijke groet,
namens de Medisch Ethische Toetsingscommissie,

BIA
De
prof. dr. W.A. Kamps
voorzitter

P. Vos
ambtelijk secretaris

cc.

- Prof. dr. E.G.E. de Vries, Medische Oncologie, DA11
- Mevrouw G. C.M. Sieling, Medische Oncologie, DA11
- CCMO(via ToetsingOnline)
- Ziekenhuisapotheek UMCG, per email (trials@apoth.umcg.nl)

De Boelelaan 1117
1081 HV Amsterdam

postbus 7057
1007 MB Amsterdam

telefoon 020 444 4444

www.VUmc.nl

mw. prof. dr. E. Boven
afd. geneeskundige oncologie
ZH 3 A 48

Medisch Ethische Toetsingscommissie
VU medisch centrum
voorzitter: prof. dr. J.A. Rauwerda
intern postadres: BS7, kamer H-565
telefoon: 020 - 44 45585
e-mail: metc@vumc.nl
website: www.vumc.nl/metc

CORRECTIE



VU medisch centrum

onderwerp
positief oordeel
geneesmiddelenonderzoek

ons kenmerk
2013.406
NL46195.029.13

datum
Amsterdam, 17 maart 2014

Geachte mevrouw Boven,

De Medisch Ethische Toetsingscommissie VU medisch centrum (bevoegd tot oordelen op grond van WMO art. 2.2.a) oordeelt thans in positieve zin omtrent de uitvoering van het onderzoek met titel:

PI3K pathway analysis in tumor tissue and circulating DNA to obtain further insight in the efficacy of everolimus when combined with exemestane: a side-study protocol attached to standard treatment with everolimus and exemestane for postmenopausal patients with hormone receptor-positive advanced metastatic breast cancer, who have progressed on anastrozole or letrozole

Aanvrager van het onderzoek: mw. prof. dr. E. Boven

Verrichter: VU medisch centrum te Amsterdam

METc VUmc registratienummer: 2013.406

Vergadering en documenten

De goedkeuring, waartoe in principe besloten is in de vergadering van 5-12-2013, is gebaseerd op de volgende documenten:

- A1 correspondentie tussen METc VUmc en onderzoeker d.d. 25-2-2014, 22-1-2014, 20-1-2014, 14-1-2014 en 12-12-2013
- A1 aanbiedingsbrief d.d. 7-11-2013 en 3-10-2013

Samenstelling commissie

prof. dr. J.A. Rauwerda	voorzitter, chirurg	dr. M. Klein	neuropsycholoog
dr. K. Hoekman	plv. voorzitter, internist-oncoloog	dr. M.D. Lagerweij	tandarts
mw. dr. C. Boer	biomedicus	mw. G. Nijman, mw. H. Hofman en	proefpersonenleden
mw. dr. M.A. Bremmer	psychiater	mw. dr. E. Steenland	
mw. drs. M.M.E. van Dijk	verpleegkundige	mw. dr. A.F.W. van der Steeg en	chirurgen
dr. B. Drukarch	arts-farmacoloog	mw. dr. E.A. te Velde	
dr. E.G. Haarman	kinderlongarts	dr. ir. P. van de Ven en	methodologen
mw. mr. A.J.G.M. Janssen en	juristen	mw. dr. C.B. Terwee	
mr. F.J. Faber		prof. dr. ir. R. Verdaasdonk en	klinisch fysici
dr. M.J.P.A. Janssens,	medisch ethici	dr. ir. ing. Th.J.C. Faes	
mw. dr. C. Widershoven en		drs. A.J. Wilhelm en	ziekenhuisapothekers-
dr. R. Houtepen		drs. P.M. Bet	klinisch farmacologen
dr. J. Killestein en			
dr. B.W. van Oosten	neurologen		

- A3 ontvangstbewijs EudraCT-nummer
- B1 ABR-formulier versie 3 d.d. 24-2-2014
- B21 goedkeuring CWO CCA d.d. 12-9-2013
- B21 goedkeuring CWO CCA_correspondentie d.d. 5-9-2013
- B21 goedkeuring CWO CCA_correspondentie d.d. 15-8-2013
- B21 goedkeuring CWO CCA_correspondentie d.d. 12-7-2013
- B24 risicoclassificatie investigator initiated onderzoek (verwaarloosbaar) d.d. 11-10-2013
- B3 EudraCT aanvraagformulier getekend d.d. 21-10-2013
- C1 onderzoeksprotocol versie 2 d.d. 31-12-2013 (tracked changes)
- C1 onderzoeksprotocol versie 2 d.d. 31-12-2013 (zonder tracked changes)
- D21 SPC Afinitor 10 mg tabletten
- D21 SPC Aromasin omhulde tabletten 25 mg
- E12 informatiebrief incl. toestemmingsverklaring VUmc versie 2 d.d. 25-2-2014 (zonder track changes)
- E12 informatiebrief incl. toestemmingsverklaring VUmc versie 2 d.d. 25-2-2014 (met track changes)
- E12 informatiebrief incl. toestemmingsverklaring template versie 2 d.d. 25-2-2014 (zonder track changes)
- E12 informatiebrief incl. toestemmingsverklaring template versie 2 d.d. 25-2-2014 (met track changes)
- G1 WMO proefpersonenverzekering CENTRAMED d.d. januari 2013
- G2 aansprakelijkheidsverzekering CENTRAMED t.b.v. VUmc d.d. januari 2013
- G3 polisvoorwaarden Centramed d.d. 2009
- H1 CV onafhankelijk arts prof. dr. G.J. Ossenkoppele
- I2 onderzoeksverklaring VUmc getekend d.d. 8-10-2013
- I31 CV hoofdonderzoeker prof. dr. E. Boven
- I32 CV uitvoerend onderzoeker D. Kruger
- K3 onderzoekscontract getekend d.d. oktober 2013

Motivering

De commissie is van oordeel dat het onderzoek voldoet aan het bepaalde in de van toepassing zijnde wet- en regelgeving, met name de WMO en, voorzover relevant, het ICH/GCP richtsnoer.

Verzekering

De METc VUmc heeft vastgesteld dat op correcte wijze uitvoering is gegeven aan de verzekерingsplicht in artikel 7 van de WMO, zoals uitgewerkt in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Naar het oordeel van de commissie gaat het onderzoek gepaard met risico.

Deelnemende centra

De goedkeuring betreft de uitvoering in het VUmc.

Het betreft een multicenteronderzoek, dat wellicht ook in een of meer andere instellingen in Nederland zal worden uitgevoerd. De coördinator van het onderzoek dient de raad van bestuur/directie van deze instelling(en) om een advies over de lokale uitvoerbaarheid te vragen. Naar aanleiding van dit advies zal de METc VUmc een nader oordeel uitspreken over de participatie van die instelling(en).

Verplichtingen

De commissie verwacht dat

- de startdatum van het onderzoek de commissie ter kennis zal worden gebracht
- elke onverwachte bijwerking die zich tijdens het onderzoek voordoet bij de proefpersonen onverwijd aan de commissie gemeld wordt, voorzien van een toelichting betreffende de consequenties voor het onderzoek
- veranderingen in het onderzoeksprotocol aan de commissie worden voorgelegd, voorzien van een toelichting betreffende de consequenties voor de proefpersonen
- jaarlijks een rapport over de voortgang van het onderzoek aan de commissie zal worden toegestuurd
- jaarlijks een veiligheidsrapportage (of development safety update report) bij de commissie wordt ingediend

- de beëindiging van het onderzoek, hetzij omdat het onderzoek voltooid is hetzij om andere redenen, de commissie ter kennis zal worden gebracht
- de resultaten van het onderzoek aan de commissie zullen worden gemeld

De commissie heeft de bevoegdheid haar positieve oordeel in te trekken als vaststaat dat de uitvoering van het onderzoek ernstig tekort schiet.
Het voorliggend oordeel verliest zijn geldigheid indien de start van het onderzoek niet binnen één jaar plaatsvindt.

Volledigheidshalve maken wij u er op attent dat het onderzoek pas mag worden uitgevoerd nadat u schriftelijk toestemming hebt gekregen van de Bevoegde Instantie (CCMO) én van (het plv. hoofd Instituut Ondersteuning Patiëntenzorg namens) de Raad van Bestuur.

Administratief beroep

Tegen dit besluit kan een belanghebbende op grond van artikel 23 WMO binnen zes weken na de dag waarop het besluit is bekend gemaakt, administratief beroep instellen bij de Centrale Commissie Mensgebonden Onderzoek (CCMO). Het beroepschrift dient u te adresseren aan: CCMO, Postbus 16302, 2500 BH Den Haag.

Met vriendelijke groet,
namens de Medisch Ethische Toetsingscommissie,

D/A *Bon Rauwerda*

prof. dr. J.A. Rauwerda, voorzitter

Bon Rauwerda

Dhr. mr. B. Quaedvlieg, secretaris

c.c.: Centrale Commissie Mensgebonden Onderzoek te Den Haag (CCMO) - digitaal uploaden
c.c.: trialoffice-onc@vumc.nl
c.c.: d.kruger@vumc.nl
c.c.: crb@vumc.nl



Medizinische Fakultät Heidelberg

Ethikkommission der Med. Fak. HD | Alte Glockengießerei 11/1 | D-69115 Heidelberg

Herrn Prof. Dr. med. Andreas Schneeweiss
Nationales Centrum für Tumorerkrankungen Heidelberg
Im Neuenheimer Feld 460
69120 Heidelberg

07.08.2014
ts/vpf-cd

Berufsrechtliche Beratung

Unser Zeichen: **S-391/2014** (Bitte stets angeben)

Titel: Prospective Academic Translational Research Network for the Optimization of the oncological Health Care Quality in the adjuvant and advanced/metastatic setting: Health Care Research, Pharmacogenomics, Biomarkers, Health Economic PRAEGNANT Breast Cancer: Advanced/Metastatic

Eingereichte Unterlagen:
Ersteinreichung vom 22.07.2014:
Anschreiben vom 22.07.2014
Zusammenfassung
Checkliste Sonstige Studien
Formular für Erstantrag vom 22.07.2014
Patientinneninformation / Einwilligungserklärung zum klinischen Diagnostikprojekt Register Version vom 26.05.2014
Zusatz-Patientinneninformation / Einwilligungserklärung zum klinischen Diagnostikprojekt Biobank Version vom 26.05.2014
Patientinneninformation / Einwilligungserklärung zum klinischen Diagnostikprojekt Register Version vom 26.05.2014
Zusatz-Patientinneninformation / Einwilligungserklärung zum klinischen Diagnostikprojekt Biobank Version vom 26.05.2014
Study protocol Version V 0.0 vom 28.05.2014
Unterschriftenseite Studienprotokoll
Stellungnahme der EK der Eberhard-Karls-Universität Tübingen vom 17.06.2014
Stellungnahme der EK bei der Landesärztekammer Hessen vom 10.07.2014
CV Prof. Dr. med. Andreas Schneeweiss vom 16.07.2014
Vollmacht von Herrn Prof. Dr. med. Andreas Schneeweiss zum Einholen der Bewertung der Studie durch die EK Heidelberg für ClinSol GmbH & Co. KG vom 16.07.2014
Liste der beteiligten Zentren
Formelle Nachreichung vom 31.07.2014:
Anschreiben vom 31.07.2014
Formular für Erstantrag vom 31.07.2014

Sehr geehrter Herr Professor Schneeweiss,

der Vorsitzende und die Geschäftsstelle haben sich im vereinfachten Verfahren mit dem oben näher bezeichneten Forschungsvorhaben befasst.



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Vorsitz:
Prof. Dr. med. Thomas Strowitzki

Stellv. Vorsitz:
Prof. Dr. med. Johannes Schröder
Prof. Dr. med. Klaus Herfarth

Geschäftsleitung:
Dr. med. Verena Pfeilschifter

Sonstige Studien:

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BLZ: 600 501 01
SWIFT/BIC Code: SOLADEST
IBAN-Nr.: DE 64600501017421500429



Die o.g. Voten werden anerkannt. Es bestehen **keine Bedenken** gegen das Vorhaben.

Voraussetzung ist jedoch, dass die hier eingereichten Unterlagen auch der primär votierenden Kommission vorgelegen haben. Andernfalls ist das Votum der primär votierenden Kommission für die uns vorliegenden Fassungen der Unterlagen nachzureichen.

Wir wünschen Ihnen bei der Durchführung des Projektes viel Erfolg.

Bitte leiten Sie das Ergebnis der berufsrechtlichen Beratung und die studienrelevante Korrespondenz allen teilnehmenden Ärzten in unserem Zuständigkeitsbereich weiter.

Mit freundlichen Grüßen

A handwritten signature in blue ink.

Digital unterschrieben von Dr.
Thomas Strowitzki;PN
DN: cn=Dr. Thomas Strowitzki;PN,
pseudonym=Dr. Thomas
Strowitzki;PN,
serialNumber=001000000001195423
0002
Datum: 2014.08.11 13:00:48 +02'00'

Prof. Dr. med. Thomas Strowitzki
Vorsitzender

A handwritten signature in blue ink.

Digital unterschrieben von Dr. med.
Verena Pfeilschifter;PN
DN: cn=Dr. med. Verena Pfeilschifter;PN,
pseudonym=Dr. med. Verena
Pfeilschifter;PN,
serialNumber=001000000011956380001
Datum: 2014.08.11 13:29:04 +02'00'

Dr. med. Verena Pfeilschifter
Geschäftsleitung

Allgemeine Hinweise:

- Änderungen in Organisation und Ablauf der Studie sind der Kommission, zusammen mit einer Bewertung der Nutzen-Risiko-Relation, umgehend mitzuteilen. Sowohl die **Antragsnummer** als auch die **geänderten Passagen** sollten in den betreffenden Unterlagen **deutlich gekennzeichnet** sein, da anderenfalls keine zügige Bearbeitung möglich ist.
- Die Ethikkommission der Medizinischen Fakultät Heidelberg arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den ICH-GCP-Richtlinien. Ihren Beratungen liegt die Deklaration des Weltärztekibundes von Helsinki in der jeweils aktuellen Fassung zugrunde.
- Unabhängig vom Beratungsergebnis macht die Ethikkommission Sie darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung der Studie bei allen teilnehmenden Ärzten liegt.

Ethik-Kommission der FAU • Krankenhausstr. 12 • 91054 Erlangen

Novartis Pharma GmbH
Frau Dr. Sabine Heidingsfelder
Manager Trial Regulations Oncology
Roonstr. 25
90429 Nürnberg

Ethik-Kommission

Vorsitzender:
Prof. Dr. med. Renke Maas
Stellv. Vorsitzende:
Prof. Dr. med. Kerstin Amann

Geschäftsstelle:
Krankenhausstr. 12, 91054 Erlangen
Telefon: +49 9131 85-22270 (V. Kreiß)
+49 9131 85-26210 (R. Kauschke)
Fax: +49 9131 85-26021
E-Mail: ethikkommission@fau.de
Internet: www.ethikkommission.fau.de

Erlangen, 14.02.2017/VK

cc:
 BfArM 61-3910-4041622
 EK Baden-Württemberg B-AM-2016-136
 EK Bayern 7/16151
 EK Niedersachsen Ar/168/2016, Pilotprojekt
 EK Saarland 262/16
 EK Sachsen-Anhalt 17/003 N1
 Uni Heidelberg ABmu-674/2016
 Uni Regensburg 16-384-113

Unser Zeichen: 261_16 Az (bitte bei Schriftwechsel angeben)

Nachträgliche Änderungen GCP-V § 10 (4); 10 zusätzliche Prüfstellen

EudraCT:	2016-002556-24
Prüfplan:	CLEE011XDE01
Studentitel:	A national phase IIIb, multi-center, open label study for women and men with hormone-receptor positive, HER2-negative locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole
Sponsor:	Novartis Pharma GmbH, Roonstr. 25, 90429 Nürnberg
Antragsteller:	Novartis Pharma GmbH, Dr. Sabine Heidingsfelder, Manager Trial Regulations Oncology, Roonstr. 25, 90429 Nürnberg
LKP:	Prof. Dr. med. Peter Fasching, Universitätsklinikum Erlangen, Frauenklinik mit Poliklinik, Universitätsstr. 21-23, 91054 Erlangen

Sehr geehrte Frau Dr. Heidingsfelder,

die Ethik-Kommission hat Ihren Antrag vom 22.12.2016 zur o.g. Studie geprüft.

Im Benehmen mit den beteiligten Ethik-Kommissionen erteilt die Ethik-Kommission eine zustimmende Bewertung zu den beantragten Änderungen (siehe Anlage).

Versagungsgründe gemäß § 42 Abs. 1 AMG liegen nicht vor.

Die Bewertung erfolgt auf der Basis der in Anhang 1 gelisteten Unterlagen.

Mit freundlichen Grüßen



Prof. Dr. med. Renke Maas
Vorsitzender der Ethik-Kommission

Anhang 1

2016-002556-24 DE 20161219 CTA PDF Form_EC
CLEE01XDE01_2016-12-16 Liste Prüfzentren
Liste der Ethik-Kommissionen 2016-12-16.
Zentrumsunterlagen Dr. Hanusch, München
Zentrumsunterlagen_ Dr. Wagner_Völklingen
Zentrumsunterlagen_ Dr. Schuster, Stuttgart
Zentrumsunterlagen_Dr.Luedtke-Heckenkamp, Georgensmarienhütte
Zentrumsunterlagen_PD. Dr. Bischoff_Roßlauf-Dessau
Zentrumsunterlagen_Prof. Decker_Wangen
Zentrumsunterlagen_Prof. Juhasz-Boess, Homburg
Zentrumsunterlagen_Prof. Schneeweiss, Heidelberg
Zentrumsunterlagen_Prof. Suedhoff, Passau

nachgereichte Unterlagen: Eingang 13.01.2017
2016-002556-24 DE 20161219 CTA_final.xml

Anlage

Liste 10 zusätzliche Prüfzentren

Ethik-Kommission
 an der Medizinischen Fakultät
 der FAU Erlangen-Nürnberg
 Krankenhausstraße 12
 91054 Erlangen

Neue Prüfstellen

Ethikkommission	Prüfstelle	Stellvertreter
Baden-Württemberg	Prof. Dr. med. Thomas Decker <u>Standort 2</u> Zweigstelle Onkologie Wangen Am Engelberg 29 88239 Wangen	Prof. Dr. med. Tobias Dechow
Baden-Württemberg	Dr. med. Jürgen Schuster Klinikum Stuttgart Frauenklinik Kriegsbergstr. 62 70174 Stuttgart	Dr. med. Isabell Janina Herzer
Bayern	Dr. med. Claus Hanusch <u>Standort 2</u> Praxis Prof. Salat / PD Dr. Stötzer Franz-Schrank-Str. 2 80638 München	Prof. Dr. med. Christoph Salat PD Dr. med. Oliver Stötzer
Bayern	Dr. med. Claus Hanusch <u>Standort 3</u> Praxis Prof. Salat / PD Dr. Stötzer / Prof. Hiller Winthirstr. 7 80639 München	Prof. Dr. med. Christoph Salat PD Dr. med. Oliver Stötzer
Heidelberg (neu)	Prof. Dr. med. Andreas Schneeweiß Nationales Zentrum für Tumorerkrankungen Universitätsklinikum Heidelberg Im Neuenheimer Feld 460 69120 Heidelberg	Prof. Dr. med. Frederik Marmé
Niedersachsen	Dr. med. Kerstin Lüdtke-Heckenkamp Zentrum für Internistische Onkologie und Hämatologie der Niels-Stensen-Kliniken Alte Rothenfelder Str. 23 49124 Georgsmarienhütte	Dr. med. Jost Wamhoff
Regensburg (neu)	Prof. Dr. med. Thomas Südhoff Klinikum Passau Innstr. 76 94032 Passau	Dr. med. Martina Troppmann
Saarland	Prof. Dr. med. Ingolf Juhasz-Böss Universitätsklinikum Saarland Klinik für Frauenheilkunde, Geburtsmedizin und Reproduktionsmedizin Kirberger Str. 9 66421 Homburg	Dr. med. Gilda Schmidt

Ethik-Kommission
an der Medizinischen Fakultät
der FAU Erlangen-Nürnberg
Krankenhausstraße 12
91054 Erlangen

Ethikkommission	Prüfstelle	Stellvertreter
Saarland	Dr. med. Joachim Wagner Gemeinschaftspraxis für Frauenheilkunde und Geburtshilfe Poststr. 14-18 66333 Völklingen	Dr. med. Axel Hefti
Sachsen-Anhalt (neu)	PD Dr. med. Joachim Bischoff MVZ des Städtischen Klinikums Dessau gGmbH Auenweg 38 06847 Dessau-Rosslau	Dr. med. Hermann Voß



Medizinische Fakultät Heidelberg

Ethikkommission der Med. Fak. HD | Alte Glockengießerei 11/1 | D-69115 Heidelberg

TFS GmbH
Frau Dr. Karina Finke
Business Center Bavaria
Radlkoferstr. 2
81373 München

cc: BfArM per E-Mail
Beteiligte Ethikkommissionen per E-Mail
- ENDGÜLTIGE SENDUNG -

06.02.2017
kh-bh

ZUSTIMMENDE BEWERTUNG (Nachträgliche Änderung gemäß § 10 Abs. 1 GCP-V)

EudraCT-Nr.: 2014-004698-17
Prüfplan-Code: MedOPPO67
Titel: A randomized, multicentre, open-label, phase II trial to evaluate the efficacy and safety of palbociclib in combination with fulvestrant or letrozole in patients with HER2 negative, ER+ metastatic breast cancer. (PARSIFAL)
Sponsor: Medica Scientia Innovation Research (MedSIR), Spanien
Antragsteller: TFS GmbH, München
LKP: Dr. med. Frederik Marmé, Heidelberg
Unser Zeichen: AFmu-290/2015 (Bitte stets angeben)



Alte Glockengießerei 11/1
D-69115 Heidelberg
+49 6221 33822-0 (Empfang)
+49 6221 3382222
ethikkommission-l@med.uni-heidelberg.de
www.medizinische-fakultaet-hd.uni-heidelberg.de/ethikkommission

Vorsitz:
Prof. Dr. med. Thomas Strowitzki

Stellv. Vorsitz:
Prof. Dr. med. Johannes Schröder
Prof. Dr. med. Klaus Herfarth

Geschäftsleitung:
Dr. med. Verena Pfeilschifter

AMG-Studien federführend:
Birgit Hochlehnert, M. Sc.
+49 6221 3382216
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Birgit.Hochlehnert@med.uni-heidelberg.de
Simone Kronemayer, Dipl. Kult.
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Dr. rer. nat. Marion Teichmann
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Marion.Teichmann@med.uni-heidelberg.de

Sehr geehrte Frau Dr. Finke,

die Ethikkommission hat Ihren Antrag auf nachträgliche Änderung nach § 10 Abs. 1 GCP-V in der Sitzung am 30.01.2017 geprüft.

Die Ethikkommission erteilt eine zustimmende Bewertung zu der nachträglichen Änderung.

Der Bewertung liegen die in Anhang 1 aufgeführten Unterlagen zugrunde.

Die Bewertung erfolgt im Benehmen mit den in Anhang 2 aufgeführten beteiligten Ethikkommissionen.

Mit freundlichen Grüßen

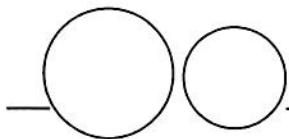
CN=Dr. Herfarth, Klaus
CN=TeleSec PKS SigG CA 29.PN
OU=DE
Montag, 6. Februar 2017 11:09 Uhr MEZ

Prof. Dr. med. Klaus Herfarth
Stellvertretender Vorsitzender

Anlage
Anhang 1-2

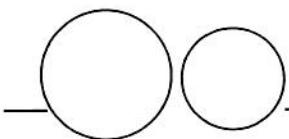


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Konto-Nr.: 7421 500 429
BLZ: 600 501 01
SWIFT/BIC Code: SOLADEST
IBAN-Nr.: DE 64600501017421500429



Die Ethikkommission gibt folgende allgemeine Hinweise:

- Die ethische und rechtliche Verantwortung für die Durchführung dieser klinischen Prüfung verbleibt beim Sponsor, bei der Leiterin / dem Leiter der klinischen Prüfung und bei den Prüferinnen/Prüfern.
- Sollten sich die Risiken für die Studienteilnehmer durch die nachträglichen Änderungen erhöhen, so ist der Versicherer darüber zu informieren und es ist sicherzustellen, dass sich die Versicherung auch auf die nachträglichen Änderungen erstreckt.
- Zusammensetzung und Arbeitsweise der Ethikkommission entsprechen nationalen Gesetzen, Vorschriften und der ICH-GCP-Leitlinie in der jeweils gültigen Fassung.
- Gegen die vorliegende Stellungnahme kann innerhalb von einem Monat nach Bekanntmachung Widerspruch erhoben werden. Der Widerspruch ist schriftlich oder zur Niederschrift bei der Geschäftsstelle der Ethikkommission der Medizinischen Fakultät Heidelberg, Alte Glockengießerei 11/1, 69115 Heidelberg einzureichen.

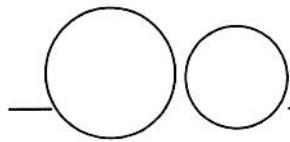


Anhang 1

Liste der eingereichten Unterlagen

Primär eingereichte Unterlagen: Schreiben vom 19.01.2017
Substantial Amendment Notification Form vom 12.01.2017
Modul 1 vom 12.01.2017
Clinical Trial Protocol, Version vom 20.12.2016 (mit und ohne Kennzeichnung der Änderungen)
Protocol Amendment # 3 vom 20.12.2016
Patienteninformation und Einwilligungserklärung, Version 5.0 vom 09.01.2017 (mit und ohne Kennzeichnung der Änderungen)
CD-ROM

10. FEB. 2017



Anhang 2

Die zustimmende Bewertung ist gültig für folgende Prüfer/Stellvertreter, Prüfstellen:

Ethikkommission	Prüfer/Stellvertreter/Prüfstelle
Ethikkommission der Medizinischen Fakultät Heidelberg Alte Glockengießerei 11/1 69115 Heidelberg	Dr. med. Frederik Marmé (LKP) Prof. Dr. med. Andreas Schneeweiss (Stellv.) Nationales Centrum für Tumorerkrankungen (NCT) Universitätskrankenhaus Heidelberg Gynäkologische Onkologie Im Neuenheimer Feld 460 69120 Heidelberg
Ethik-Kommission des Landes Sachsen-Anhalt Geschäftsstelle Postfach 1802 06815 Dessau-Roßlau	PD Dr. med. Joachim Bischoff (P) Dr. med. Hermann Voß (Stellv.) Medizinisches Versorgungszentrum des Städtischen Klinikum Dessau Auenweg 38 06847 Dessau-Roßlau



Ethikkommission

Universität Ulm • Ethikkommission • 89069 Ulm

Alcedis GmbH
Frau Dr. Christine Heidel
Winchesterstraße 3
35394 Gießen

-EINGELANGEN
10. Juni 2016

Unser Zeichen
113/15 – CL/se.

Vorsitz: Prof. Dr. O. Zolk

Geschäftsführung: Prof. Dr. Ch. Lenk
Geschäftsstelle: Iris Seitz

Hausadresse:
Helmholtzstraße 20 (Oberer Eselsberg)
89081 Ulm
Telefon: +49 - (0)731 - 500-22050, 22052
Telefax: +49 - (0)731 - 500-22036
Email: ethik-kommission@uni-ulm.de
<http://www.uni-ulm.de/ethikkommission/>

Durchwahl
22052

Datum
07.06.2016

cc: BfArM, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Vorlage-Nr.: unbekannt
mitbeteiligte Ethikkommissionen

Unsere Geschäfts-Nr. (bitte immer angeben): 113/15

Titel: Eine multizentrische, randomisierte Phase III-Studie zum Vergleich einer Chemo- versus einer endokrinen Therapie in Kombination mit einer dualen HER2-gerichteten Herceptin® (Trastuzumab)/ Perjeta® (Pertuzumab)-Therapie bei Patientinnen mit HER2-positivem und hormonrezeptorpositivem metastasiertem Brustkrebs (DETECT V / CHEVENDO); a multi-center, randomized phase III study to compare chemo- versus endocrine therapy in combination with dual HER2-targeted therapy of Herceptin® (trastuzumab) and Perjeta® (pertuzumab) in patients with HER2 positive and hormone-receptor positive metastatic breast cancer

Prüfplan-Nummer: D-V

EudraCT-Nr.: 2014-002249-22

Sponsor: Universitätsklinikum Ulm (AöR), Albert-Einstein-Allee 29, 89081 Ulm

LKP: Prof. Dr. med. Jens HUOBER, Universitätsklinikum Ulm, Frauenklinik, Prittitzstraße 43, 89075 Ulm

Hier: Bewertung Prüfstelle – Ihre Meldung vom 24.02.2015

Sehr geehrte Frau Dr. Heidel,

die folgende bislang ausstehende Bewertung kann nun erfolgen.

Die Qualifikation des folgenden Prüfers und Stellvertreters sowie die Eignung der folgenden Prüfstelle werden zustimmend bewertet:

- Prof. Dr. med. Andreas Schneeweis (Prüfer), Dr. med. Frederik Marmé (Stellvertreter) – Universitätsklinikum Heidelberg (NCT), Gynäkologische Onkologie, Frauenklinik, Im Neuenheimer Feld 460, 69120 Heidelberg

Die Bewertung erfolgt im Benehmen mit der beteiligten Ethikkommission.

Für die Ethikkommission der Universität Ulm

Prof. Dr. Ch. Lenk
Geschäftsführer

Mitglieder der Kommission: Prof. Dr. Th. Becker (Stellvertr. Vorsitz), Frau Prof. Dr. M. Dudeck, Prof. Dr. P. Gierschik, J. Glembek, Prof. Dr. H. Gundel, Prof. Dr. J. Högel, Prof. Dr. M. Kühl, Prof. Dr. D. Rothenbacher, Pfarrer E. Schäfer, Prof. Dr. Ch. Scholz, Prof. Dr. H. Schrezenmeier, Frau K. Stascheit, Prof. Dr. D. Steinbach, Prof. Dr. S. Stilgenbauer, Prof. Dr. O. Zolk (Vorsitz)



Universität Ulm • Ethikkommission • 89069 Ulm

Alcedis GmbH
Frau Ina Santjer-Schnabel
Winchesterstraße 3
35394 Gießen

EINGEGANGEN
17. Juli

Eck...
Unser Zeichen
113/15 – Zo/se.

Vorsitz: Prof. Dr. O. Zolk

Geschäftsleitung: PD Dr. Ch. Lenk

Geschäftsstelle: Iris Seitz

Hausadresse:

Helmholtzstraße 20 (Oberer Eselsberg)
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Telefon: +49 - (0)731 - 500-22052

Telefax: +49 - (0)731 - 500-22036

Email: ethik-kommission@uni-ulm.de
<http://www.uni-ulm.de/ethikkommission/>Durchwahl
22052Datum
15.07.2015

cc: BfArM, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Vorlage-Nr.;
cc: mitbeteiligte Ethikkommissionen [per Fax]

Unsere Geschäfts-Nr. (bitte immer angeben): **113/15**

Titel: Eine multizentrische, randomisierte Phase III-Studie zum Vergleich einer Chemo- versus einer endokrinen Therapie in Kombination mit einer dualen HER2-gerichteten Herceptin® (Trastuzumab)/ Perjeta® (Pertuzumab)-Therapie bei Patientinnen mit HER2-positivem und hormonrezeptorpositivem metastasiertem Brustkrebs (DETECT V / CHEVENDO); a multi-center, randomized phase III study to compare chemo- versus endocrine therapy in combination with dual HER2-targeted therapy of Herceptin® (trastuzumab) and Perjeta® (pertuzumab) in patients with HER2 positive and hormone-receptor positive metastatic breast cancer

Prüfplan-Nummer: D-V

EudraCT-Nr.: 2014-002249-22

Sponsor: Universitätsklinikum Ulm (AöR), Albert-Einstein-Allee 29, 89081 Ulm

LKP: Prof. Dr. med. Jens HUOBER, Universitätsklinikum Ulm, Frauenklinik, Prittwitzstraße 43,
89075 Ulm

Sehr geehrte Frau Santjer-Schnabel,

die Ethikkommission der Universität Ulm ist als federführende Ethikkommission mit der Bewertung der o.g. multizentrischen klinischen Prüfung beauftragt. Sie hat auf Basis der eingereichten, unten gelisteten Unterlagen in ihrer Sitzung am 04.05.2015 beraten.

Die zusätzlich angeforderten Informationen und revidierten Dokumente sind am 19.06.2015 sowie 13.07.2015 eingegangen.

Die Ethikkommission der Universität Ulm erteilt eine zustimmende Bewertung.

Begründung: Versagungsgründe gemäß § 42 Abs. 1 AMG liegen nicht vor.

Der Bewertung liegen die in Anhang 1 aufgeführten Unterlagen zugrunde. Bei mehreren Versionen eines Dokumentes bezieht sich die Bewertung auf die jeweils letzte Version.

Die Bewertung ist für die in Anhang 2 aufgeführten Prüfer, Stellvertreter und Prüfstellen gültig.

Die Bewertung erfolgt im Benehmen mit den in Anhang 3 aufgeführten beteiligten Ethikkommissionen.

Allgemeine Hinweise:

- Die ethische und rechtliche Verantwortung für die Durchführung dieser klinischen Prüfung verbleibt beim Sponsor, bei der Leiterin/dem Leiter der klinischen Prüfung und bei den Prüferinnen/Prüfern.

- Zusammensetzung und Arbeitsweise der Ethikkommission der Universität Ulm entsprechen nationalen Gesetzen, Vorschriften und der ICH-GCP-Leitlinie in der jeweils gültigen Fassung.
- Gegen die vorliegende Stellungnahme kann innerhalb von einem Monat nach Bekanntmachung Widerspruch erhoben werden. Der Widerspruch ist schriftlich bei der Geschäftsstelle der federführenden Kommission zusammen mit einer Begründung einzureichen.

Für die Ethikkommission der Universität Ulm


Prof. Dr. med. O. Zolk
Vorsitzender

Anlagen:

Anhang 1: Liste der ein- und nachgereichten Unterlagen

Eingereichte Unterlagen [Eingang am 20.03.2015]:

Begleitschreiben der Alcedis GmbH an die federführende Ethikkommission der Universität Ulm vom 18.03.2015 zur Ersteinreichung nebst Eingangsbestätigung | Kostenübereinmachungsbestätigung des Sponsors vom 05.01.2015 | Modul 1, unterzeichnet am 18.03.2015 | Modul 2, unterzeichnet am 18.03.2015 | Liste der Stellvertreter, Version vom 16.03.2015 | Vollmacht des Sponsors vom 21.11.2014 für den Vertreter des Sponsors | Vollmacht des Sponsorvertreters für Alcedis GmbH vom 05.01.2015 | Bestätigung der EudraCT-Nummer vom 23.05.2014 | Datenschutzerklärung des Sponsors und Erklärung betreffend die Aufklärung über die Weitergabe pseudonymisierter Daten vom 05.01.2015 | Liste der Prüfer, Version vom 16.03.2015 | Checkliste, unterzeichnet am 18.03.2015 | Erklärung des Sponsors vom 05.01.2015 betreffend die Einbeziehung abhängiger Personen | Lebenslauf des LKP's Prof. Dr. med. Jens Huober vom 25.02.2015 | Liste der zuständigen Ethikkommissionen | Prüfplan, Nr.: DETECT V / CHEVENDO, Version 1.0 vom 03.12.2014 nebst Unterschriftenseite des Sponsorvertreters und des LKP's | Deutsche Prüfplansynopse, Version 1.0 vom 03.12.2014 | Fachinformation Tamoxifen (Tamoxifen-ratiopharm® 10 mg/20 mg/30 mg Tabletten), Stand März 2011 | Fachinformation Paclitaxel (Paclitaxel-GRY® 6 mg/ml Konzentrat zur Herstellung einer Infusionslösung), Stand August 2014 | Fachinformation Docetaxel (Docetaxel-ratiopharm® 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung), Stand Mai 2013 | Fachinformation Exemestan (Exemestan-ratiopharm® 25 mg Filmtabletten), Stand März 2011 | Fachinformation Letrozol (Letrozol-ratiopharm® 2,5 mg Filmtabletten), Stand August 2012 | Fachinformation Anastrozol (Anastrozol-ratiopharm® 1 mg Filmtabletten), Stand November 2011 | Fachinformation Pertuzumab (Perjeta® 420 mg Konzentrat zur Herstellung einer Infusionslösung), Stand September 2013 | Fachinformation Trastuzumab (Herceptin® i.v. 150 mg Pulver zur Herstellung eines Infusionslösungskonzentrats), Stand Dezember 2013 | Fachinformation Trastuzumab (Herceptin® s.c. 600 mg/5 ml Injektionslösung), Stand Dezember 2013 | Fachinformation Capecitabin (Xeloda® 150 mg und 500 mg Filmtabletten), Stand Januar 2015 | Fachinformation Vinorelbine (Vinorelbine-HAEMATO 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung), Stand April 2012 | Fachinformation Fulvestrant (Faslodex® 250 mg Injektionslösung), Stand Januar 2013 | Patientinnen-Information Teil 1 (Hauptstudie), Version 1.0 vom 12.10.2014 | Patientinnen-Information Teil 2 (TRAFO-Projekt), Version 1.0 vom 12.10.2014 | Patientinnen-Einwilligungserklärung Teil 1 (Hauptstudie), Version 1.0 vom 12.10.2014 | Patientinnen-Einwilligungserklärung Teil 2 (TRAFO-Projekt), Version 1.0 vom 12.10.2014 | Brief der Ecclesia Mildenberger Hospital GmbH vom 12.01.2015 mit der vorläufigen Proben-Versicherungsbestätigung (Jahresvertrag) der HDI Gerling Industrie Versicherung AG, Düsseldorf, vom 09.01.2015 zur Vers.-Schein-Nr.: 57 010315 03015 nebst den Allgemeinen Versicherungsbedingungen (AVB-Prob/AMG-JV) - U 199 | Entwurf des Prüfervertrags, deutsche Version | Liste Stellvertreter Ulm, Version vom 16.03.2015 | Qualifikationsnachweise des Prüfers Prof. Dr. med. Wolfgang Janni: Lebenslauf vom 06.10.2014, Formular "Angaben zur Qualifikation des Prüfers" vom 06.10.2014, Ausführliche Auflistung der Studienerfahrung vom 08.09.2014, GCP-Zertifikat vom 13.04.2013, Financial Disclosure Formular vom 14.10.2014 und Erklärungen vom 06.10.2014 gem. § 7 Abs. 3 Nr. 4 GCP-V, gem. § 7 Abs. 3 Nr. 7 GCP-V, gem. § 7 Abs. 3 Nr. 15 GCP-V, § 7 Abs. 2 Nr. 15 GCP-V und gem. § 40 Abs. 1 Satz 3 Nr. 7 AMG | Qualifikationsnachweise des Stellvertreters Prof. Dr. med. Jens Huober: Lebenslauf vom 07.10.2014, Formular "Angaben zur Qualifikation des Stellvertreters" vom 07.10.2014, Ausführliche Auflistung der Studienerfahrung vom 07.10.2014, GCP-Zertifikat vom 13.04.2013, Financial Disclosure Formular vom 07.10.2014 und Erklärungen vom 07.10.2014 gem. § 7 Abs. 3 Nr. 4 GCP-V, gem. § 7 Abs. 3 Nr. 7 GCP-V, gem. § 7 Abs. 3 Nr. 15 GCP-V, § 7 Abs. 2 Nr. 15 GCP-V und gem. § 40 Abs. 1 Satz 3 Nr. 7 AMG | Qualifikationsnachweis der Prüfstelle und der Prüfgruppe Ulm, unterzeichnet durch den Prüfer Prof. Dr. med. Wolfgang Janni am 15.10.2014 und durch den Stellvertreter Prof. Dr. med. Jens Huober am 07.10.2014 | Liste Prüfer Ulm, Version vom 16.03.2015 | Qualifikationsnachweise der beteiligten Prüfzentren sowie deren Prüfgruppen, Prüfer und Stellvertreter für folgende Prüfzentren: Dr. med. Jochen Potenberg, Ev. Waldkrankenhaus Spandau, Berlin – Dr. med. Jörg Schilling, Praxis Dr. Schilling, Berlin – Dr. med. Axel Gerhardt, Universitätsklinikum Mannheim gGmbH – Dr. med. Leonid Basovski, Praxis an der Kreisklinik Biberach – Dr. Grischa Wachsmann, Klinikum Sindelfingen-Böblingen – Prof. Dr. med. Thorsten Kühn, Klinikum Esslingen – Dr. med. Matthias Zaiss, Praxis für Interdisziplinäre Onkologie & Hämatologie GbR, Freiburg – Frau Dr. med. Birgit Euchenhofer, Internistische Gemeinschaftspraxis, Friedrichshafen – Dr. med. Oliver Tomé, St. Vincentius Kliniken gAG, Karlsruhe – Frau Dr. med. Elke Faust, Kreiskliniken Esslingen – Nürtingen – Frau Wilma Charlotte Ehrle, Paracelsus-Krankenhaus Ostfildern-Ruit – Prof. Dr. med. Thomas Decker, Studienzentrum Onkologie Ravensburg – Prof. Dr. med. Thomas Decker, Onkologie Wangen – Frau Dr. med. Lelia Bauer, Krankenhaus Weinheim – Prof. Dr. med. Elmar Stickeler, Universitätsklinikum Freiburg – PD Dr. Florian-Andrei Taran, Universitätsfrauenklinik Tübingen – Dr. med. Markus Hahn, Gemeinschaftspraxis Ansbach – Dr. med. Bernhard Heinrich, Gemeinschaftspraxis Augsburg – Dr. med. H. Tanzer, Gemeinschaftspraxis Bad Reichenhall – Dr. med. Hermann Zoche, Klinikum Coburg gGmbH – Frau Dr. med. Jutta Neteler, Helios Amper Klinikum Dachau – Dr. med. Helmut Lambertz, Klinikum Garmisch-Partenkirchen GmbH – Frau Dr. Christina Bechtner, Klinikum Memmingen – Dr. med. W. Abenhardt, MVZ MOP Dr. Abenhardt, München – Dr. med. Oliver Stoet-

zer, Gemeinschaftspraxis München – Univ. Prof. Dr. med. Heinz Scholz, Klinikum Neumarkt – Prof. Dr. Arthur Wischnik, Klinikum Augsburg – Frau PD Dr. med. Brigitte Rack, Klinikum der Universität München Innenstadt – Prof. Dr. med. Thomas Beck, RoMed Klinikum Rosenheim – Prof. Dr. med. Peter A. Fasching, Universitätsfrauenklinik Erlangen – Frau Dr. med. Gabriele Doering, Gemeinschaftspraxis Bremen – PD Dr. med. Gernot Seipelt, Gemeinschaftspraxis Bad Soden – Prof. Dr. med. Heinz-Gert Höffkes, MVZ Osthessen GmbH, Fulda – PD Dr. med. Thomas Müller, Klinikum Hanau GmbH – Frau Dr. med. Angelika Ober, Krankenhausgesellschaft St. Vincenz mbH, Limburg – Prof. Dr. med. Christian Jackisch, Sana Klinikum Offenbach – Dr. med. Bernd Flath, HOPA Praxis für Ambulante Onkologie im Krankenhaus Jerusalem, Hamburg – Prof. Dr. med. Gerhard Gebauer, Kath. Marienkrankenhaus Hamburg – Dr. med. Volkmar Müller, Universitätsklinikum Hamburg-Eppendorf – Prof. Dr. med. habil. Bernd Gerber, Universitätsfrauenklinik Rostock am Klinikum Süd – Frau Dr. med. Antje Kristina Belau, Ernst-Moritz-Arndt-Universität Greifswald – Dr. med. Carsten Hielscher, g.SUND Gynäkologie Kompetenzzentrum Stralsund – Dr. med. Lothar Müller, Onkologie Leer-Emden-Papenburg – Dr. med. Lothar Müller, MVM mbH, Leer – Frau Dr. med. Kristina Lübbe, Diakoniekrankenhaus Henriettastiftung Hannover – Frau Dr. Beatrice Goldmann, Gemeinschaftspraxis Lüneburg – Dr. med. Tobias Hesse, Agaplesion Diakonieklinikum Rotenburg (Wümme) – Dr. med. Joachim Haessner, Gemeinschaftspraxis Wolfsburg – PD Dr. med. Peter Staib, St. Antonius-Hospital Eschweiler – Dr. med. Kai Severin, Praxis für Hämatologie und Onkologie Köln – Dr. med. Hans-Christian Kolberg, Marienhospital Bottrop gGmbH – Frau Anne Bremer, MVZ Media Vita GmbH, Münster – Frau Prof. Dr. med. Tanja Fehm, Universitätskliniken Düsseldorf – Frau Dr. Bahriye Aktas, Universitätsklinikum Essen – PD Dr. med. Stefan Krämer, Universitätsklinik Köln – Dr. med. Marcus Schmidt, Universitätsmedizin Mainz – Frau Prof. Dr. Pauline Wimberger, Universitätsklinik Dresden – Dr. med. Thomas Göhler, Gemeinschaftspraxis Dresden – Frau Dr. med. Gabriele Prange-Krex, Gemeinschaftspraxis Dresden – Frau Dr. med. Dagmar Guth, Praxis Dr. Guth, Plauen – Frau Dr. med. Astrid Schlosser, Klinikum Obergöltzscht Rodewisch – Frau Dr. med. Elke Simon, Kreiskrankenhaus Torgau – Frau Dr. Ina Lenk, Praxis Dr. Lenk, Zwickau – Frau Dr. med. Bärbel Schädlich, Gemeinschaftspraxis Halle

Nachgereichte Unterlagen [Eingang am 01.04.2015]:

Formular Kostenreduzierung für Ethikkommission Erlangen vom 01.04.2015

Nachgereichte Unterlagen [Eingang am 07.04.2015]:

Brief der Alcedis GmbH vom 01.04.2015, Antwort zur Stellungnahme der beteiligten Ethikkommission des Landes Berlin nebst Unterlagen | Brief der Alcedis GmbH vom 01.04.2015, Antwort zur Stellungnahme der beteiligten Ethikkommission Greifswald nebst Unterlagen | Brief der Alcedis GmbH vom 01.04.2015, Antwort zur Stellungnahme der beteiligten Ethikkommission der LÄK Baden-Württemberg nebst Unterlagen | Brief der Alcedis GmbH vom 01.04.2015, Antwort zur Stellungnahme der beteiligten Ethikkommission Mannheim nebst Unterlagen | Brief der Alcedis GmbH vom 01.04.2015, Antwort zur Stellungnahme der beteiligten Ethikkommission der LÄK Hessen nebst Unterlagen

Nachgereichte Unterlagen [Eingang am 14.04.2015]:

Nachgereichte Liste der vorgelegten Unterlagen, Stand 22.08.2013 | Nachgereichter Brief Prof. Dr. Janni, Klinik für Frauenheilkunde Ulm vom 01.04.2015_Stellungnahme zur Finanzierung | Brief der Alcedis GmbH vom 10.04.2015, Antwort zur Stellungnahme der beteiligten Ethikkommission der Universität Köln nebst Unterlagen | Begleitschreiben der Alcedis GmbH vom 09.04.2015 an die federführende Ethikkommission zu den nachgereichten Unterlagen | Modul 1_Seite 3 (Ergänzung C2) | Schreiben der Ecclesia Mildenberger Hospital GmbH, Detmold vom 02.12.2014 zum Jahresvertrag der Probanden-Versicherung Nr. 57 010315 03015 bei der HDI-Gerling Versicherung AG

Nachgereichte Unterlagen [Eingang am 16.04.2015]:

Brief der Alcedis GmbH vom 14.04.2015, Antwort zur Stellungnahme der beteiligten Ethikkommission Sachsen nebst Unterlagen

Nachgereichte Unterlagen [Eingang am 20.04.2015]:

Brief der Alcedis GmbH vom 17.04.2015, Antwort zur Stellungnahme der beteiligten Ethikkommission Westfalen-Lippe nebst Unterlagen

Nachgereichte Unterlagen [Eingang am 22.04.2015]:

Brief der Alcedis GmbH vom 20.04.2015, Antwort zur Stellungnahme der beteiligten Ethikkommission der LÄK Baden-Württemberg nebst Unterlagen

Eingereichte Unterlagen gem. Mängelberichte der federführenden Ethikkommission vom 07.05.2015 und 05.06.2015 [Eingang am 19.06.2015]:

Stellungnahme des Sponsors vom 15.06.2015 zu den inhaltlichen Nachforderungen der federführenden Ethikkommission Ulm | Begleitschreiben der Alcedis GmbH an die federführende Ethikkommission Ulm vom 18.06.2015 zu den inhaltlichen Nachforderungen nebst Eingangsbestätigung und Verzeichnis der beigefügten Unterlagen | Modul 1 mit Unterschriftenseite vom 18.06.2015 | Liste der Prüfer Ulm, Stand 18.06.2015 | Liste der Stellvertreter Ulm, Stand 18.06.2015 |

Mitglieder der Kommission: Prof. Dr. Th. Becker (Stellvertr. Vorsitz), Prof. Dr. P. Gierschik, J. Glembek, Prof. Dr. H. Gündel, Prof. Dr. J. Högel, Prof. Dr. P. Kern, Prof. Dr. M. Kühl, Prof. Dr. D. Rothenbacher, Pfarrer E. Schäfer, Prof. Dr. H. Schrezenmeier, Frau K. Stascheit, Prof. Dr. D. Steinbach, Prof. Dr. O. Zolk (Vorsitz)

Geänderte Deutsche Protokoll-Synopse, Version 1.0 vom 03.12.2014 in Reinversion | Geänderte Deutsche Protokoll-Synopse, Version 1.0 vom 03.12.2014 im Änderungsmodus | Geänderter Prüfplan, Nr.: DETECT V / CHEVENDO, Version 1.0 vom 03.12.2014 in Reinversion | Geänderter Prüfplan, Nr.: DETECT V / CHEVENDO, Version 1.0 vom 03.12.2014 im Änderungsmodus | Geänderte Patientinnen-Information Teil 1 (Hauptstudie), Version 1.0 vom 12.10.2014 in Reinversion | Geänderte Patientinnen-Information Teil 1 (Hauptstudie), Version 1.0 vom 12.10.2014 im Änderungsmodus | Geänderte Patientinnen-Information Teil 2 (TRAFO-Projekt), Version 1.0 vom 12.10.2014 in Reinversion | Geänderte Patientinnen-Information Teil 2 (TRAFO-Projekt), Version 1.0 vom 12.10.2014 im Änderungsmodus | Wegen Prüfer- und Stellvertreterwechsel aktualisierter Qualifikationsnachweis der Prüfstelle und der Prüfgruppe Ulm, unterzeichnet durch den Prüfer am 08.06.2015 und durch den Stellvertreter am 17.06.2015; Qualifikationsnachweise des jetzigen Prüfers Prof. Dr. med. Jens Huober: Lebenslauf vom 25.02.2015, Formular "Angaben zur Qualifikation des Prüfers" vom 08.06.2015, Ausführliche Auflistung der Studienerfahrung vom 07.10.2014, GCP-Zertifikat vom 13.04.2013, Financial Disclosure Formular vom 08.06.2015 und Erklärungen vom 08.06.2015 gem. § 7 Abs. 3 Nr. 4 GCP-V, gem. § 7 Abs. 3 Nr. 7 GCP-V, gem. § 7 Abs. 3 Nr. 15 GCP-V, § 7 Abs. 2 Nr. 15 GCP-V und gem. § 40 Abs. 1 Satz 3 Nr. 7 AMG; Qualifikationsnachweise des jetzigen Stellvertreters Prof. Dr. med. Wolfgang Janni: Lebenslauf vom 06.10.2014, Formular "Angaben zur Qualifikation des Prüfers" vom 17.06.2015, Ausführliche Auflistung der Studienerfahrung, Stand 27.05.2015, nicht unterzeichnet, GCP-Zertifikate vom 13.04.2013 und vom 10.04.2014, Financial Disclosure Formular vom 17.06.2015 und Erklärungen vom 27.06.2015 gem. § 7 Abs. 3 Nr. 4 GCP-V, gem. § 7 Abs. 3 Nr. 7 GCP-V, gem. § 7 Abs. 3 Nr. 15 GCP-V, § 7 Abs. 2 Nr. 15 GCP-V und gem. § 40 Abs. 1 Satz 3 Nr. 7 AMG | Konformitätserklärung vom 18.12.2013 betreffend CellTracks® Analyzer II®, Code 9555 und Celltracks® Remote Review Workstation (RRW), Code 9542 | Konformitätserklärung vom 18.12.2013 betreffend CellTracks-AutoPrep® Instrument Buffer, Code 7901003 | Konformitätserklärung vom 18.12.2013 betreffend CellTracks®-AutoPrep®, Code 9541 | Konformitätserklärung vom 18.12.2013 betreffend CellSearch® Circulating Tumor Cell (CTC) Kit, Code 7900001 und CellSearch® Circulating Tumor Cell (CTC) Control Kit, Code 7900993 | ISO-Zertifikat_Janssen LLC, Nr.: QS1 13 08 85614 001 vom 18.12.2013 | Konformitätserklärung vom 18.12.2013 betreffend CellSaveTube® 100-Pack, Code 7900005 und CellSave Tube® 20-Pack, Code 952820

Eingereichte Unterlagen gem. Stellungnahme der federführenden Ethikkommission vom 29.06.2015 [Eingang am 13.07.2015]:

Stellungnahme des Sponsors vom 09.07.2015 zu den weiteren Nachforderungen der federführenden Ethikkommission Ulm | Begleitschreiben der Alcedis GmbH an die federführende Ethikkommission Ulm vom 08.07.2015 zu den weiteren Nachforderungen nebst Verzeichnis der beigefügten Unterlagen und Eingangsbestätigung | Geänderter Prüfplan, Nr.: DETECT V / CHEVENDO, Version 1.1 vom 03.06.2015 in Reinversion | Geänderter Prüfplan, Nr.: DETECT V / CHEVENDO, Version 1.1 vom 03.06.2015 im Änderungsmodus | Geänderte Deutsche Protokoll-Synopse, Version 1.1 vom 03.06.2015 in Reinversion | Geänderte Deutsche Protokoll-Synopse, Version 1.1 vom 03.06.2015 im Änderungsmodus | Geänderte Patientinnen-Information Teil 1 (Hauptstudie), Version 1.1 vom 03.06.2015 in Reinversion | Geänderte Patientinnen-Information Teil 1 (Hauptstudie), Version 1.1 vom 03.06.2015 im Änderungsmodus | Geänderte Patientinnen-Information Teil 2 (TRAFO-Projekt), Version 1.1 vom 03.06.2015 in Reinversion | Geänderte Patientinnen-Information Teil 2 (TRAFO-Projekt), Version 1.1 vom 03.06.2015 im Änderungsmodus

Anhang 2: Die vorliegende zustimmende Bewertung der Ethikkommission der Universität Ulm ist ausschließlich gültig für folgende Prüfer, Stellvertreter und Prüfzentren:

- Prof. Dr. med. Jens Huober (Prüfer), Prof. Dr. med. Wolfgang Janni (Stellvertreter) – Universitätsklinikum Ulm, Frauenklinik, Prittwitzstraße 43, 89075 Ulm
- Dr. med. Jochem Potenberg (Prüfer), Dr. med. Börn Beurer (Stellvertreter) – Ev. Waldkrankenhaus Spandau, Innere Medizin, Strandstraße 555 – 561, 13589 Berlin
- Dr. med. Jörg Schilling (Prüfer), Dr. med. Angelika Till (Stellvertreterin) – Praxis Dr. Schilling, Dr. Till, Wönnichstr. 64/66, 10317 Berlin
- Dr. med. Axel Gerhardt (Prüfer), Prof. Dr. med. Marc Sütterlin (Stellvertreter) – Universitätsmedizin Mannheim, Frauenklinik, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim
- Dr. med. Leonid Basovski (Prüfer), Dr. med. Holger Kohlhammer (Stellvertreter) – Hämatologisch-Onkologische Praxis an der Kreisklinik Biberach, Ziegelhausstraße 50, 88400 Biberach
- Dr. med. Lelia-Eveline Bauer (Prüferin), Dr. med. Bettina Müller (Stellvertreterin) – GRN Klinik Weinheim, Gynäkologie und Geburtshilfe, Röntgenstraße 1, 69469 Weinheim
- Prof. Dr. med. Thomas Decker (Prüfer), PD Dr. med. Tobias Dechow (Stellvertreter) – Studienzentrum Onkologie Ravensburg, Elisabethenstraße 19, 88212 Ravensburg
- Prof. Dr. med. Thomas Decker (Prüfer), PD Dr. med. Tobias Dechow (Stellvertreter) – Onkologische Praxis, Am Engelberg 33 a, 88239 Wangen im Allgäu
- Dr. med. Wilma Ehrle (Prüferin), Dr. med. Elke Faust (Stellvertreterin) – Paracelsus-Krankenhaus Ruit, Abteilung für Frauenheilkunde und Geburtshilfe, Hedelfinger Straße 166, 73760 Ostfildern
- Dr. med. Birgit Euchenhofer (Prüferin), Dr. med. Ina Seidenspinner (Stellvertreterin) – Internistische Gemeinschaftspraxis, Frauenklinik, Röntgenstraße 14, 88048 Friedrichshafen
- Dr. med. Elke Faust (Prüferin), Prof. Dr. med. Andreas Funk (Stellvertreter) – Kreiskliniken Esslingen, Frauenheilkunde und Geburtshilfe, Auf dem Säer 1, 72622 Nürtingen
- Prof. Dr. med. Thorsten Kühn (Prüfer), Dr. med. Cornelia Kurz (Stellvertreterin) – Klinikum Esslingen, Klinik für Frauenheilkunde und Geburtshilfe, Hirschlandstraße 97, 73730 Esslingen
- Dr. med. Oliver Tomé (Prüfer), Dr. med. Claudia Holtkotten (Stellvertreterin) – St. Vincentius Kliniken gAG, Abteilung für Frauenheilkunde, Edgar-von-Gierke-Straße 2, 76135 Karlsruhe
- Dr. med. Grischa Wachsmann (Prüfer), Dr. med. Wanda Marchina (Stellvertreterin) – Klinikum Sindelfingen-Böblingen, Frauenklinik, Bunsenstraße 120, 71032 Böblingen
- Dr. med. Matthias Zaiss (Prüfer), Dr. med. Norbert Marschner (Stellvertreter) – Praxis für interdisziplinäre Onkologie & Hämatologie, Wirthstraße 11c, 79110 Freiburg
- Prof. Dr. med. Elmar Stickeler (Prüfer), Dr. med. Beate Rautenberg (Stellvertreterin) – Universitätsklinikum Freiburg, Klinik für Frauenheilkunde, Hugstetter Straße 55, 79106 Freiburg
- Dr. med. Florin-Andrei Taran (Prüfer), Dr. med. Andreas Hartkopf (Stellvertreter) – Universitätsfrauenklinik Tübingen, Klinik für Gynäkologie und Geburtshilfe, Calwerstraße 7, 72076 Tübingen
- Dr. med. Markus Hahn (Prüfer), Dr. med. Sebastian Müller (Stellvertreter) – Gemeinschaftspraxis Dr. Hahn / Dr. Müller, Schöneckerstraße 4, 91522 Ansbach
- Dr. med. Bernhard Heinrich (Prüfer), Prof. Dr. med. Markus Bangerter (Stellvertreter), Dr. med. Olaf Brudler (Stellvertreter) – Gemeinschaftspraxis Dr. Brudler / Dr. Heinrich / Prof. Dr. Bangerter, Halderstraße 29, 86150 Augsburg
- Dr. med. Helmut Tanzer (Prüfer), Dr. med. Christian Stöberl (Stellvertreter) – Internistische Schwerpunktpraxis, Wittelsbacherstraße 10a, 83435 Bad Reichenhall
- Dr. med. Hermann Zoche (Prüfer), Thomas Barsch (Stellvertreter) – Klinikum Coburg, Frauenklinik, Ketschendorfer Straße 33, 96450 Coburg
- Dr. med. Jutta Neteler (Prüferin), Dr. med. Gesche Brannolte (Stellvertreterin) – Onkologisches Zentrum, Brustzentrum, Krankenhausstraße 15, 85221 Dachau
- Dr. med. Helmut Lambertz (Prüfer), Dr. med. Lothar Schulz (Stellvertreter) – Klinikum Garmisch-Partenkirchen, Innere Medizin, Auenstraße 6, 82467 Garmisch-Partenkirchen
- Christina Bechtner (Prüferin), Sabine Kleiber (Stellvertreterin) – Klinikum Memmingen, Brustzentrum, Bismarckstraße 23, 87700 Memmingen
- Dr. med. Wolfgang Abenhadt (Prüfer), PD Dr. med. Peter Bojko (Stellvertreter) – Münchner Onkologische Praxis Elisenhof, Prielmayer Straße 1, 80335 München
- Dr. med. Oliver Stoetzer (Prüfer), PD Dr. med. Michael Braun (Stellvertreter), Claus Hanusch (Stellvertreter), Prof. Dr. med. Christoph Salat (Stellvertreter) – Hämatologisch-Onkologische Gemeinschaftspraxis, Franz-Schrank-Straße 2, 80638 München
- Prof. Dr. med. Heinz Scholz (Prüfer), Kari Buss (Stellvertreter) – Klinikum Neumarkt, Frauenklinik, Nürnberger Straße 12, 92318 Neumarkt

- Prof. Dr. med. Arthur Wischnik (Prüfer), Dr. med. Jacqueline Sagasser (Stellvertreterin) – Klinikum Augsburg, Frauenklinik, Stenglinstraße 2, 86156 Augsburg
 - PD Dr. med. Brigitte Rack (Prüferin), Prof. Dr. med. Nadia Harbeck (Stellvertreterin) – Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Klinikum der Universität München Innenstadt, Maistraße 11, 80337 München
 - Prof. Dr. med. Thomas Beck (Prüfer), Dr. med. Tonja Bartl (Stellvertreterin) – RoMed Klinikum, Abteilung für Gynäkologie und Geburtshilfe, Pettenkofer Straße 10, 83022 Rosenheim
 - Prof. Dr. med. Peter Fasching (Prüfer), PD Dr. med. Christian Löbberg (Stellvertreter) – Universitätsklinikum Erlangen, Frauenklinik, Universitätsstraße 21-23, 91054 Erlangen
 - Dr. med. Gabriele Doering (Prüferin), Dr. med. Carsten Schreiber (Stellvertreter) – Praxis für Hämatologie / Onkologie, Schwachhauser Heerstraße 50, 28209 Bremen
- Hinweis der lokalen Ethikkommission: Das Prüfzentrum nimmt an Studien teil, in die Patientinnen in der neoadjuvanten Situation eingeschlossen werden sollen. Die Kommission bittet um eine Stellungnahme zu der Frage, ob das Prüfzentrum an konkurrierenden Forschungsvorhaben teilnimmt und wie mit Konkurrenzen umgegangen werden soll.
- PD Dr. med. Gernot Seipelt (Prüfer), Dr. med. Ursula Koch (Stellvertreterin) – Gemeinschaftspraxis Dr. Seipelt & Dr. Koch, Kronberger Straße 36 b, 65812 Bad Soden
 - Prof. Dr. med. Heinz-Gert Höffkes (Prüfer), Dr. med. Andrea Distelrath (Stellvertreterin) – MVZ Osthesen GmbH, Pacelliallee 4, 36043 Fulda
 - PD Dr. med. Thomas Müller (Prüfer), Roland Fricker (Stellvertreter) – Klinikum Hanau GmbH, Klinik für Gynäkologie und Geburtshilfe, Leimenstraße 20, 63450 Hanau
 - Angelika Christiane Ober (Prüferin), Dr. med. Peter Scheler (Stellvertreter) – St. Vincenz-Krankenhaus, Brustzentrum / Frauenklinik, Auf dem Schafsberg, 65549 Limburg
 - Prof. Dr. med. Christian Jackisch (Prüfer), Sabine Seiler (Stellvertreterin) – Sana Klinikum Offenbach GmbH, Klinik für Gynäkologie und Geburtshilfe, Starkenburgring 66, 63069 Offenbach
 - Dr. med. Bernd Flath (Prüfer), Dr. med. Julia Dittrich (Stellvertreterin) – HOPA Praxis für Ambulante Onkologie im Krankenhaus Jerusalem, Schäferkampsallee 34, 20357 Hamburg
 - Prof. Dr. med. Gerhard Gebauer (Prüfer), Dr. med. Małgorzata Joanna Banys (Stellvertreterin) – Kath. Marienkrankenhaus, Alfredstraße 9, 22087 Hamburg
 - Dr. med. Volkmar Müller (Prüfer), Dr. med. Isabell Witzel (Stellvertreterin) – Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Gynäkologie, Martinistraße 52, 20246 Hamburg
 - Prof. Dr. med. Bernd Gerber (Prüfer), Dr. med. Max Dieterich (Stellvertreter) – Universitätsfrauenklinik Rostock am Klinikum Südstadt, Südring 81, 18059 Rostock
 - Dr. med. Antje Belau (Prüferin), Dr. med. Margrit Nehmzow (Stellvertreterin) – Ernst-Moritz-Arndt-Universität Greifswald, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Ferdinand-Sauerbruch-Straße, 17475 Greifswald
 - Dr. med. Carsten Hielscher (Prüfer), Dr. med. Frank Ruhland (Stellvertreter) – G.SUND Gynäkologie Kompetenzzentrum, Große Parower Str. 47-53, 18435 Stralsund
 - Dr. med. Lothar Müller (Prüfer), Carsten Janßen (Stellvertreter) – Onkologie Leer-Emden-Papenburg, Praxis Dr. med. Lothar Müller, Annenstraße 11 26789 Leer und Bolardusstraße 20a, 26721 Emden
 - Dr. med. Kristina Lübbe (Prüferin), Dr. med. Angela Kentsch (Stellvertreterin) – Diakoniekrankenhaus Henriettenstiftung gGmbH, Frauenklinik, Schwemannstraße 17-19, 30559 Hannover
 - Dr. med. Beatrice Goldmann (Prüferin), Dr. med. Juliane Ebert (Stellvertreterin) – Gemeinschaftspraxis Dres. B. Goldmann / J. Ebert, Schildsteinweg 26, 21339 Lüneburg
 - Tobias Hesse (Prüfer), Sebastian Bauer (Stellvertreter) – Agaplesion Diakonieklinikum Rotenburg gGmbH, Frauenklinik, Elise Averdiek Straße 17, 27356 Rotenburg
 - Dr. med. Joachim Haessner (Prüfer), Dr. med. Thomas Gabrysiak (Stellvertreter) – Gemeinschaftspraxis, Kaufhofpassage 5-7, 38440 Wolfsburg
 - PD Dr. med. Peter Staib (Prüfer), Dr. med. Frank Schlegel (Stellvertreter) – St. Antonius-Hospital, Klinik für Hämatologie / Onkologie, Dechant-Deckers-Straße 8, 52249 Eschweiler
 - Dr. med. Kai Severin (Prüfer), Prof. Dr. med. Stephan Schmitz (Stellvertreter), Dr. med. Hans Tilmann Steinmetz (Stellvertreter) – Praxis für Hämatologie und Onkologie, Sachsenring 69, 50677 Köln
 - Dr. med. Hans-Christian Kolberg (Prüfer), Leyla Akpolat-Bascı (Stellvertreterin) – Marienhospital Bottrop gGmbH, Klinik für Gynäkologie und Geburtshilfe, Josef-Albers-Straße 70, 46236 Bottrop
 - Dr. med. Anne Ira Bremer (Prüferin), Dr. med. Oliver Albrecht (Stellvertreter) – MVZ Media Vita GmbH, Hohenzollernring 68, 48145 Münster
 - Prof. Dr. med. Tanja Fehm (Prüferin), PD Dr. med. Eugen Ruckhäberle (Stellvertreter) – Universitätsklinikum Düsseldorf, Frauenklinik, Moorenstraße 5, 40225 Düsseldorf
 - PD Dr. med. Bahriye Aktas (Prüferin), Dr. med. Dagmar Nierwetberg (Stellvertreterin) – Universitätsklinikum Essen, Klinik für Frauenheilkunde und Geburtshilfe, Hufelandstraße 55, 45122 Essen

- PD Dr. med. Stefan Krämer (Prüfer), Dr. med. Marina Wirtz (Stellvertreterin) – Universitätsklinik Köln, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Kerpener Straße 34, 50931 Köln
- PD Dr. med. Marcus Schmidt (Prüfer), Dr. med. Marco Battista (Stellvertreter) – Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Klinik und Poliklinik für Geburtshilfe und Frauenheilkunde, Langenbeckstraße 1, 55131 Mainz
- Prof. Dr. med. Pauline Wimberger (Prüferin), Dr. med. Karin Kast (Stellvertreterin) – Universitätsklinik Carl Gustav Carus der Technischen Universität Dresden, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Fetscherstraße 74, 01307 Dresden
- Dr. med. Thomas Göhler (Prüfer), Dipl. Med. Steffen Dörfel (Stellvertreter) – Gemeinschaftspraxis Dr. Göhler, Dörfel, Bold, Leipziger Straße 118, 01127 Dresden
- Dr. med. Gabriele Prange-Krex (Prüferin), Dr. med. Johannes Mohm (Stellvertreter) – Gemeinschaftspraxis Dr. med. Mohm & Dr. med. Prange-Krex, Pfotenauerstr. 55, 01307 Dresden
- Dr. med. Dagmar Guth (Prüferin), Astrid Schlosser (Stellvertreterin) – Praxis Dr. Guth, Plauener Straße 33 A, 08525 Plauen
- Astrid Schlosser (Prüferin), Dr. med. Barbara Stephan (Stellvertreterin) – Klinikum Obergöltzschtal-Rodewisch, Abteilung Gynäkologie und Geburtshilfe, Stiftstraße 10, 08228 Rodewisch
- Dr. med. Eike Simon (Prüfer), Dr. med. Christian Döring (Stellvertreter) – Kreiskrankenhaus Torgau, Frauenklinik, Christianistraße 1, 04860 Torgau
- Dr. med. Ina Lenk (Prüferin), Astrid Schlosser (Stellvertreterin) – Praxis Dr. Lenk, Goethestraße 21, 08060 Zwickau
- Dr. med. Bärbel Schädlich (Prüferin), Dr. med. Marion Schmalfeld (Stellvertreterin) – Gemeinschaftspraxis für Innere Medizin, Hämatologie, Onkologie und Gastroenterologie, Niemeyerstraße 22, 06110 Halle
- Dr. med. Kristina Freese (Prüferin), Dr. med. Michael Böhme (Stellvertreter) – Klinik Sankt Marienstift, Frauenheilkunde / Brustzentrum, Harsdorfer Straße 30, 39110 Magdeburg

Anhang 3: Zur zustimmenden Bewertung haben folgende beteiligte Ethikkommissionen beigetragen:

1. Ethikkommission des Landes Berlin
2. Ethikkommission der Medizinischen Fakultät Mannheim der Universität Heidelberg
3. Ethikkommission bei der Landesärztekammer Baden-Württemberg
4. Ethikkommission der Albert-Ludwigs-Universität Freiburg
5. Ethikkommission der Universität Tübingen
6. Ethikkommission der Bayerischen Landesärztekammer
7. Ethikkommission bei der Ludwig-Maximilians-Universität München
8. Ethikkommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg
9. Ethikkommission des Landes Bremen
10. Ethikkommission bei der Landesärztekammer Hessen
11. Ethikkommission der Ärztekammer Hamburg
12. Ethikkommission an der Medizinischen Fakultät der Universität Rostock
13. Ethikkommission an der Universitätsmedizin Greifswald
14. Ethikkommission der Ärztekammer Niedersachsen
15. Ethikkommission der Ärztekammer Nordrhein
16. Ethikkommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster
17. Ethikkommission der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf
18. Ethikkommission der Medizinischen Fakultät der Universität Duisburg-Essen
19. Ethikkommission der Universität zu Köln
20. Ethikkommission der Landesärztekammer Rheinland-Pfalz
21. Ethikkommission an der Technischen Universität Dresden
22. Ethikkommission der Sächsischen Landesärztekammer
23. Ethikkommission des Landes Sachsen-Anhalt

*Hooyte C***Universitair Medisch Centrum Groningen****Medisch Ethische Toetsingscommissie**

Aan
 Dr. C.P. Schröder
 Medische Oncologie
 DA11

Telefoon (050) 361 4204
 Fax (050) 361 4351

Bijlage(n)
 Kenmerk M16.190951

Datum	7 april 2016
Onderwerp	METc 2015/396
Titel onderzoek	FDHT-PET to visualize the effect on the androgen receptor level by bicalutamide.
ABR nr	[NL53358.042.15]
EudraCT	[2015-001634-17]

De Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen (METc UMCG) heeft uw, bij brief van 1 maart 2016 ingediend amendement#1 op het onderzoeksprotocol met bovengenoemde titel besproken in haar vergadering van 31 maart jongstleden en beoordeeld in het kader van de Wet medisch-wetenschappelijk onderzoek met mensen (WMO).

De METc UMCG besloot tot een nader positief oordeel over amendement#1.

Bij de beoordeling zijn o.a. de volgende documenten betrokken:

- Onderzoeksprotocol getiteld 'FDHT-PET to visualize the effect on the androgen receptor level by bicalutamide.', versie 1.3, d.d. 26-02-2016;
- ABR-formulier [NL53358.042.15], versie 4, d.d. 01-03-2016;
- EudraCT Substantial Amendment Notification Form [2015-001634-17] gedateerd en ondertekend d.d. 01-03-2016.

Naar aanleiding van het positieve oordeel wil de METc UMCG u wijzen op het volgende:

- Het door de METc UMCG uitgesproken oordeel is een oordeel als bedoeld in art. 3 WMO.
- Op grond van art. 23 WMO kan degene wiens belang rechtstreeks bij dit besluit is betrokken daartegen binnen zes weken na de dag waarop het besluit bekend is gemaakt administratief beroep aantekenen bij de Centrale Commissie Mensgebonden Onderzoek (CCMO), Parnassusplein 5, 2511 VX DEN HAAG (correspondentieadres: Postbus 16302, 2500 BH DEN HAAG).



- Een afschrift van dit oordeel zal in ToetsingOnline worden verwerkt.

Met vriendelijke groet,
namens de Medisch Ethische Toetsingscommissie,

W.A. Kamps
prof. dr. W.A. Kamps
voorzitter

P. Vos
mw. P. Vos
ambtelijk secretaris

cc.

- Prof. dr. J. A. Gietema, Medische Oncologie DA11
- Drs. C.M. Venema, Medische Oncologie DA11
- CCMO (via ToetsingOnline)
- Ziekenhuisapotheek UMCG, per email (trials@apoth.umcg.nl)



INFORME DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Doña INMACULADA FUENTES CAMPS, Secretaria en funciones del Comité Ético de Investigación Clínica de l'Hospital Universitari Vall d'Hebrón, de Barcelona,

CERTIFICA

Que este Comité ha evaluado en su reunión del día 27 de junio de 2014 la propuesta del promotor:

NKI-AVL

para que sea realizado en este Centro, el ensayo clínico código **M14POS / POSEIDON** / EudraCTnº: **2013-003947-51**, titulado:

Ensayo clínico aleatorizado, prospectivo, comparativo, en fase I y II sobre la eficacia de tamoxifeno combinado con el inhibidor selectivo isoforma de Pi3K GDC-0032 y el tamoxifeno aLONe en pacientes con cáncer de mama metastásico HER2 negativo, con receptor hormonal positivo, previamente tratados con terapia hormonal. Ensayo POSEIDON

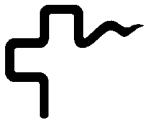
Protocolo en inglés, versión 1.0 de 23 de mayo de 2014.

Resumen en español, versión 1.0 de 23 de mayo de 2014.

HIP/CI fase I, versión 2.0 de 23 junio de 2014.

HIP/CI fase II, versión 2.0 de 23 de junio de 2014.

- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.
- Son adecuados tanto el texto de la hoja de información al paciente, como el procedimiento para obtener el consentimiento informado así como también la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.
- El alcance de las compensaciones económicas no interfiere con el respeto a los postulados éticos.
- Y que este Comité acepta que dicho ensayo clínico sea realizado por la Dra. Mafalda Antunes de Melo e Oliveira como investigadora principal..



Que el Comité tanto en su composición como en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 223/2004, y su composición actual es la siguiente:

Presidenta: Gallego Melcón, Soledad. Médico
Vicepresidente: Segarra Sarries, Joan. Abogado
Secretaria: Navarro Sebastián, Mireia. Química
Vocales : Armadans Gil, Lluís. Médico
Azpiroz Vidaur, Fernando. Médico
Corona Pérez-Cardona, Pablo. Médico
Cucurull Folguera, Esther. Médico Farmacóloga
Latorre Arteche, Francisco. Médico
De Torres Ramírez, Inés M. Médico
Fernández Liz, Eladio. Farmacéutico de Atención Primaria
Ferreira González, Ignacio. Médico
Fuentelsaz Gallego, Carmen. Diplomada Enfermería
Fuentes Camps, Inmaculada. Médico Farmacóloga
Guardia Massó, Jaume. Médico
Hortal Ibarra, Juan Carlos. Profesor de Universidad de Derecho
Montoro Ronsano, J. Bruno. Farmacéutico Hospital
Rodríguez Gallego, Alexis. Médico Farmacólogo
Sánchez Raya, Judith. Médico
Solé Orsola, Marta. Diplomada Enfermería
Suñé Martín, Pilar. Farmacéutica Hospital
Vargas Blasco, Víctor, Médico
Vilca Yengle, Luz M^a. Médico

Que en dicha reunión del Comité Ético de Investigación Clínica se cumplió el quórum preceptivo legalmente.

Que en el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, éste se ausentará de la reunión durante la discusión del proyecto.

Lo firmo en Barcelona, a 27 de junio de 2014

Firmado: Dra. Inmaculada Fuentes
Secretaria en funciones del CEIC

VALL D'HEBRON UNIVERSITY HOSPITAL ETHICS OF CLINICAL RESEARCH COMMITTEE AND COMMISSION OF INQUIRY REPORT

Mrs. Mireia Navarro Sebastián, Secretary of the Clinical Research Ethics Committee at the Hospital Universitari Vall d'Hebron from Barcelona,

CERTIFIES

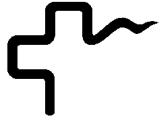
The Hospital Universitari Vall d'Hebron Clinical Research Ethics Committee , in which the research project commission is integrated, met in regular session No 232 last 29/05/2015 and evaluated the Enmienda_7 , of the Research Project PR(IR)53/2010 entitled "*Tumorigenity and study of drug sensitivity in xenoimplant models derived from breast cancer biopsies from patients in active treatment*". whose principal investigator Dr. Violeta Serra Elizalde, Experimental Therapies Service of our center.

The result of the evaluation was as follows:

DICTAMEN FAVORABLE

The Committee in its composition as in the SOP (Standard Operating Procedure) meets GCP (CPMP/ICH/135/95) and Royal Decree 223/2004, and its current composition is:

Chair person: Gallego Melcón, Soledad. Doctor
Vice President: Segarra Sarries, Joan. Lawyer
Secretary: Navarro Sebastián, Mireia. Chemist
Vocals: Armadans Gil, Lluís. Doctor
Azpiroz Vidaur, Fernando. Doctor
Corona Pérez-Cardona, Pablo. Doctor
Cucurull Folgera, Esther. Physician Pharmacologist
Latorre Arteche, Francisco. Doctor
De Torres Ramírez, Inés M. Doctor
Fernández Liz, Eladio. Primary care Pharmaceutics
Ferreira González, Ignacio. Doctor
Fuentelsaz Gallego, Carmen. Nurse
Fuentes Camps, Inmaculada. Physician Pharmacologist



Guardia Massó, Jaume. Doctor
Hortal Ibarra, Juan Carlos. Law University Profesor
Montoro Ronsano, J. Bruno. Hospital Pharmacologist
Rodríguez Gallego, Alexis. Physician Pharmacologist
Sánchez Raya, Judith. Doctor
Solé Orsola, Marta. Nurse
Suñé Martín, Pilar. Hospital Pharmacologist
Vargas Blasco, Víctor. Doctor
Vilca Yengle, Luz María. Doctor

At the meeting of the Clinical Research Ethics Committee fulfilled the quorum provisions of law.

In the case of a project to evaluate where a member is a researcher / collaborator, he will be absent from the meeting during discussion of the project.

Mrs. Mireia Navarro
Secretary of the Clinical Research Ethics Committee
Hospital Universitario Vall d'Hebron
Barcelona, May 29th, 2015



Medizinische Fakultät Heidelberg

Ethikkommission der Med. Fak. HD | Alte Glockengießerei 11/1 | D-69115 Heidelberg

Herrn Prof. Dr. Hermann Brenner
Division of Clinical Epidemiology
and Aging Research (DKFZ)
& Division of Preventive Oncology (NCT)
Im Neuenheimer Feld 581
69120 Heidelberg

—
13.06.2016
ts-cd



Alte Glockengießerei 11/1
D-69115 Heidelberg

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✉ ethikkommission-l@med.uni-heidelberg.de

www.medizinische-fakultaet-hd.uni-heidelberg.de/ethikkommission

Vorsitz:
Prof. Dr. med. Thomas Strowitzki

Stellv. Vorsitz:
Prof. Dr. med. Johannes Schröder
Prof. Dr. med. Klaus Herfarth

Geschäftsleitung:
Dr. med. Verena Pfeilschifter

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Dr. rer. nat. Sabine Vogel
☎ +49 6221 3382219
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✉ Sabine.Vogel@med.uni-heidelberg.de

Unser Zeichen: **S-392/2015** (Bitte stets angeben)

Titel: Gebt dem Krebs keine Chance - Onkocheck (GEKKO)
Forschungsprogramm Krebsfrüherkennung und Screening am Nationalen Centrum für Tumorerkrankungen (NCT)

Eingereichte Unterlagen: Nachträgliche Änderung vom 03.05.2016:
Anschreiben vom 03.05.2016
Formular für Änderungsantrag vom 04.05.2016
Teilnehmerinformation für Teilnehmer der Koloskopie (Studienarm A) Version 1.3 vom 03.05.2016 (mit Markierung der Änderungen)
Teilnehmerinformation für den klinischen Studienteil (Studienarm B) Version 1.3 vom 03.05.2016 (mit Markierung der Änderungen)
Einverständniserklärung für Teilnehmer der Koloskopie (Studienarm A) Version 1.3 vom 03.05.2016 (mit Markierung der Änderungen)
Einverständniserklärung für den klinischen Studienteil (Studienarm B) Version 1.3 vom 03.05.2016 (mit Markierung der Änderungen)
Übereignungsvereinbarung für Teilnehmer der Koloskopie (Studienarm A) Version 1.3 vom 03.05.2016 (mit Markierung der Änderungen)
Übereignungsvereinbarung für den klinischen Studienteil (Studienarm B) Version 1.3 vom 03.05.2016 (mit Markierung der Änderungen)
Study Protocol Version 1.3 vom 03.05.2016 (mit Markierung der Änderungen)
CV Prof. Dr. med. Tom Michael Ganter vom 24.03.2016
Teilnahmebestätigung GCP-Refresher für Prof. Dr. med. Tom M. Ganter vom 28.01.2016
Zertifikat Onlineschulung ICH-GCP-konforme Durchführung klinischer Studien für PD Dr. med. Tom Ganter 12.03.2014
Teilnahmebescheinigung Prüfärztkurs „Rahmenbedingungen und Durchführung klinischer Prüfungen“ für Dr. Tom Ganter vom 31.07.2008
Einschätzung der Ethikkommission der Medizinischen Fakultät Heidelberg vom 18.02.2016



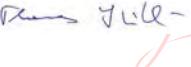
Bankverbindung:
Baden-Württembergische Bank Stuttgart
Konto-Nr.: 7421 500 429
BLZ: 600 501 01
SWIFT/BIC Code: SOLADEST
IBAN-Nr.: DE 64600501017421500429

Sehr geehrter Herr Professor Brenner,

die Ethikkommission hat sich in ihrer Sitzung am 06.06.2016 mit den oben näher bezeichneten Unterlagen befasst und hat **keine Bedenken gegen die Änderung**.

Bitte leiten Sie das Ergebnis der berufsrechtlichen Beratung und die studienrelevante Korrespondenz allen teilnehmenden Ärzten in unserem Zuständigkeitsbereich weiter.

Mit freundlichen Grüßen

 Digital unterschrieben von Dr.
Strowitzki, Thomas
DN: c=DE, cn=Dr. Strowitzki,
Thomas, serialNumber=1
Datum: 2016.06.16 14:15:07
+02'00'

Prof. Dr. med. Thomas Strowitzki
Vorsitzender

Allgemeine Hinweise:

- Änderungen in Organisation und Ablauf der Studie sind der Kommission, zusammen mit einer Bewertung der Nutzen-Risiko-Relation, umgehend mitzuteilen. Sowohl die **Antragsnummer** als auch die **geänderten Passagen** sollten in den betreffenden Unterlagen **deutlich gekennzeichnet** sein, da anderenfalls keine zügige Bearbeitung möglich ist.
- Innerhalb von einem Jahr nach Studienende sollte die Studienleitung der Kommission einen Abschlussbericht vorlegen, der eine Zusammenfassung der Ergebnisse und Schlussfolgerungen der Studie enthält, unabhängig davon, ob diese vollständig abgeschlossen oder vorzeitig beendet wurde. Dafür ist die auf der Homepage der Kommission abrufbare Mustervorlage „Abschlussbericht“ zu verwenden (Pfad: → Sonstige Studien → Vorlagen).
- Jedes Forschungsvorhaben, an dem Versuchspersonen beteiligt sind, ist vor der Rekrutierung der ersten Versuchsperson in einer öffentlich zugänglichen Datenbank zu registrieren.
- Die Ethikkommission der Medizinischen Fakultät Heidelberg arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den ICH-GCP-Richtlinien. Ihren Beratungen liegt die Deklaration des Weltärztekongresses von Helsinki in der jeweils aktuellen Fassung zugrunde.
- Unabhängig vom Beratungsergebnis macht die Ethikkommission Sie darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung einer Studie beim Leiter der Studie und bei allen teilnehmenden Ärzten liegt.

Universitair Medisch Centrum Groningen**Medisch Ethische Toetsingscommissie**

Aan
 BOOG Study Center
 T.a.v. mevrouw A.E. van Leeuwen-Stok
 Postbus 9236
 1006 AE Amsterdam

Telefoon (050) 361 4204
 Fax (050) 361 4351

Bijlage(n) ---
 Kenmerk M13.142041

Datum 19 augustus 2013
 Onderwerp METc 2013.291
 Titel onderzoek **Male Breast Cancer: prospective into perspective.**
 ABR nr NL45204.042.13

De Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen (METc UMCG) heeft het bovengenoemde onderzoek besproken in haar vergadering van 15 augustus 2013.

Over mannen met borstkanker is veel bekend vanuit retrospectieve studies. De detectie is vaak later dan bij vrouwen, waardoor veelal pas detectie in een verder gevorderd stadium. De gemiddelde leeftijd bij mannen ligt hoger dan bij vrouwen. Gecorrigeerd voor ernst en leeftijd is de prognose beter. Over de mannen met borstkanker zijn weinig psychosociale aspecten goed bekend. Het primaire doel van het huidige onderzoek is het opstellen van een nationale registratie van voorkomen, behandeling, uitkomsten en bijeffecten.

In deze prospectieve cohortstudie worden veel klinische data vastgelegd. Apart wordt kwaliteit van leven beschreven. Bij entree, na 1 jaar en na 5 jaar wordt de patiënt (proefpersoon) gevraagd een vragenlijst in te vullen (15 min). Hierbij merkt de commissie op dat dit idealiter als onderdeel van de standaard zorg zou moeten zijn. Dan zouden deze gegevens via het medisch dossier beschikbaar zijn voor de onderzoekers.

Er worden veel gegevens uit het tumormateriaal gehaald:

- Histologie
- Prognostische markers die in de retrospectieve studies zijn geïdentificeerd.

Deze gegevens worden geassocieerd met follow-up data. Bij voldoende power wordt de reactie van behandelingen geëvalueerd.

Er wordt bestudeerd of bekende mutaties bij vrouwen met borstkanker ook bij mannen voorkomen (genoom onderzoek).



Het extra af te nemen bloed is bedoeld voor toekomstige studies. De analyse daarvan valt buiten de scope van het huidige onderzoek. Er is hier sprake van het opzetten van een *biobank* waarvoor een biobankreglement moet worden opgesteld, zoals gebruikelijk in het UMCG.

Informed consent wordt gevraagd voor de gevalideerde vragenlijsten en het gebruik van het tumorweefsel (optioneel), en een apart informed consent het opslaan van bloed (ook optioneel).

De beoogde onderzoeksperiode is 3 jaar en wordt zonodig verlengd als er nog geen 200 mannen geïncludeerd zijn. Het onderzoek (meer specifiek de dataverzameling) loopt tot 5 jaar na de laatste inclusie.

Samenvattend concludeert de METc dat er sprake is van een *registratie* van patiënten in een nationale database, het gebruik van restmateriaal (tumormateriaal) en het afnemen van extra bloed ten behoeve van een biobank. Het enige dat, zoals de METc begrijpt, extra ten behoeve van het onderzoek gebeurt, is het afnemen van vragenlijsten teneinde inzicht te krijgen over de kwaliteit van leven van de patiënten. En daarvan is de METc van mening, dat deze vragenlijsten weinig belastend zijn en de geboden zorg evalueren.

Gelet op het bovenstaande is de METc UMCG van mening dat bovengenoemd onderzoek *geen* medisch wetenschappelijk onderzoek met mensen is, zoals bedoeld in de Wet medisch-wetenschappelijk onderzoek met mensen (WMO).

De METc UMCG besluit zodoende dat u geen positief WMO-oordeel behoeft, alvorens u met bovengenoemd onderzoek mag aanvangen.

Met vriendelijke groet,
namens de Medisch Ethische Toetsingscommissie,

prof. dr. W.A. Kamps
voorzitter

drs. J.W.G. Ummels
ambtelijk secretaris

cc:

- Prof. dr. E.G.E. de Vries, Medische Oncologie, DA11
- Dr. C.P. Schröder, Medische oncologie, DA11



Dr.ir. J.W.M. Martens
Afd. Interne Oncologie
Kamer Be 400
Erasmus MC

Doorkeurnummer +31 10 7033625/34428
Faxnummer
Kamernummer Fd 209
E-mail metc@erasmusmc.nl
Ons kenmerk ASM/is/113588
Datum 14 januari 2011

Betreft: MEC-2011-015, Besluit onderzoek is niet WMO-plichtig
Multicenter, Stichting BOOG initieert

Protocol titel: Project plan MALE BREAST CANCER - Based on EORTC protocol
10085

Protocol versie: 2 d.d. 10 december 2010

Postadres
Postbus 2040
3000 CA Rotterdam

Bezoekadres
Dr. Molewaterplein 50
3015 GE Rotterdam

De commissie verzoekt u bij alle correspondentie m.b.t. dit onderzoek bovenstaand MEC nummer te vermelden.

Geachte heer Martens,

De Medisch Ethische Toetsings Commissie Erasmus MC heeft het door u ingediende bovenvermeld onderzoeksvoorstel, ontvangen op 20 december 2010 ter beoordeling van de WMO-plichtigheid.

Het dagelijks bestuur van de commissie heeft beoordeeld of dit onderzoek al dan niet binnen de reikwijdte van de WMO valt. In verband hiermee is het dagelijks bestuur tot de conclusie gekomen dat:

- er wel sprake is van een medisch-wetenschappelijke vraagstelling in dit protocol;
- de proefpersonen niet aan een handeling worden onderworpen en er wordt hen geen gedragswijze opgelegd. **Het betreft immers onderzoek met reeds verzamelde gegevens en reeds afgenoemde materiaal.**

Omdat aan één van beide voorwaarden voor WMO-plichtigheid niet is voldaan, heeft het dagelijks bestuur van de commissie d.d. 10 januari 2011 besloten dat bovenvermeld onderzoek niet WMO-plichtig is. U mag dit onderzoek uitvoeren in het Erasmus MC en u kunt de resultaten te zijner tijd voor publicatie aanbieden aan een wetenschappelijk tijdschrift.

De commissie attendeert u op de volgende punten

- De commissie heeft enkel de WMO-plichtigheid beoordeeld. Er heeft verder geen inhoudelijke toets van het onderzoek plaatsgevonden.

Voorzitters
Prof.dr. H.W. Tilanus
Prof.dr. H.J. Metselaar

Vice voorzitter
Prof.dr. T. van Gelder

Secretarissen
Mw. mr. C.P. Bron-van Vliet
Mw. drs. A.I.J.M. Schellevis-Mintiens
Mw.dr.ir. M.M.C. de Vries-Velraeds

Secretaries
Mw. G.J. Slag
Mw. S. Sneevliet

Adm. medewerkers
Mw. A.E. van Huksloot
Mw. E. Ruseler

Het secretariaat is geopend van maandag tot en met vrijdag van 08.30 tot 17.00 uur

- U en uw afdeling zijn verantwoordelijk voor de correcte uitvoering van het onderzoek volgens de geldende wet- en regelgeving. In het geval van dit onderzoek vestigen wij er uw aandacht op het volgende:
 - o Voor retrospectief onderzoek, waarbij gegevens van proefpersonen gecodeerd worden verzameld en verwerkt is toestemming van de proefpersonen nodig. U vindt een voorbeeld patiëntinformatie- en toestemmingsformulier voor niet WMO-plichtig onderzoek op de site van de METC ([www.erasmusmc.nl /commissies/metc/](http://www.erasmusmc.nl/commissies/metc/)).
(Bij retrospectief *anoniem* onderzoek is toestemming niet verplicht, hierbij zijn de gegevens nooit meer herleidbaar tot de proefpersonen.)
 - o Wanneer in een onderzoek gegevens worden verzameld van proefpersonen, dient hiermee correct te worden omgegaan zoals bepaald in de Gedragscode Gezondheidsonderzoek (Code Goed Gedrag), het Privacy Reglement Erasmus MC, en de Wet bescherming persoonsgegevens.
U vindt hierover meer informatie op de website van de METC ([www.erasmusmc.nl /commissies/metc/](http://www.erasmusmc.nl/commissies/metc/)) en op de website van FEDERA (www.federa.org).
 - o Wanneer in een onderzoek (lichaams)materiaal van proefpersonen wordt verzameld en verwerkt dient hiermee correct te worden omgegaan zoals bepaald in de Code Goed Gebruik. U vindt hierover meer informatie op de website van FEDERA (www.federa.org).
 - o Amendementen en/of addenda bij dit onderzoek dienen aan de commissie ter beoordeling te worden voorgelegd zodat kan worden beoordeeld of het onderzoek nog steeds buiten de reikwijdte van de WMO blijft, of dat er door het amendement/addendum sprake is van WMO-plichtig onderzoek.
- De commissie verzoekt u haar op de hoogte te brengen van de volgende gegevens betreffende dit onderzoek:
 - Startdatum (datum inclusie eerste proefpersoon)
 - einddatum (datum stop studie laatste proefpersoon)
 - publicaties en/of eindrapport

Wanneer u vragen heeft over het opzetten, financieren, of uitvoeren van wetenschappelijk onderzoek, kunt u terecht bij het Consultatiecentrum Patiëntgebonden Onderzoek (CPO) voor advies en hulp. Het CPO organiseert ook meerdere keren per jaar de BROK cursus (Basiscursus Regelgeving en Organisatie van Klinisch Onderzoek), die door de commissie van harte wordt aanbevolen. Het volgen van de BROK cursus is, conform landelijke afspraken, alleen verplicht bij WMO-plichtig onderzoek. Voor informatie over de inhoud van de BROK-cursus kunt u terecht bij dr. R.E. Juttmann, Directie O&O, intern tel.nr. 32192. Voor praktische informatie (zoals data waarop de cursus plaatsvindt en inschrijving) kunt u contact opnemen met het Congresbureau, intern tel.nr. 31621.

Op de site van de METC kunt u links terugvinden naar de hierboven vermelde wet- en regelgeving. Wanneer u vragen heeft over dit METC besluit kunt u contact opnemen met het secretariaat van de METC.

Met vriendelijke groet,
namens de Medisch Ethische Toetsings Commissie Erasmus MC,


Mw.drs. A.I.J.M. Schellevis-Mintiens
Secretaris

Cc. Mw. M. Mol, Unithoofd Interne Oncologie
Prof.dr. J. Verweij
Drs. A.P. Bandel, Manager Clusterbureau 2

PATIENTENINFORMATION

Zur Aufbewahrung und Analyse entnommener Gewebe- und Blutproben in der „Patienten-Tumorbahn der Hoffnung“ der Stiftung PATH

Sehr geehrte Patientin,

wir freuen uns, dass Sie Interesse an einer Teilnahme bei PATH haben, der weltweit ersten patienten-eigenen Tumorbahn. Die nachfolgenden Informationen sollen Ihnen helfen, eine Entscheidung zu treffen. Wenn Sie mit dem Nachfolgenden einverstanden sind, dann lesen und unterschreiben Sie bitte die beiliegende Einverständniserklärung. Für Fragen steht Ihnen Ihr behandelnder Arzt zur Verfügung. Wenn Sie weitere Fragen haben, können Sie sich gern schriftlich oder telefonisch an uns wenden.

A. Allgemeines

Bösartige Tumorerkrankungen werden heute in vielen Fällen erfolgreich durch Operation, Chemotherapie, Bestrahlung und andere Therapieformen behandelt. Aber immer noch ist nicht jede Krebserkrankung heilbar. Das macht es notwendig, neue Diagnoseverfahren und innovative Medikamente zu entwickeln sowie deren Wirksamkeit besser vorherzusagen. Um dieses Ziel zu erreichen, wird in der Krebsforschung die Rolle des menschlichen Erbgutes bei der Entstehung bösartiger Tumoren untersucht. Für diese Forschungsarbeiten werden Blut und Tumorgewebe benötigt, die bei tiefsten Temperaturen eingefroren werden.

Wenn Sie sich für eine Teilnahme entscheiden, werden Ihnen entnommenes Tumorgewebe und Blut in einer der Tiefkühltruhen der Stiftung PATH eingelagert, die sich in unseren Kooperationskliniken befinden. Mit Ihrer Teilnahme treffen Sie in einer schwierigen Situation die richtige Entscheidung. Mehrere unserer Vorstandsmitglieder sind selbst von Brustkrebs betroffen und kennen aus eigenem Erleben die Gefühle von Panik und Verzweiflung rund um Diagnose und Behandlung – und auch die Angst, dass die Krankheit zurückkommen könnte.

Mit der Blut- und Gewebeeinlagerung bei PATH lassen Sie sich mögliche Diagnose- und vielleicht auch Behandlungsoptionen für später offen. Darüber hinaus leisten Sie mit Ihrer Blut- und Gewebespende an die Forschungsbahn von PATH einen wichtigen Beitrag zur Brustkrebsforschung. Wir wissen, dass in der Forschung vieles auf dem Weg ist, aber der wirkliche Durchbruch bei der endgültigen Heilung von Krebs ist noch nicht erreicht. Die Forschung braucht deshalb so zukunftsorientierte Frauen, so mündige Patientinnen wie Sie.

Mit den Blut- und Gewebeeinlagerungen bauen wir eine Forschungsbahn auf, die erfordert, dass jede eingefrorene Probe auch mit den dazugehörigen Informationen über Untersuchungsergebnisse und Behandlungsschritte versehen ist. Erst wenn Forscher wissen, welche Beschaffenheit (genetische Eigenschaften, Art des Tumors) Ihr Tumorgewebe hat und welche Behandlungen (Operation, Chemotherapie, Bestrahlung, Anti-Hormon-Therapie) Sie bereits bekommen haben, kann Forschung gezielt angegangen werden.

Deshalb bitten wir Sie herzlichst um Ihr Einverständnis zur Aufbewahrung und Analyse des Ihnen entnommenen Tumorgewebes und Blutes sowie der dazugehörigen Daten in der „Patienten-Tumorbahn der Hoffnung“ der Stiftung PATH.

PATH

Die weltweit
einige Tumorbanks
von Patienten für Patienten

B. Aufbewahrung und Analyse der entnommenen Gewebe- und Blutproben

Im Rahmen einer Operation werden Ihnen Tumorgewebe und Blut entnommen und unter anderem für die feingewebliche Untersuchung Ihres Tumors verwendet. Diese Proben würden normalerweise im Anschluss an die Untersuchung vernichtet. Da Ihre Proben allerdings – wie bereits eingangs erwähnt – einen wichtigen Beitrag zur Brustkrebsforschung leisten können, möchten wir Sie fragen, ob nach Abschluss der diagnostisch notwendigen Untersuchungen der eventuell verbleibende Rest des Gewebes und Blutes – mit Ihrem Einverständnis – in der Tumorbank der Stiftung PATH eingelagert werden kann. Dafür wird Ihnen kein zusätzliches Gewebe entnommen. Die Probensammlung ist auf das im Rahmen des operativen Eingriffs ohnehin entnommene Tumorgewebe beschränkt. Das Blut wird ebenfalls im Rahmen der Routine-Blutentnahme bei der Operation entnommen.

In manchen Fällen muss allerdings das gesamte Gewebe- und Blutmaterial für die diagnostisch notwendigen Untersuchungen verwendet werden. In diesem Falle kann keine Gewebe- und Blutprobe eingelagert werden.

Falls jedoch nach den diagnostisch notwendigen Untersuchungen der Ihnen entnommenen Gewebe- und Blutproben ein Rest verbleibt, dann wird dieser – nach Ihrem Einverständnis – aufgeteilt und für folgende Zwecke verwendet:

1. Patientenprobe

Ein Teil Ihres Gewebes und Blutes wird für Sie persönlich aufbewahrt, für den Fall, dass es in Zukunft neue wissenschaftliche Erkenntnisse in der Untersuchung und Behandlung von Krebserkrankungen gibt (Patientenprobe). Diese Probe bleibt in Ihrem Eigentum.

Sie können jederzeit und ohne Angabe von Gründen auf Ihre Probe zugreifen, wenn Sie beispielsweise im Fall eines Wiederauftretens Ihrer Tumorerkrankung Ihr Gewebe für neue diagnostische Verfahren nutzen möchten. Zu den personenbezogenen Daten Ihrer Probe haben Dritte keinen Zugang, es sei denn, aufgrund gesetzlicher Befugnisse.

Weitergehende, auf Ihre Initiative veranlasste Untersuchungen nebst Transportkosten sind allerdings von Ihnen selbst zu tragen.

2. Forschungsprobe

Den anderen Teil Ihres Tumorgewebes und Blutes spenden Sie an die „Patienten-Tumorbank der Hoffnung“ der Stiftung PATH für die Sammlung von Tumorgewebe und Blut und leisten damit einen wichtigen Beitrag zur Krebsforschung (Forschungsprobe). Sie übertragen uns an der Forschungsprobe Ihre Eigentumsrechte und können nach Einlagerung in der Tumorbank der Stiftung PATH über diese Teile Ihrer Probe nicht mehr verfügen. Sie können aber jederzeit und ohne Angabe von Gründen einer weiteren Verwendung der Forschungsprobe widersprechen. Nach einem Widerspruch werden wir die Forschungsprobe vernichten.

Über die Vergabe der gespendeten Gewebeproben für anwendungsbezogene Vorhaben in der Krebsforschung entscheiden der Vorstand beraten durch das Kuratorium und den wissenschaftlichen Beirat der Stiftung PATH.

C. Unentgeltlichkeit

Ihre Teilnahme an PATH ist für Sie kostenlos. Dies gilt insbesondere für die Verarbeitung und Verwahrung Ihrer Patientenprobe. Sie erhalten für die Überlassung Ihres Tumorgewebes und Blutes an die Stiftung PATH kein Entgelt und haben auch keinerlei Ansprüche auf Vergütung, Tantieme oder sonstige Beteiligung an finanziellen Vorteilen oder Gewinnen, die möglicherweise auf der Basis der Forschung mit Ihrem Tumorgewebe bzw. Blut erlangt werden.

D. Haftungsbeschränkung

Ihr eingelagertes Tumorgewebe und Blut kann aus vielfältigen Gründen unbrauchbar werden, beispielsweise weil das Kühlssystem ausgefallen ist. Da die Stiftung PATH eine gemeinnützige Stiftung ist, kann sie keine ausufernde und kostspielige Haftung für alle denkbaren Zwischenfälle übernehmen. Daher sind wir darauf angewiesen, unsere Haftung zu beschränken.

Die Stiftung PATH haftet daher Ihnen gegenüber nur in folgenden Fällen für Schäden:

1. ohne Begrenzung des Umfangs der verursachten Schäden für Vorsatz oder grobe Fahrlässigkeit ihrer gesetzlichen Vertreter oder leitenden Angestellten;
2. unter Begrenzung auf die vertragstypisch vorhersehbaren Schäden
 - a) für die schuldhafte Verletzung wesentlicher Vertragspflichten,
 - b) für grobe Fahrlässigkeit oder Vorsatz ihrer Erfüllungsgehilfen und
 - c) für die schuldhafte Verursachung von Personenschäden.

E. Entbindung von der ärztlichen Schweigepflicht und Weitergabe der Daten

Wie bereits oben ausgeführt, erfordert die Forschungsbank, die die Stiftung PATH mit den Forschungsproben aufbaut, dass jede eingefrorene Probe auch mit den dazugehörigen Untersuchungsergebnissen und Behandlungsschritten versehen wird. Denn erst wenn die Forscher wissen, welches Tumorprofil das Gewebe hat und welche Behandlungen (z. B. Operation, Chemotherapie, Bestrahlung, Anti-Hormon-Behandlung) Sie bekommen haben, kann Forschung gezielt angegangen werden.

Aus diesem Grund sind wir darauf angewiesen, dass Sie die Ärzte und das Klinikpersonal Ihrer behandelnden Klinik von der ärztlichen Schweigepflicht gegenüber der Stiftung PATH entbinden und gestatten, dass alle Behandlungsdaten und Befunde seitens der Klinik an die Stiftung PATH übermittelt und durch die Stiftung PATH angefordert werden dürfen (per Telefax oder Brief), sofern dies zur Erreichung der vorstehend unter B aufgeführten Zwecke erforderlich ist. Eine entsprechende Erklärung ist in der beiliegenden Einverständniserklärung enthalten.

Ihre Behandlungsdaten und Befunde unterliegen bei der Stiftung PATH zwar keiner gesetzlichen Schweigepflicht. Wir können Ihnen jedoch versichern, dass die Daten (hierzu gehören insbesondere auch Krankheitsdaten aus Ihren Krankenunterlagen) an Dritte nur zum Zwecke der Krebsforschung und nur in verschlüsselter Form („pseudonymisiert“) weitergegeben werden. Dritte erhalten so weder Ihren Namen noch Ihre Adresse, es sei denn, aufgrund gesetzlicher Befugnisse. Zudem verpflichten wir unsere Mitarbeiterinnen und Mitarbeiter ausdrücklich zur Verschwiegenheit.

F. Information über Ergebnisse der Forschungsarbeiten

Es ist uns leider nicht möglich, Ihnen individuelle Rückinformationen über die Ergebnisse von Forschungsarbeiten zu geben, für die die Stiftung PATH Gewebematerial zur Verfügung stellt. Denn aufgrund der Vielzahl an Patientinnen und Forschungsvorhaben würde eine individuelle Mitteilung einen erheblichen finanziellen und organisatorischen Mehraufwand bedeuten, den wir nicht bewältigen können.

PATH

Die weltweit
einige Tumorbank
von Patienten für Patienten

G. Widerruf der Zustimmung bzw. Widerspruch

Ihre Gewebespende ist freiwillig. Sie können über Ihre Patientenprobe jederzeit ohne Angabe von Gründen verfügen. Darüber hinaus können Sie auch jederzeit und ohne Angabe von Gründen einer weiteren Aufbewahrung und Nutzung der Forschungsprobe widersprechen. Nach einem entsprechenden Widerspruch werden wir die Forschungsprobe vernichten. Auch Ihre Zustimmung zur Verwendung Ihrer Daten sowie die Entbindung von der ärztlichen Schweigepflicht können Sie jederzeit und ohne Angabe von Gründen mit Wirkung für die Zukunft widerrufen. Der Widerruf bzw. Widerspruch hat keinen Einfluss auf Ihre etwaige weitere ärztliche Behandlung. Allerdings behält sich die Stiftung PATH vor, die Vereinbarung über die Aufbewahrung Ihrer Patientenprobe zu kündigen, falls Sie Ihre Zustimmung zur Datenverwendung oder zur Entbindung von der ärztlichen Schweigepflicht widerrufen bzw. einer weiteren Verwendung der Forschungsprobe widersprechen.

H. Kontaktierung durch die Stiftung PATH

Wir möchten mit Ihnen und den anderen Teilnehmerinnen bei PATH für Rückfragen zum Krankheitsverlauf kommunizieren. Unser regelmäßiger Newsletter informiert Sie über die neuesten Ergebnisse und Erkenntnisse aus der Krebsforschung. Bitte teilen Sie uns dazu sowohl Ihre Adresse als auch Ihre Telefonnummer und/oder E-Mail-Adresse mit. Wenn Sie daran kein Interesse haben, können Sie auf der Einverständniserklärung ein entsprechendes Kästchen ankreuzen.

Vielen Dank, dass Sie sich die Zeit genommen haben, die vorliegende Patienteninformation zu lesen. Wenn Sie mit den genannten Bedingungen einverstanden sind und die Stiftung PATH mit Ihrer Tumor- und Blutprobe unterstützen wollen, dann lesen und unterschreiben Sie bitte die beiliegende Einverständniserklärung. Sie leisten damit einen wichtigen Beitrag zur Brustkrebsforschung.

Mit herzlichen Grüßen



Ulla Ohlms



Doris C. Schmitt



Carmen Waldner

Der Vorstand der Stiftung PATH:

Doris C. Schmitt, Kommunikationstrainerin, Brustkrebspatientin,
Ulla Ohlms, Erziehungswissenschaftlerin, Brustkrebspatientin,
Carmen Waldner, Diplom Informatikerin, Brustkrebspatientin
(von links nach rechts)

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Patienteninformation

(Stand September 2014, Version 1)

Sehr geehrte Patientin, sehr geehrter Patient,
vielen Dank, dass Sie in Betracht ziehen, unser Forschungsprojekt „**Identifikation von Biomarkern in biologischen Flüssigkeiten und Geweben von Krebspatienten und Patienten mit entzündlichen Erkrankungen**“ zu unterstützen und an einer freiwilligen Blutentnahme sowie einer freiwilligen Abgabe von Urin – und Speichelprobe teilzunehmen. Eine Spende von Liquor wird bei Ihnen nur dann vorgenommen, wenn aus anderen Gründen eine medizinische Notwendigkeit für eine Lumbalpunktion besteht.

Ihre Blut- und Liquorspende sowie die Spende von Urin und Speichel sind von entscheidender Bedeutung für die medizinische Grundlagenforschung.

Erkenntnisse aus den genannten Experimenten sollen dazu beitragen, ein besseres Verständnis über die Veränderungen der Zusammensetzung biologischer Flüssigkeiten (Blut, Liquor, Urin, Speichel) bei Krebserkrankungen und entzündlichen Erkrankungen zu erhalten und spezifische Biomarker für Krebserkrankungen und entzündliche Erkrankungen zu entwickeln. In der Zukunft könnte ein besseres Verständnis dieser Mechanismen dabei helfen entzündliche Erkrankungen oder Krebserkrankungen zu diagnostizieren und zu behandeln.

Welche Proben sollen untersucht werden?

Im Rahmen dieser Studie wird Ihnen Blut, mit einem Volumen von insgesamt maximal 200 ml abgenommen werden, wobei der Zeitaufwand für die Blutspende ca.

30 min entspricht. Aus Ihrer Spende werden Serum und ggf. Tumor- oder Immunzellen isoliert und mittels umfassender Analysen in Bezug auf ihre genetische Information, die darin enthaltenen Eiweiße und Moleküle untersucht.

Weiterhin wird, sofern bei Ihnen eine medizinische Indikation zu einer Lumbalpunktion besteht, Liquor mit einem Volumen von insgesamt maximal 3 ml (nur in dem Fall, dass Liquor verworfen würde, wird mehr untersucht) gewonnen und in Bezug auf seine genetische Information, die darin enthaltenen Eiweiße und Moleküle untersucht.

Weiterhin werden Urin- und Speichelproben gewonnen, die ebenfalls in Bezug auf ihre genetische Information, die darin enthaltenen Eiweiße und Moleküle hin untersucht werden.

Solch eine Analyse von biologischen Flüssigkeiten (Serum, Liquor, Urin, Speichel) ermöglicht das akkurate Erfassen möglichst vieler Bestandteile und somit ein umfassendes Verständnis von Unterschieden zwischen Patienten mit Krebskrankungen oder entzündlichen Erkrankungen und gesunden Kontrollen. Insbesondere soll durch Vergleich der biologischen Flüssigkeiten der Patienten ermittelt werden, ob die Veränderungen für bestimmte Eigenschaften (wie z.B. klinische Parameter, molekulare Veränderungen, Tumorgrad, Metastasierung, akute versus chronische Entzündung etc.) kennzeichnend sind und durch welche Einflussfaktoren (z.B. Therapien) sie verändert werden.

Um zu ermitteln, ob die beobachteten Veränderungen in den biologischen Flüssigkeiten in der Tat repräsentativ für das Tumorgewebe oder das entzündliche Gewebe sind, soll wenn in der NCT oder GEZEH Gewebebank Heidelberg vorhanden, Ihr Tumorgewebe oder Ihr entzündliches Gewebe vergleichend untersucht werden. Zudem sollen Primärtumoren und Metastasen sowie in die Blutbahn gestreute Tumorzellen mittels kombinierter Analyse auf verschiedenen Ebenen in Bezug auf ihre genetische Information, die darin enthaltenen Eiweiße und Moleküle verglichen werden.

Habe ich Nachteile, wenn ich an der Studie teilnehme?

Als Folge möglicher Komplikationen bei der Blutentnahme könnten ein Bluterguss (Hämatom) oder Schmerzen an der Einstichstelle auftreten. In sehr seltenen Fällen könnte es zu einer Verletzung von Nerven durch die Entnahmekanüle (Nervenläsion) kommen.

Eine Lumbalpunktion erfolgt lediglich sofern bei Ihnen andere medizinische Notwendigkeiten hierfür vorliegen. Dabei kann es zu folgenden Nebenwirkungen kommen:

-Häufig: Unterdrucksyndrom: 1-2 Tage nach der Lumbalpunktur können bei einigen Patienten Kopfschmerzen auftreten, die mitunter auch heftig und von Schwindel und Übelkeit begleitet sein können. Die Symptome bessern sich beim Hinlegen und halten einige Tage an, selten auch bis zu 2 Wochen. Man sollte in dieser Zeit viel Flüssigkeit zu sich nehmen. In schwereren Fällen kann das Unterdrucksyndrom auch medikamentös behandelt werden.

-Selten: Doppelzehen, Ohrgeräusche, Hörstörungen (Hörsturz)

-Sehr selten: Schädigung einer Nervenwurzel beim Einstechen, Auslösung einer Entzündung (Hirnhautentzündung) im Nervenwasserraum, Flüssigkeitserguß im Schädel unter der Hirnhaut (subdurales Hygrom), Blutungen.

Durch die Gewinnung von Urin und Speichel sind uns keine erkennbaren Nachteile oder Nebenwirkungen bekannt.

Es wird ausdrücklich darauf hingewiesen, dass Ihre Teilnahme an der Studie / Untersuchung freiwillig ist. Sie können jederzeit, auch ohne Angabe von Gründen, Ihre Teilnahme widerrufen, ohne dass Ihnen irgendwelche Nachteile daraus entstehen. Bei Rücktritt wird bereits gewonnenes Material vernichtet, es sei denn, Sie stimmen zu, dass Sie trotz Ihres Rücktritts mit der Auswertung des Materials einverstanden ist.

Was habe ich für Vorteile, wenn ich an der Studie teilnehme?

Sie können mit der Spende und Ihrem Einverständnis zur Untersuchung ihrer Blut-, Liquor-, Urin- und Speichelprobe und Gewebeproben, die in der NCT Gewebebank

oder GEZEH Gewebebank vorliegen, zur Erforschung von entzündlichen Erkrankungen und Krebserkrankungen, sowie zur Entwicklung neuer Diagnose- und Behandlungsmethoden beitragen. Damit leisten Sie einen wichtigen Beitrag zur Forschung und damit auch zur weiteren Verbesserung der medizinischen Versorgung. Die Teilnahme an der Studie beinhaltet für Sie keinen direkten persönlichen Nutzen. Es ist nicht beabsichtigt, Sie persönlich über Forschungsergebnisse zu informieren.

Was geschieht mit meinen Blut-, Liquor-, Urin- und Speichelproben?

Die Proben werden bis zur wissenschaftlichen Untersuchung in den **Einrichtungen des DKFZ** oder der **Universität Heidelberg** gelagert. In Zukunft gibt es möglicherweise neue wissenschaftliche Fragestellungen im Rahmen der genannten Zielsetzungen, die mithilfe Ihrer Probe beantwortet werden können. Deshalb kann heute noch nicht festgelegt werden, wie lange Ihre Probe aufbewahrt wird. Zur Analyse erfolgt die Weitergabe von Proben an Dritte, die jedoch aufgrund der Tatsache, dass die Proben mit einem Zahrcode verschlüsselt sind, keine Rückschlüsse auf Ihre Person ziehen können. Ihre Proben werden unter Umständen auch an andere Stellen (z.B. Labore), gegebenenfalls auch ins Ausland, verschickt. Gleichwohl haben Sie jederzeit das Recht, die Vernichtung Ihrer Proben zu verlangen. Bereits erhobene Daten verbleiben auch nach Vernichtung der Proben in der Studie. Es besteht kein Personenbezug mehr.

Was passiert mit meinen Daten?

Die elektronische Speicherung und Verarbeitung von Daten erfüllt alle Anforderungen des Datenschutzes. Es wird sichergestellt, dass eine Rückverfolgung der Daten auf Ihre Person oder eine Verknüpfung mit ihrer Krankengeschichte durch Dritte nicht möglich ist. Das gesammelte Proben- und Datenmaterial wird in pseudonymisierter Form, d.h. ohne Namen oder Sie kennzeichnende Daten, aufbewahrt. Dazu werden die Blut-, Liquor, Urin-und Speichelproben und Gewebeproben und persönliche Daten mittels eines Nummerncodes verschlüsselt. Auf diese

verschlüsselten Daten haben nur autorisierte Mitarbeiter des Forschungsprojekts Zugriff. Ein Rückschluss auf Ihre Person für nicht ausdrücklich vorgesehene Zwecke soll damit ausgeschlossen werden.

Eine Weitergabe von Daten an unberechtigte Dritte (z.B. Arbeitgeber, Versicherungen) ist ausgeschlossen.

Der Vergleich der wissenschaftlichen Ergebnisse mit den pseudonymisierten Daten erhöht entscheidend die wissenschaftliche Aussagekraft der Untersuchung. Indem Sie die beiliegende Einverständniserklärung unterschreiben, geben Sie ihre Zustimmung zur oben beschriebenen Handhabung Ihrer Blut-, Liquor-, Urin- und Speichelproben, ihrer Gewebeproben sowie ihrer Daten. Wir planen die pseudonymisierten Ergebnisse unserer Analysen verbunden mit Angaben zu Geschlecht, Alter und Krankheitsstatus, jedoch ohne Möglichkeit eines Rückschlusses auf Ihre Person, in öffentliche wissenschaftliche Datenbanken einzuspeisen. Dadurch stehen die Daten der Gemeinschaft der Wissenschaftler für weitere Analysen zur Verfügung. Eine solche Archivierung von Daten bietet vielfältige Möglichkeiten, auch für andere Forscher, diese zu nutzen. Dies erlaubt es, neue Fragestellungen mit bereits erhobenen Daten zu bearbeiten.

Was mache ich, wenn ich noch weitere Fragen habe?

Für weitere Fragen bezüglich der Studie wenden Sie sich bitte an **Frau Dr. med. Christiane Opitz (06221-42 3839)**.

Dokumentation der gestellten Fragen:

Einwilligungserklärung

(Stand September 2014, Version 1)

Ich erkläre mich bereit, die Studie zu unterstützen.

Ich bin von Herrn/Frau (Dr. med.) ausführlich und verständlich über die Studie

Identifikation von Biomarkern in biologischen Flüssigkeiten und Geweben von Krebspatienten und Patienten mit entzündlichen Erkrankungen.

sowie deren Tragweite aufgeklärt worden. Ich habe darüber hinaus den Text der Patienteninformation erhalten, und sowohl diesen als auch die Einverständniserklärung gelesen und verstanden. Aufgetretene Fragen wurden mir vom aufklärenden Arzt verständlich und ausreichend beantwortet.

Ich wurde darüber informiert, dass ich jederzeit ohne Nachteile meine Einwilligung widerrufen kann.

Bei Rücktritt bin ich mit der Auswertung des schon gewonnenen Materials in pseudonymisierter Form einverstanden.

(Zutreffendes bitte ankreuzen):

Ja Nein

Ich bin zugleich damit einverstanden, dass meine im Rahmen der Studie ermittelten Daten aufgezeichnet werden. Meine Daten und die Auswertung meiner Blut, Urin, Speichel, Liquor und Gewebeproben können zu einem besseren Verständnis der Entstehung und Entwicklung von Krebs und anderen Erkrankungen, der Ansprechbarkeit auf die Behandlung, und der Vorhersagbarkeit des Behandlungserfolges beitragen; und möglicherweise zur Entwicklung von neuen Therapien und Diagnostika führen. Ein kommerzieller Nutzen der Ergebnisse kann daher nicht ausgeschlossen werden. Ich bin darüber informiert, dass die Teilnahme an der Studie für mich keinen persönlichen Vorteil oder kommerziellen Nutzen beinhaltet. Alle Rechte, die mit der Entwicklung neuer Therapien und Diagnostika, neuen Erkenntnissen oder der Entstehung schützenswerten Eigentums verbunden sind, übertrage ich dem DKFZ und den beteiligten Forschungspartnern.

Ich wurde darüber aufgeklärt und stimme zu, dass meine in der Studie erhobenen Daten in pseudonymisierter Form aufgezeichnet werden können. Dritte erhalten jedoch keinen Einblick in personenbezogene Unterlagen. Bei der Veröffentlichung von Ergebnissen der Studie wird mein Name ebenfalls nicht genannt.

Ort, Datum (Unterschrift Patient/in) Name Patient/in DRUCKBUCHSTABEN

Ort, Datum (Unterschrift Arzt/in) Name Arzt/in DRUCKBUCHSTABEN

INFORMATION SHEET FOR THE STUDY OF TUMOURIGENICITY AND ANALYSIS OF DRUG SENSITIVITY IN BIOPSIES FROM PATIENTS WITH CANCER IN ACTIVE TREATMENT IMPLANTED IN IMMUNOSUPPRESSED MICE

Research project entitled: "Tumourigenicity and analysis of drug sensitivity in biopsies from patients with cancer in active treatment implanted in immunosuppressed mice".

Main researcher: Violeta Serra Elizalde

Collaborating researchers: Dr Cristina Saura Manich, Dr Mafalda Oliveira, Dr Cristina Cruz and Dr Jordi Rodón Ahnert

Service: VHO and Medical Oncology

Objectives:

Your participation is requested in this project, the purpose of which is research into molecular alterations in cancer, its possible implications for prognostics and its impact on the response/resistance to different oncological treatments.

Benefits:

It is possible that your participation in this study will not obtain any direct benefit. However, the identification of possible prognostic and/or predictive factors of the cancer may benefit patients in the future who suffer from it and contribute to greater understanding and treatment of this disease.

DNA is the element that is present in all of your cells. It is passed down from your parents and contains a code in the form of "genes" that determines your physical features such as eye and skin colour, etc. The differences between some people and others can help us to explain why some develop diseases and others do not.

Study procedures:

Biopsies of primary tumours and breast cancer metastasis will only be taken from patients where it is clinically indicated. If you have benefitted from the treatment and if a loss in its efficacy is subsequently experienced, a second biopsy will be proposed. The initial biopsies enable us to identify factors that predict the efficacy of the treatment, while the biopsies of a patient who has benefitted from a specific treatment and who later stopped responding enables to identify acquired-resistance mechanisms. Neoplastic biological liquid (e.g. pleural, peritoneal, pericardial, etc.) would be only drained when clinically indicated, the main objective of which is to alleviate symptomatology secondary to the progression of the disease.

The obtained samples will be implanted into immunosuppressed mice with the aim of obtaining sufficient tumour to carry out subsequent studies.

Your authorisation is also requested to analyse the tumour obtained as well as tumour samples previously or subsequently acquired, which will be conserved in the Vall d'Hebron University Hospital Pathological Anatomy Service. If these samples are in the Pathological Anatomy Service of another care centre, your authorisation is requested to collect them in order to be able to use them.

Tumour DNA will be extracted from the tumour samples in order to study the presence of genetic alterations by means of sequencing techniques that can analyse a large number of genes. Other molecular characteristics of the tumours will also be analysed, including RNA and proteins. These determinations will be made in the Vall d'Hebron Oncology Institute as well as laboratories that are specialised in sequencing.

These novel genetic studies require internal control of the patient, for which a blood sample is required. The same sequencing technique will be carried out on your genome in-depth. This entails the acquisition of information that may have implications that are relevant to your health and the health of your family (see chapter Implications of the information obtained in the study). From your blood sample, plasma will also be isolated, from which the presence of tumour mutations in the circulating DNA will be analysed.

Discomfort and possible risks:

Taking the biopsy may cause discomfort in the puncture area. The possibility cannot be discounted that complications such as bruising or bleeding may arise secondary to the puncture and the extraction of blood, which will depend on the area or organ from which the biopsy is taken.

Place of carrying out the analysis and use of the samples:

The tumour samples will be implanted into mouse models in the Experimental Therapies Group and will be classified by the Molecular Pathology Laboratory (VHIO). The genetic studies will be carried out in the Cancer Genomics Group (VHIO) or in collaborating centres specialised in ultra-sequencing. For these analyses we will use the tumour biopsies obtained by means of this protocol and if appropriate those from previous/future occasions, as well as your blood sample.

Personal data protection:

Pursuant to Law 15/1999 about Personal Data Protection, the personal data obtained will be necessary to fulfil the purposes of the study. None of the reports of the study will contain your name, and your identity will not be revealed to any person except to fulfil the purposes of the study, or in the case of urgent medical or legal requirement. Any personal data that may be identifiable will be conserved using electronic methods under secure conditions by the Vall Hebron University Hospital, or by an institution designated by it. Access to this information will be restricted to personnel appointed for this purpose or authorised medical personnel who are obliged to maintain the confidentiality of the information. The party legally responsible for the data file for the study is the primary researcher in the study (Violeta Serra Elizalde).

Pursuant to current law, you have the right to access your personal data and, if it is justified, you have the right to modify and cancel it. If you wish, you may request to do so through the doctor caring for you in this study.

Implications of the information obtained in the study:

If you decide to participate in the study, it is possible that information that is relevant to your health or that of your family may be obtained from the analysis of your biological samples. Pursuant to current legislation, you have the right to be informed about the genetic data obtained in the course of study.

If you would like to know the genetic data obtained that is relevant to your health, please ask your doctor about the implications that this information may have for you and for your family.

This information will be communicated to you if you wish, or if you prefer not to be informed, your decision will be respected.

Future use of the samples

You are also requested to consent to authorise the research to store your samples for making other genetic studies related to cancer. If you provide authorisation for the biological material to be used in this research, your data will be kept coded with the aim of guaranteeing confidentiality in its use, pursuant to current law.

The samples will be conserved as a private collection with registration No. C0003435 in the name of Dr Josep Tabernero Caturla. These samples, as previously informed, will be used for the purpose of carrying out this study, as well as to be able to participate in future studies of this research group or those of other groups dedicated to oncological research, always after the approval of the corresponding ethical committees. The samples will be conserved for the period of time equal to the duration of the study and will be stored for a period of ten years after its completion.

Once the research is completed, it is possible that there may be surplus samples. In relation to these, the person responsible for collecting them may offer different options:

- a) Their destruction once the research is completed.
- b) Their conservation in an anonymous manner for use in future projects related to this line of research. The anonymous nature means that the link will be broken between the coding of the samples and the identifying data that the doctor of the study maintains.
- c) Free transfer of the sample to a bio-bank.
- d) The subsequent use of the sample for a line of research related to the one initially proposed, including by a third party by means of free transfer, in which case your consent will be requested again.

Right to revoke your consent:

Your participation in the study is totally voluntary and therefore you must provide written consent. If you decide not to participate in the study, your medical care will be equally guaranteed and you can cancel your participation whenever you wish.

If you change your mind after providing consent for the use of your tissue sample, you can withdraw it.

If you have doubts or questions related to your participation please contact Dr Violeta Serra (93-2746000; extension 6766).

**INFORMED CONSENT FOR THE USE OF TISSUE SAMPLES FOR THE STUDY OF
TUMOURIGENICITY AND ANALYSIS OF DRUG SENSITIVITY IN BIOPSES FROM PATIENTS
WITH CANCER IN ACTIVE TREATMENT IMPLANTED IN IMMUNOSUPPRESSED MICE**

I, _____, have read the information sheet I have been given and have understood the objectives of the oncogenic alterations study as well as the potential risks and benefits of my participation in it.

I have been able to ask questions about the study.

I have spoken to: _____ (name of the researcher).

I understand that my participation is voluntary.

I agree to participate according to the conditions and procedures established and understand that I may cancel my participation whenever I wish, without having to provide explanations and without there being any repercussions on my medical care.

I DO I DO NOT voluntarily provide my consent for my tumour sample to be implanted into an immunosuppressed mouse.

I DO I DO NOT voluntarily provide my consent for study about possible genetic factors related to cancer to be carried out on my tissue sample.

I DO I DO NOT voluntarily provide my consent for my blood to be collected and my DNA from normal tissue and my DNA circulating in blood to be sequenced with the aim of purging normal variations of my genome in the tumour and identifying tumour-associated mutations in blood.

I DO I DO NOT voluntarily provide my consent for my samples to be stored for use in other studies about genetic factors related to cancer. My tissue and my DNA will be identified with a coded number and my identity will be kept secret.

I DO I DO NOT give permission for researchers to request my samples from the Pathological Anatomy Service of other care centres, in the case that they are not in the Vall d'Hebron University Hospital Pathological Anatomy Service.

I understand that it is not very likely that my participation in the studies carried out will have direct implications for my health. However, if the information obtained had direct importance for the development of diseases in me or in my family,

I DO I DO NOT give permission for this information to be communicated to me.

Patients, family member or legal representative (indicate)

Date

Researcher

Date



MESI-STRAT Consortium Coordinator
 Prof. dr. K. Thedieck
 Lab for Metabolic Signaling
 Department of Pediatrics
 University Medical Center Groningen
 Internal Zip Code EA12
 Antonius Deusinglaan 1
 9713 AV GRONINGEN

Arnhem, 20 March 2017

Subject: Letter of intent

International Advisory Board for the project "Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)"

Dear prof. dr. Thedieck,

It is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

I am willing to advise the MESI-STRAT consortium, if the project proposal is accepted for funding by the EC.

As a pharmaceutical company focused among others on the discovery and development of new therapeutic interventions to treat breast cancer, we endorse your efforts to develop tools that may help us predict which patients respond to endocrine therapy or become resistant.

Therefore, we would like to show our support through this letter, and I will join the International Advisory Board (IAB) to represent Novartis Oncology.

The IAB is composed of external experts recognized in the fields of basic and clinical breast cancer research, signaling & metabolism in breast cancer, systems medicine, companies active in the pharma sector and systems medicine, and patient representatives.

The role of the IAB will be to advise the MESI-STRAT Strategic Board (SB) on the project strategy and research directions, interaction/collaboration with other breast cancer-related consortia and research initiatives, as well as dissemination and communication to stakeholders in the academia, the commercial sector, patients and their families, and society.



I will keep all information confidential that pertains to the structure as well as the technical content of the MESI-STRAT proposal set-up, and I will only disclose said information to third parties upon the coordinator's approval.

I wish MESI-STRAT success and I look forward to acting on the IAB.

With best regards,
Novartis Oncology

A handwritten signature in blue ink, appearing to read 'Eric Hoedemaker', is written over a blue curved line.

Eric Hoedemaker
Medical Director Oncology

medische oncologie

Annex 3.4.1: International Advisory Board & Annex 3.4.3 Collaborating clinical trials and biobanks

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MESI-STRAT Consortium Coordinator

Prof. Dr. Kathrin Thedieck

Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands



Amsterdam, 24 March 2017

**Letter of Support for the
H2020 Research and Innovation Actions proposal
“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient
Stratification (MESI-STRAT)”**

Dear Prof. Thedieck,

It is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

As a medical oncologist involved as a principal investigator in the Everolimus Biomarker Study carried out under the auspices of the BOOG research center, Amsterdam, I endorse your efforts to develop tools that may help predict which patients respond to endocrine therapy or become resistant.

I would like to show my support through this letter, willing to share blood samples from the patients included in the Everolimus Biomarker Study for objectives specified in the MESI-STRAT project. I will also join the MESI-STRAT International Advisory Board (IAB), to share my expertise on liquid biomarker discovery and related trials for BC, and advise on the project strategy and research directions, interaction/collaboration with other breast cancer-related consortia and research initiatives, as well as dissemination and communication to stakeholders in the academia, the commercial sector, patients and their families, and society.

In conclusion, I support the MESI-STRAT initiative and look forward to a productive interaction.

Yours sincerely,

A handwritten signature in blue ink, appearing to read "Epie Boven".

Name: prof. Epie Boven, MD, PhD
Position: Medical Oncologist
Affiliation: VU University medical center
Address: De Boelelaan 1117, Amsterdam, NL
Email: e.boven@vumc.nl





Beth Israel Deaconess Medical Center



Gerburg Wulf MD, PhD.
Associate Professor of Medicine
Harvard Medical School
Department of Medicine
Beth Israel Deaconess Medical Center

CLS 441, 330 Brookline Ave
Boston, Massachusetts 02215
617.667.1910 tel,
gwulf@bidmc.harvard.edu

The MESI-STRAT Consortium Coordinator

Prof. Dr. Kathrin Thedieck

Laboratory for Metabolic Signaling
Department of Pediatrics
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Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Name: Gerburg M Wulf MD PhD
Position: Associate Professor, Attending Physician
Affiliation: Harvard Medical School, Dana Farber Harvard Cancer Center, Beth Israel Deaconess Medical Center
Address 330 Brookline Ave, Boston MA 02215
Telephone +1 617 667 1910
Email gwulf@bidmc.harvard.edu

Boston, April 4, 2017

Letter of Intent

International Advisory Board

For the project “Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)”

Dear Prof. Thedieck,

It is my pleasure to herewith express my interest in MESI-STRAT.

I will be honored to advise the MESI-STRAT consortium, if the project proposal is accepted for funding by the EC.

I will join the International Advisory Board (IAB) as a physician scientist running clinical breast cancer trials and as an expert in breast cancer metabolism. I am active laboratory investigator and clinical trialist, including ECOG and NCI-sponsored studies. In addition, I conduct correlative and translational studies and serve as a project leader for the CTEP (Cancer Therapy Evaluation Program) of the NCI (National Cancer Institute). My cancer metabolism focus has been so far on energy and nucleotide metabolism, but we recently expanded our focus to tryptophan and NAD metabolism which both play important roles in breast cancer as well. Therefore, I expect strong synergies of our research with MESI-STRAT and I will be happy to advise MESI-STRAT on research directions and clinical validation of the findings.

The IAB is composed of external experts recognized in the fields basic and clinical breast cancer research, signaling & metabolism in breast cancer, systems medicine, companies active in the pharma sector and systems medicine, and patient representatives.

The role of the IAB will be to advise the MESI-STRAT Strategic Board (SB) on the project strategy and research directions, interaction/collaboration with other breast cancer-related consortia and research initiatives, as well as dissemination and communication to stakeholders in the academia, the commercial sector, patients and their families, and society.

I will keep all information confidential that pertains to the structure as well as the technical content of the MESI-STRAT proposal set-up, and I will only disclose said information to third parties upon the coordinator's approval.

I wish MESI-STRAT success and I look forward to serving on the IAB.

With best regards,



Gerburg Wulf, MD, PhD



**Oslo
University Hospital
Radiumhospitalet**

Prof. Emerita Anne-Lise Børresen-Dale
Institute for Cancer Research
Department of Cancer Genetics
Montebello, 0310 Oslo
Visiting address:
Ullernchausséen 70
Phone: +47 22781373/92854455
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MESI-STRAT Consortium Coordinator

Prof. Dr. Kathrin Thedieck

Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Oslo 12/3-2017

Letter of intent

International Advisory Board

for the project “Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)”

Dear Prof. Dr. Thedieck,

It is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy (ET) in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

I am willing to advise the MESI-STRAT consortium, if the project proposal is accepted for funding by the EC.

As a breast cancer expert and member of the European Working group of Breast Cancer Research and the EU funded BASIS project (breast cancer somatic genetic study), that is part of the ICGC (International Cancer Genome Consortium), and having built up the Oslo2 study (> 2500 samples incl. molecular data) with strong collaboration to other large biobanks like METABRIC, I consider MESI-STRAT as highly complementary with ongoing efforts in breast cancer research. Hence, I fully endorse your plan to identify metabolic marker panels, measurable in body fluids, that help us

predict which patients respond to ET or become resistant, and to guide targeted therapies for ET resistant patient subgroups.

Therefore, I would like to show my support through this letter, and I will join the MESI-STRAT International Advisory Board (IAB).

The IAB is composed of external experts recognized in the fields of basic and clinical breast cancer research, signaling & metabolism in breast cancer, systems medicine, companies active in the pharma sector and systems medicine, and patient representatives.

The role of the IAB will be to advise the MESI-STRAT Strategic Board (SB) on the project strategy and research directions, interaction/collaboration with other breast cancer-related consortia and research initiatives, as well as dissemination and communication to stakeholders in the academia, the commercial sector, patients and their families, and society.

Recognizing and making use of synergies between different projects and initiatives in the breast cancer field is key to fully exploit the European investment in systems medicine. As members of the MESI-STRAT IAB we will act to further this goal.

I will keep all information confidential that pertains to the structure as well as the technical content of the MESI-STRAT proposal set-up, and will only disclose said information to third parties upon the coordinator's approval.

I wish MESI-STRAT success and we look forward to acting on the IAB.

Yours sincerely



Anne-Lise Børresen-Dale
Professor Emerita, PhD, MD (h.c.)
Department of Cancer Genetics
Institute for Cancer Research



President
R. Briz
Spain

Name: Susan Knox
Position: Chief Executive Officer
Affiliation: EUROPA DONNA – The European Breast Cancer Coalition
Address: Piazza Ameondola, 3, Milan 20149, Italy
Telephone: +39 02 365 92280
Email: susan.knox@europadonna.org

Vice President
E. Papadopoulos
Cyprus

Treasurer
M. Knoteck-Rogggenbauer
Austria

B. Dodeva
Macedonia

To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Executive Director
S. Knox

Milan, 13 March 2017

Letter of intent
International Advisory Board
for the project “Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)”

Dear Prof. Dr. Thedieck,

It is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

Founding President
G. Freilich
Founder
Prof. U. Veronesi

As a patient organization representing breast cancer patients across Europe, Europa Donna endorses your efforts to develop tools that may help predict from measurements in body fluids which patients respond to endocrine

therapy or become resistant. Of particular importance to the patients, the marker panels developed by MESI-STRAT will not only predict the risk of progression to metastatic disease, but they will guide decisions for targeted therapies at different stages of the disease.

Currently, for patients with ER-positive breast cancer no markers in body fluids exist to guide decisions for targeted therapies or for prolongation of endocrine therapies. MESI-STRAT aims to develop such marker panels that predict which ER-positive subgroups are responsive or resistant toward different targeted therapies, and which patients are most likely to profit from prolonged endocrine therapies.

Therefore, we would like to show our support through this letter.

The MESI-STRAT International Advisory Board (IAB) is composed of external experts recognized in the fields of basic and clinical breast cancer research, signaling & metabolism in breast cancer, systems medicine, companies active in the pharma sector and systems medicine, and patient representatives.

The role of the IAB will be to advise the MESI-STRAT Strategic Board (SB) on the project strategy and research directions, interaction/collaboration with other breast cancer-related consortia and research initiatives, as well as dissemination and communication with stakeholders in the academia, the commercial sector, patients and their families, and society.

If the project proposal is accepted for funding by the EC, Europa Donna will join the IAB of MESI-STRAT to represent the patients' view across Europe. We will pay specific attention to the need of the patients in terms of communication and compliance with the patients' benefit.

We will keep all information confidential that pertains to the structure as well as the technical content of the MESI-STRAT proposal set-up, and we will only disclose said information to third parties upon the coordinator's approval.

We wish MESI-STRAT success and we look forward to acting on the IAB.
With best regards,



Susan Knox, Chief Executive Officer Europa Donna

Doris Christiane Schmitt
Staader Thalweg 4
78464 Konstanz
Germany

T +497531-9413075 M +4916097304549 Mail DorisC.Schmitt@t-online.de

To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
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Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

20 March 2017

Letter of intent
International Advisory Board
for the project “Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)”

Dear Prof. Dr. Thedieck,
dear Kathrin,

It is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

Currently, for patients with ER-positive breast cancer no markers in body fluids exist to guide decisions for targeted therapies or for prolongation of endocrine therapies. MESI-STRAT aims to develop computational models that can predict such marker panels. Of particular importance to the patients, the marker panels developed by MESI-STRAT will not only indicate the risk of progression to metastatic disease, but they will guide decisions for targeted therapies at different stages of the disease. Thorough validation in existing patient cohorts and prospective clinical trials will ensure the quality and predictive value of the models and marker panels developed by MESI-STRAT in the clinical setting.

As a patient expert, PATH co-chair and executive board member of EUPATI (European Patient Academy) Germany, I fully endorse your efforts, and I am willing

to advise the MESI-STRAT consortium, if the project proposal is accepted for funding by the EC.

The MESI-STRAT International Advisory Board (IAB) is composed of external experts recognized in the fields of basic and clinical breast cancer research, signaling & metabolism in breast cancer, systems medicine, companies active in the pharma sector and systems medicine, and patient representatives.

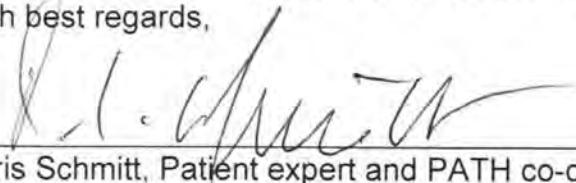
The role of the IAB will be to advise the MESI-STRAT Strategic Board (SB) on the project strategy and research directions, interaction/collaboration with other breast cancer-related consortia and research initiatives, as well as dissemination and communication with stakeholders in the academia, the commercial sector, patients and their families, and society.

I will join the IAB of MESI-STRAT to represent the patients' view. With the diagnosis breast cancer myself, and the background of education in pedagogy and psychology, I have specialized in training Health Care Professional in Doctor-Patient-Communication. I will pay specific attention to the need of the patients in terms of communication and compliance with the patients' benefit.

Toward the same aims, I will also participate in the organization of the MESI-STRAT patient days.

I will keep all information confidential that pertains to the structure as well as the technical content of the MESI-STRAT proposal set-up, and we will only disclose said information to third parties upon the coordinator's approval.

I wish MESI-STRAT success and I look forward to acting on the IAB.
With best regards,



Doris Schmitt, Patient expert and PATH co-chair

NAME Doris Christiane Schmitt	POSITION TITLE Consulting and Training Doctor-Patient-Communication		
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University Institut für Personalführung Köln		1980-1986 1987-1989	Psychology and Education Communication Sciences

A. Personal Statement

Since 1999 I am proud to have fought breast cancer successfully. As a breast cancer survivor, the last 18 years have taught me much about the science and the psychology of breast cancer. The motivation all over the planet to eradicate this disease is impressive, however not enough has been done yet. Early detection and the successful treatment of breast cancer are essential for the survival of a breast cancer patient. Advanced and metastatic breast cancer on the other hand has to be seen as a different disease than early stage breast cancer. Surveys have shown that women with metastatic breast cancer do not get the attention they need. Therefore it is vital raising awareness in public and policy makers what this highly vulnerable group and their families need in order to deal with the disease with best quality of life.

Patient information and counseling are the basis for successful treatment compliance and quality of life. Equally important the doctor must be informed by the patient to understand patient's aims as well as justified and unjustified concerns. The mechanism of this communication is an understudied area of research. Miscommunication can lead to suboptimal treatment, low participation in screening or a slow recruitment to clinical studies. Especially in the preventive situation, informing women at high risk is a challenging task and might be crucial for the success of a drug prevention study. My expectations for the upcoming projects are the integration of aims that truly match the best scientific rationale and genuine patients' expectations.

B. Positions and Honors

Positions and Employment

1964-1967	Flight Attendant Pan American World Airways
1987-Present	Coach for Communication Improvement
2006-2008	Chair of mamazone e.V. (Patient Advocacy Group)
2008-present	Co-Chair of the biomaterial bank Patients' Tumor Bank of Hope (PATH)
2008-present	Member of the scientific advisory board German Breast Cancer Association (Brustkrebs Deutschland e.V.)
2008-present	Consultant in national and international Advisory Boards and Advisory Panels

Research Experience

2002-2007	Patient Information and Treatment Decision Study (Gut Informieren, gemeinsam entscheiden)
2008-present	Scientific Advisor Prepare-Study (Phase IV Study to assess the pharmacogenetic markers and phamacoconomic markes in the treatment of postmenopausal, hormone receptor positive breast cancer)
2007-2009	Scientific Advisor PACT Study (Patient Compliance Study concerning Aromatase Inhibitors)
2007-2009	Advisory Board Member ALTTO-Study (Phase III Study in the adjuvant treatment of HER2 positive breast cancer)
2008-present	Advisory Board Member SUCCESS A and C Studies (Phase III Adjuvant Chemotherapy Breast Cancer Studies)
2009-present	Advisory Board Member DETECT III Study (Phase III Study in HER2 positive metastatic breast cancer)
2010-2014	Steering Board Member Skeletal Care Academy

Further Education in Cancer Research

Breast Cancer, NSCLC, (therapy options, treatment of side effects, QoL, oncology psychology, political situation and communication of access to best practice, doctor-patient-communication)

Annual attendance of national and international conferences (attendee and/or speaker):

Germany

Senologie Kongress (Association of Senology)
DKK - Deutscher Krebskongress (German Cancer Conference)
COMBATing Breast Cancer

Europe

EBCC – European Breast Cancer Conference
ESMO-ECCO
ABC – Advanced Breast Cancer Conference Lisbon/Portugal
St. Gallen Consensus Conference - Vienna/Austria

USA

SABCS – San Antonio Breast Cancer Symposium, San Antonio/Texas
ASCO – American Society of Clinical Oncology Orlando/Chicago/Il

Asia

ESMO Asia – Singapore/South East Asia

Online Education Stanford University

Palliative Care

C. Selected Publications (published abstracts and peer reviewed) Most relevant to the current application

Schmitt, D. C. (2008). PATH – Patients' Tumorbank of Hope. *Breast Care* **3**(5), 366-367.

Schmitt, D. C. (2009). Communication and compliance - the success of treatment depends on the physician-patient communication. *Breast Care* **4**(2), 128-129.

Schmitt, D.C. (2009) Aims and limits of Patient Advocacy Groups. [Zielvorstellungen, Möglichkeiten und Grenzen von Selbsthilfegruppen] in Dorfmüller, M., Dietzfelbinger H. (Editors) Psychoonkologie, Urban and Fischer, Munich, pp339-343

Anzeneder, T. R., Ohlms, U., **Schmitt, D. C.**, and Waldner, C. (2009). 5 Years Experience in Collecting Tumor Specimen at Patient's Tumor Bank of Hope (PATH) - A Decentralized, Independent Biobank in Germany Controlled by Patients. *Cancer Research* **69**(24), 670s-670s.

Jackisch, C. H., Harbeck, N., Blettner, M., Hadji, P., Luck, H. J., **Schmitt, D. C.**, Haidinger, R., Kohler, U., Zaun, S., and Kreienberg, R. (2009). The patient's anastrozole compliance to therapy programme (PACT): evaluating the influence of a standardized information service on compliance in postmenopausal women with early breast cancer. *Ejc Supplements* **7**(2), 271-271.

Hadji, P., Blettner, M., Haidinger, R., Harbeck, N., Jackisch, C., Luck, H. J., Martins, R. R., von Fircks, A. R., **Schmitt, D. C.**, and Kreienberg, R. (2008). Patient's Anastrozole Compliance to Therapy Programme (PACT) influence of the addition of a standardized information and reminder service on compliance in comparison to standard clinical care alone in women with early breast cancer. *Ejc Supplements* **6**(7), 127-127.

Lux, M. P., Radosavac, D., Kara, H., Taenzer, T. D., Loehberg, C. R., **Schmitt, D. C.**, Haidinger, R., Overbeck-Schulte, B., Schulte, H., Mueller, U., Beckmann, M. W., and Fasching, P. A. (2008). Breast cancer patients and theirs doctors differ in the demand for the magnitude of the therapy effect of chemotherapy and endocrine treatment-results of the gut informieren - Gemeinsam entscheiden!-study. *Onkologie* **31**, 40-40.

Lux, M. P., Radosavac, D., Taenzer, T. D., Kara, H., Bani, M. R., Schrauder, M., **Schmitt, D. C.**, Haidinger, R., Overbeck-Schulte, B., Schulte, H., Beckmann, M. W., and Fasching, P. A. (2008). Patients' imagination of therapy efficacy and correlation to the willingness to accept chemotherapy and endocrine therapy of breast cancer results of the gut informieren - Gerneinsam entscheiden! study. *Onkologie* **31**, 39-39.

Lux, M. P., Radosavac, D., Tanzer, T. D., Kara, H., Bani, M. R., Schrauder, M., **Schmitt, D. C.**, Haidinger, R., Overbeck-Schulte, B., Schulte, H., Beckmann, M. W., and Fasching, P. A. (2008). Influence factor of patients with a mama carcinoma on the introduction over therapy effectivity and acceptance of therapy options - Results of a Good Information - Gemeinsam Entscheiden! Study. *Geburtshilfe Und Frauenheilkunde* **68**(5), 556-556.

Lux, M. P., Radosavac, D., Tanzer, T. D., Kara, H., Bani, M. R., Schrauder, M., **Schmitt, D. C.**, Haidinger, R., Overbeck-Schulte, B., Schulte, H., Beckmann, M. W., and Fasching, P. A. (2008). Patients with a mamma carcinoma and their doctors differentiating in the evaluation of the essential benefits of therapy option - Results of a Good Information - Gemeinsam Entscheiden! Study. *Geburtshilfe Und Frauenheilkunde* **68**(5), 555-556.

Lux, M. P., Taenzer, T. D., Radosavac, D., Kara, H., Bani, M. R., Kreis, H., Beckmann, K., **Schmitt, D. C.**, Haidinger, R., Overbeck-Schulte, B., Schulte, H., Beckmann, M. W., and Fasching, P. A. (2008). Doctors' imagination of therapy efficacy and correlation to the willingness to indicate chemotherapy and endocrine therapy in breast cancer patients results of the gut informieren - Gemeinsam entscheiden! study. *Onkologie* **31**, 39-40.

Lenz, C.F.W., **Schmitt, D.C.** (2014) Understanding the perceptions and unmet needs of advanced breast cancer patients. JOURNAL PHARMAKOL.U.THER. 4/2014 23, 111-115.

Derick Mitchell, Jan Geissler, Alison Parry Jones, Hans Keulen, **Doris C. Schmitt**, Rosaria Vavassori, Balwir Matharoo-Ball, Biobanking from the patient perspective, RESEARCH INVOLVEMENT AND ENGAGEMENT 2015, 1:4



Dr. Andreas Raue
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One Kendall Square
Building 700, Suite B7201
Cambridge, MA 02139
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To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Cambridge, 3/13/2017

Letter of intent
International Advisory Board
For the project “Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)”

Dear Prof. Dr. Thedieck,

It is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

I am willing to advise the MESI-STRAT consortium, if the project proposal is accepted for funding by the EC.

In my current role at Merrimack Pharmaceuticals, I am leading the early stage immuno-oncology development and biomarker discovery. Merrimack Pharmaceuticals is a successful and growing company focused on the use of systems approaches to develop precisely engineered cancer drugs and conduct clinical trials tailored to the patient

population most likely to benefit. Therefore, we endorse your efforts to develop tools that may help us predict which BC patients respond to endocrine therapy or become resistant, and to guide targeted therapies for ET resistant patient subpopulations.

I am anticipating strong synergies between Merrimack's and MESI-STRAT's aims, and would like to show our support through this letter. Further, I will join the International Advisory Board (IAB) of MESI-STRAT. The MESI-STRAT IAB is composed of external experts recognized in the fields of basic and clinical breast cancer research, signaling & metabolism in breast cancer, systems medicine, companies active in the pharma sector and systems medicine, and patient representatives. The role of the IAB will be to advise the MESI-STRAT Strategic Board (SB) on the project strategy and research directions, interaction/collaboration with other breast cancer-related consortia and research initiatives, as well as dissemination, exploitation, and communication with stakeholders in the academia, the commercial sector, patients and their families, and society.

I will keep all information confidential that pertains to the structure as well as the technical content of the MESI-STRAT proposal set-up, and I will only disclose said information to third parties upon the coordinator's approval.

I wish MESI-STRAT success and I look forward to acting on the IAB.

With best regards,



Andreas Raue, Principal Scientist



FACULTEIT DER NATUURWETENSCHAPPEN, WISKUNDE EN INFORMATICA

Swammerdam Institute for Life Sciences

Letter of intent

International Advisory Board

Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification
(MESI-STRAT)

MESI-STRAT Consortium Coordinator

Prof. Dr. Kathrin Thedieck

Lab for Metabolic Signaling

Department of Pediatrics

University Medical Center Groningen (UMCG)

Internal Zip Code EA12, Antonius Deusinglaan 1

9713 AV Groningen, The Netherlands

Amsterdam, 13-3-2017,

Dear Prof. Dr. Thedieck,

It is our pleasure to herewith express our support for your H2020 proposal MESI-STRAT aiming to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

We are very interested in the MESI-STRAT proposal since its topic is closely connected to our EU H2020 Marie Skłodowska-Curie Innovative Training Network (MSCA-ITN) entitled 'EpiPredict' focusing on epigenetic regulation of resistance development during endocrine therapy treatment of estrogen receptor positive breast cancer patients. Within EpiPredict, we employ a systems medicine approach to obtain mechanistic, detailed insights in to how changes of a patient's epigenome can affect gene expression, pathway activation and metabolic rewiring through a defined set of resistance involved pathways. We combine multidisciplinary research strategies and next generation innovative technologies (epigenetic, gene expression, protein pathway activation, metabolic pathway profiling, gene-specific epigenetic interference and computational approaches) developing epigenetic diagnostic tools to predict and monitor treatment outcome, which we believe, will open-up an unexplored field of research with great potential for personalized medicine.

We look forward to advise the MESI-STRAT consortium if the project proposal is accepted for funding by the EC, to identify metabolic marker panels also in body fluids. Therefore, we would like to show our support through this letter, and we will join the International Advisory Board (IAB) to represent EpiPredict and enable a collaborative effort.

The IAB is composed of external experts recognized in the fields of basic and clinical breast cancer research, signaling & metabolism in breast cancer, systems medicine, companies active in the pharma sector and systems medicine, and patient representatives. The role of the IAB will be to advise the MESI-STRAT Strategic Board (SB) on the project strategy and research directions, interaction/collaboration with other breast cancer-related consortia and research initiatives, as well as dissemination and communication to stakeholders in the academia, the commercial sector, patients and their families, and society.

Recognizing and making use of collaborative synergies is key to fully exploit the European investment in systems medicine. As members of the MESI-STRAT IAB we are looking forward to further this goal.

We will keep the project information confidential that pertains to the structure as well as the technical content of the MESI-STRAT proposal set-up, and we will only disclose given information to third parties upon the coordinator's approval.

We wish MESI-STRAT success and we look forward to acting on the IAB.

With best regards,

Pernette J. Verschure, PhD
Coordinator EU H2020 Marie Skłodowska-Curie ITN EpiPredict
www.EpiPredict.eu
(Associate) Professor
Synthetic Systems Biology and Nuclear Organization
Swammerdam Institute for Life Sciences
University of Amsterdam
Science Park 904, 1098 XH Amsterdam
P.O. Box 94215, 1090 GE
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Phone 31 20 5255151
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Dr. H.G.J. Hoedemaker
Medical Director Oncology

Novartis Pharma B.V.
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MESI-STRAT Consortium Coordinator
Prof. dr. K. Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV GRONINGEN

Arnhem, 20 March 2017

**Subject: Letter of Support for the
H2020 Research and Innovation Actions proposal “Systems Medicine of
Metabolic-Signaling networks: A New Concept for Breast Cancer Patient
Stratification (MESI-STRAT)”**

Dear prof. dr. Thedieck,

It is my pleasure to write in support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

As a pharmaceutical company focused among others on the discovery and development of new therapeutic interventions to treat breast cancer, we can endorse your efforts to develop computational models and metabolite marker panels, measurable in body fluids, that may help us predict which patients will respond to endocrine therapy (ET) or become resistant, and which of the ET resistant patient subgroups respond or are resistant to Novartis' targeted combinatorial therapies, such as ribociclib or everolimus.

Therefore, we would like to confirm our support through this letter.

As we have discussed, Novartis is committed to supporting Investigator Initiated Trials (IITs) as a part of the drug discovery and development process. Scientific research that is produced by qualified third-party investigators is key to complementing Novartis-sponsored research to help better understand the benefit/risk profile of our therapies as well as explore new opportunities to address unmet medical needs.

If MESI-STRAT identifies marker panels predicting response or resistance to combinatorial ET therapies with Novartis substances, MESI-STRAT can, in

accordance with our guidelines

(<https://www.novartis.com/sites/www.novartis.com/files/novartis-investigator-initiated-trials.pdf>) apply for support of clinical studies (IIT or umbrella trials) developed and sponsored by an academic partner of MESI-STRAT. Novartis requires that clinical research undertaken through IITs be based on the need to address meaningful scientific and/or clinical objectives supported by valid scientific designs while respecting the privacy rights, safety and welfare of patients. Collaboration with multiple funding partners or support of an umbrella trial is also feasible, as illustrated by the Novartis participation in the Drug Rediscovery Protocol (DRUP), initiated by the Centre for Personalized Cancer Treatment in the Netherlands.

An IIT may be either a clinical or non-clinical study, conducted without the participation of Novartis for which the sponsor has requested that Novartis provide funding, drug product or both. Novartis provides financial support and/or drug product for clinical trials according to a written agreement, which requires that third-party sponsors comply with applicable local laws and regulatory requirements.

We look forward to a productive interaction with MESI-STRAT.

Yours sincerely,
Novartis Oncology



Eric Hoedemaker
Medical Director Oncology



Sandra Orchard
Team Leader – Molecular
Interactions
Tel.: +44 1223 494675
E-mail: orchard@ebi.ac.uk

21 March 2017

Dr. Sushma Grellscheid
Department of Biosciences
Durham University, UK

MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Letter of Support for the H2020 Research and Innovation Actions proposal:
“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)”

Dear Dr. Grellscheid, Dear Prof. Thedieck,

It is my pleasure to write in support for your H2020 proposal MESI-STRAT.

We have enjoyed discussing your proposal and the concept of integrating a bottom up approach of metabolic and signaling network driven modelling with a top down approach of bioinformatics and network analysis is very timely and exciting. We see great value in the proposal to carry out integrated RNASeq and proteomics data analysis based on matched samples that will be generated as a part of the project. We would be pleased to support the bioinformaticians employed at MESI-STRAT as visitors at EBI and share our expertise on network analysis and of multi-level datasets, that is well established within our IntACT project. We also agree to host the storage of raw proteomics data within PRIDE. When this data is submitted to the ProteomXchange Consortium via PRIDE, it will be compliant with MIAPE data standards and accessible at both the ProteomeXchange and PRIDE websites, and assures long-term storage and reuse of data by the community.

We look forward to a productive interaction with MESI-STRAT.

Yours sincerely,

A handwritten signature in black ink that reads "Sandra Orchard".

Sandra Orchard

Molecular Interactions Team Leader



EMBL-European Bioinformatics Institute
Wellcome Trust Genome Campus
Hinxton, Cambridge CB10 1SD
United Kingdom
Tel.: +44 (0)1223 494444

13 March 2017

To
Dr. Sushma Grellscheid
Department of Biosciences
Durham University, UK

And

MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics; Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

**Letter of Support for the H2020
Research and Innovation Actions proposal:
“Systems Medicine of Metabolic-Signaling networks: A New Concept
for Breast Cancer Patient Stratification (MESI-STRAT)”**

Dear Dr. Grellscheid,
Dear Prof. Thedieck,

It is my pleasure to write in support of the application to establish the MESI-STRAT project that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

As Gene Expression Team Leader at EMBL-EBI, I see great value in the proposal to carry out integrated RNASeq and proteomics data analysis based on matched samples that will be generated as a part of the MESI-STRAT project. When this data is submitted to ArrayExpress/ENA via our ontology driven submission tool, Annotare, it will be compliant with the MINSEQE standard, highly curated, analysed via standardized pipelines and then visualized in Expression Atlas, the EMBL-EBI value added resource for functional ‘omics data. Data uploaded to

ENA ensures long-term data preservation as well as ease of availability to the scientific community.

By removing sample specific biases, the use of matched samples across ‘omics studies makes for a much more accurate expression profiling, that will add great value to the existing data in Expression Atlas, and thus help disseminate the value to a broader scientific community.

We will be very happy to include bioinformaticians employed at MESI-STRAT as visitors to our team so that they can be well integrated and trained using this platform.

We look forward to a fruitful interaction with MESI-STRAT.

Yours faithfully,

A handwritten signature in black ink, appearing to read "R. petryszak".

Robert Petryszak, Gene Expression Team Leader, Functional Genomics

Name: Dr Sam Whitehouse
Position: Chief Operating Officer
Affiliation: QuantuMDx Group Ltd
Address Lugano Building, 57 Melbourne Street, Newcastle Upon Tyne, NE1 2JQ
Telephone: 07788230385
Email: sam.whitehouse@quantumdx.com

10th march 2017

To
Dr. Sushma Grellscheid
Department of Biosciences
Durham University, UK

and

MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

**Letter of Support for the H2020 Research and Innovation Actions proposal:
“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast
Cancer Patient Stratification (MESI-STRAT)”**

Dear Prof. Thedieck,
Dear Dr. Grellscheid,

On behalf of QuantuMDx Group Ltd, it is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

As a vibrant and dedicated biotech company focused on the development of portable diagnostics, providing access to such diagnostics to every man, woman and child on this planet, regardless of race, country or creed, QuantuMDx is pleased to support your efforts to develop tools that may help predict which breast cancer patients respond to endocrine therapy or become resistant. Early diagnosis and effective treatment of disease can lead to prevention and cure if run alongside humanitarian programs for training and education in new skills and infrastructure. Q-POC™, our novel handheld device, is being developed to provide access to gold standard molecular diagnostic testing and to meet the strict regulatory requirements that will enable it to become the diagnostic device of choice for all health professionals, police, rapid responders, vets and farmers.

We think that the results of the MESI-STRAT program will lead to very valuable biomarkers which we could potentially develop further in our Q-POC™ platform. Therefore, we fully support this initiative.

We look forward to a fruitful interaction.

Yours faithfully,

A handwritten signature in black ink, appearing to read "SW".

Dr Sam Whitehouse PhD
MRSC Chief Operating Officer QuantuMDx Group Ltd



To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Basel, March 16, 2017

**Letter of Support for the
H2020 Research and Innovation Actions proposal
“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast
Cancer Patient Stratification (MESI-STRAT)”**

Dear Prof. Thedieck,

On behalf of Cellec Biotek AG and relating to earlier discussion with our staff, it is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

CELLEC BIOTEK AG was founded as a spin-off of a lab of University Hospital Basel, Switzerland. We develop and commercialize bioreactors for 3D cell culture and tissue generation. Our products allow growing 3D living tissues, as advanced model systems for tissue development and drug testing, applied to life sciences and pharmaceutical research, and potentially as biological grafts for tissue and organ regeneration, applied to clinical translation in regenerative medicine. Recently, the U-CUP bioreactor has been exploited for the ex-vivo culture of freshly isolated primary tumor tissue, in particular breast cancer both ER+ and TNBC. Preliminary results are showing the possibility to preserve the tumor microenvironment in terms of cellular composition. This allowed testing drugs on model mimicking better the living tissue and to understand how the different cellular components react to a given treatment.

As a biotech company active in the innovative field of Tumor Engineering, we endorse your efforts to develop tools that may help predict which patients respond to endocrine therapy or become resistant.



We will provide technical support for the acquisition, implementation, and development of a bioreactor-based ex-vivo culture protocol for freshly isolated primary breast cancer specimens as a tool for patient specific drug test.

We look forward to a productive interaction and remain in the meantime

Sincerely yours,

A handwritten signature in blue ink, appearing to read "Werner M. Enz".

Dr. med. Werner M. Enz,
Cellec Biotek AG, President of the Board of Directors

c/o ErfindungsVerwertung AG (EVA)
Hochbergerstrasse 60c,
4057 Basel
Switzerland

Telephone: +41 61 283 8485
Email: wenz@cellecbiotek.com

Romy Kirsten, PhD
Head NCT Liquid Biobank
National Center of Tumor Diseases (NCT) Heidelberg
Im Neuenheimer Feld 460
69121 Heidelberg
Germany
Telephone 0049 6221 56 38946
Email romy.kirsten@nct-heidelberg.de

To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Heidelberg, 14.3.2017

**Letter of Support for the
H2020 Research and Innovation Actions proposal
“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast
Cancer Patient Stratification (MESI-STRAT)”**

Dear Prof. Thedieck,

On behalf of the NCT biobank, it is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

As a biobank focused on high-quality sample handling and storage as well as management processes ensuring that samples are prepared and stored in consistent conditions, we endorse your efforts to develop tools that may help predict which patients respond to endocrine therapy or become resistant.

Therefore, we would like to show our support through this letter, confirming that we will provide the infrastructure and support for quality-assured handling and storage of the samples collected in the frame of the MESI-STRAT project.

We fully support the MESI-STRAT initiative and we look forward to a productive interaction.

Yours sincerely,



Romy Kirsten
Head NCT Liquid Biobank



NATIONAL CENTER
FOR TUMOR DISEASES
HEIDELBERG

supported by
German Cancer Research Center (DKFZ)
Heidelberg University Medical Center
Hospital for Thoracic Diseases
German Cancer Aid

NCT | Im Neuenheimer Feld 460 | D-69120 Heidelberg

To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Heidelberg, 03.04.2017

**Letter of Support for the
H2020 Research and Innovation Actions proposal
“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast
Cancer Patient Stratification (MESI-STRAT)”**

Dear Prof. Thedieck,

it is our pleasure to herewith express our support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

We endorse your efforts to develop tools that may help predict which patients respond to endocrine therapy or become resistant.

In the frame of the GEKKO study a unique data- and liquid biobank for early cancer detection is currently being built up, focusing on enhanced screening strategies and on the detection and evaluation of novel biomarkers or biomarker signatures for the detection of cancer.

The GEKKO cohort currently encompasses 190 breast cancer patients, of which serum, plasma and urine are available at diagnosis.

We would like to show our support through this letter stating that we are willing to share serum and urine samples for the measurement of MESI-STRAT markers in the frame of this study.

Therefore, we fully support the MESI-STRAT initiative and look forward to a productive interaction.

Yours sincerely,

A handwritten signature in blue ink, appearing to read "H. Brenner".

Prof. Dr. H. Brenner,
PI GEKKO Study

**National Center for
Tumor Diseases Heidelberg**

Division of Preventive Oncology
Head: Prof. Dr. Hermann Brenner
Im Neuenheimer Feld 460
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Phone +49 (0) 6221 565230
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www.nct-heidelberg.de
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Radiooncology
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Thoracic Tumors
Tumors of the Head and Neck
Urological Tumors

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Cancer Information Service (KID)
Nutrition
Psycho-Oncology
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Physical Activity and Cancer

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Medical Oncology, University Hospital Heidelberg

Deputy Chairs
Peter Lichten, PhD
Molecular Genetics, DKFZ
Jürgen Debus, MD, PhD
Radiooncology, University Hospital Heidelberg

Medical Oncology

Annex 3.4.3 Collaborating clinical trials and biobanks

De Boelelaan 1117
1081 HV Amsterdam
The Netherlands

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1007 MB Amsterdam
The Netherlands

telephone no.: (0)20 444 4300
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To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
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VU University
Medical Center
Amsterdam

Date
Amsterdam, 6th of April 2017
Concerning

Direct dial
+31 (0)20 4444321

**Letter of Support for the
H2020 Research and Innovation Actions proposal
“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient
Stratification (MESI-STRAT)”**

Dear Prof. Thedieck,

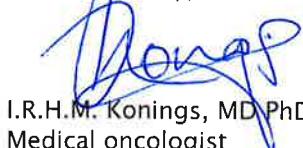
it is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

I endorse your efforts to develop tools that may help predict which patients respond to endocrine therapy or become resistant.

As principal investigator I am currently working on setting up a multi-center clinical trial in the Netherlands, in which we aim to compare endocrine therapy in combination with Cdk4/6 inhibitor versus a delay in CDK4/6 inhibitor treatment until disease progression occurs. In this trial, it is the intention to include substantial biomarker research for optimal patient selection. In this setting, if the trial is initiated as intended, it would be conceivable to collect biological samples that might also be used for the measurements of MESI-STRAT markers.

Therefore, I fully support the MESI-STRAT initiative.

Yours sincerely,



A handwritten signature in blue ink, appearing to read "Douma". Below the signature, the name "I.R.H.M. Konings, MD PhD" is printed in a standard black font.

I.R.H.M. Konings, MD PhD
Medical oncologist

Prof. H.M.W. Verheul, M.D., Ph. D, chair
A.J.M. van den Eertwegh, M.D., Ph. D, deputy chair

Outpatients clinic:
J. Buter, M.D., Ph. D.
Mrs. I.R.H.M. Konings, M.D., Ph. D.
Mrs. M. Labots, M.D.
Mrs. M.E. van Linde, M.D.
Mrs. C.W. Menken, M.D., Ph. D.
J.J. v.d. Vliel, M.D., Ph. D.
J. Voortman, M.D., Ph. D.

Fellows:
Mr. J. Douma, M.D.
Mrs. M. Wijnkes, M.D.
Mrs. F. Afran, M.D.
Mrs. T. Buffart, M.D.
Mrs. K. Versteeg, M.D.
Mrs. L. Mammatas, M.D.

Research laboratory:
Prof. G.J. Peters, chair
Prof. V. van Beusechem, Ph. D.
Mrs. prof. C.R. Jiménez, Ph. D.
Prof. A.W. Griffioen, Ph. D.
Mrs. prof. T.D. de Gruijl, Ph. D.



PRAEGNANT BREASTCancer
ACADEMIC
TRANSLATIONAL
RESEARCH NETWORK

Lead

Prof. Dr. med. Diethelm Wallwiener
Prof. Dr. med. Hans Tesch

Steering Board

Prof. Dr. med. Peter A. Fasching
Prof. Dr. med. Sara Brucker

Dr. med. Johannes Ettl

Prof. Dr. med. Tanja Fehm

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Prof. Dr. med. Michael P. Lux

Dr. med. Friedrich Overkamp

Prof. Dr. med. Andreas Schneeweiss

Prof. Dr. Florin-Andrei Taran

Prof. Dr. med. Markus Wallwiener

06 April 2017

PRAEGNANT – ACADEMIC TRANSLATIONAL RESEARCH NETWORK

MESI-STRAT Consortium Coordinator

Prof. Dr. Kathrin Thedieck

Lab for Metabolic Signaling

Department of Pediatrics

University Medical Center Groningen (UMCG)

Internal Zip Code EA12

Antonius Deusinglaan 1

9713 AV Groningen

The Netherlands

Letter of Support for the

H2020 Research and Innovation Actions proposal

“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)”

Study Coordiantion- & Management

Dr. Erik Belleville

Dr. Thomas Spall

ClinSol GmbH & Co. KG

Kantstraße 27

97074 Wuerzburg

Tel. +49 931 730416 36

Fax +49 931 730416 9936

www.praegnant.org

Dear Prof. Thedieck,

dear PD Dr. Schott, dear Prof. Schneeweiss, dear Dr. Opitz,

It is my pleasure to write in support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

- 1 -

The PRAEGNANT study network (*NCT02338167, Prospective Academic Translational Research Network for the Optimization of Oncological Health Care Quality in the Advanced Therapeutic Setting*) has been set up, among others, to carry out molecular tests under study conditions and to identify breast cancer patients suitable for specific, targeted treatments.

The PRAEGNANT study focuses on patients with advanced, incurable, metastatic breast cancer. One of the aims of PRAEGNANT is to develop evaluation methods which can be carried out without requiring biopsies of metastatic tissue, for example by testing the patient's blood. For this

Supported by



**Deutsche Gesellschaft
für Senologie**



DGHO
DEUTSCHE GESELLSCHAFT FÜR
HÄMATOLOGIE UND ONKOLOGIE



AGO
ARBEITSGEMEINSCHAFT
GYNAKOLOGISCHE
ONKOLOGIE E.V.



EG
Forschungsinstitut für Frauengesundheit
Baden-Württemberg

purpose, PRAEGNANT focuses on circulating tumor cells, circulating nucleic acids, leukocyte RNA and microRNA that could be used for this type of analysis.

As MESI-STRAT focuses on metabolites, PRAEGNANT and MESI-STRAT are highly complementary. Hence, we fully endorse your efforts to identify metabolic marker panels, measurable in body fluids, that can guide targeted therapies for endocrine therapy resistant patient subgroups. We therefore grant MESI-STRAT access to samples collected by PRAEGNANT.

The PRAEGNANT cohort currently encompasses samples from more than 1900 patients and aims to include a total study population of around 3500 patients. This should ensure that approximately 150 patients receiving first-line and 150 patients receiving second-line treatment in the metastatic setting will be included in the study for every molecular subtype.

Inclusion in this study concept is not limited to patients receiving specific treatment lines. All breast cancer patients who have either metastasis or inoperable loco-regional disease can be included. Disease progression must be objectively evaluable. Tumor re-evaluation is done according to each centers local routine with additional assessments carried out if disease continues to progress and after every change of treatment line. The collected blood samples include serum and plasma.

PRAEGNANT is supported academically and partially by Novartis, Celgene and Pfizer.

We look forward to a productive collaboration with MESI-STRAT.

Yours Sincerely


Prof. Dr. med. Diethelm Wallwiener


Prof. Dr. med. Hans Tesch


Prof. Dr. med. Peter A. Fasching


Prof. Dr. med. Sara Y. Brucker



Deutsches Krebsforschungszentrum | M100 | PF 101949 | 69009 Heidelberg

To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Krebsinformationsdienst
M100
Leiterin:
Dr. med. Susanne Weg-Remers

Im Neuenheimer Feld 280
69120 Heidelberg
Telefon +49622142-2100
Telefax +49 6221 40-1806
s.weg-remers@dkfz.de
www.krebsinformationsdienst.de

Heidelberg, den 15.03.17

***Letter of support
for the project "Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)"***

Dear Prof. Dr. Thedieck, dear Dr. Opitz,

On behalf of the German Cancer Information Service, a division of the German Cancer Research Center, it is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

The German Cancer Information Service (KID, Krebsinformationsdienst) supports cancer patients, their families and friends, as well as health care professionals since more than 30 years with independent up-to-date and high quality information for questions and decision making regarding diagnostics, therapies and choice of treatment possibilities and centers. Cancer is among the most-feared diseases in our society. High-quality reliable information and patient-centered communication are essential to empower patients and their families to deal with their fears and to actively take part in the decision making on their therapies. Reducing their fear by informed decision making is also important to strengthen adherence of the patients to their therapies.

Therefore, we endorse your efforts to develop tools that may help predict from measurements in body fluids which patients respond to endocrine therapy or become resistant, and guide decisions for targeted therapies at different stages of the disease.

In the frame of the International cancer information service group (ICISG), KID collaborates with Cancer Information Services across Europe, including the UK, Norway and the Netherlands.

In particular, KID will support MESI-STRAT by

- co-organizing the MESI-STRAT patient days together with the patient organization PATH at the clinical partner centers. In

Stiftung des öffentlichen Rechts

Stiftungsvorstand
Prof. Dr. med. Michael Baumann
Prof. Dr. rer. pol. Josef Puchta

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Deutsche Bundesbank Karlsruhe
IBAN: DE39 6600 0000 0067 0019 02
BIC (SWIFT): MARK DEF 1660

particular, we will advise on frequent questions that are relevant to breast cancer patients and on how to communicate the results of MESI-STRAT best to the patients. In this context, it is important to put the given information into context by clarifying to the patients what is the timeline at which a specific MESI-STRAT outcome can be translated to the clinic. It is also important to choose ways of communication that strengthen the self-confidence of the patients such that the information empowers them to actively take part in decision making in their own therapy process and to be able to cope with their fears.

- perform a telephone survey on frequent questions of breast cancer patients, relevant to MESI-STRAT. KID supports 6,000 breast cancer patients per year by counseling via phone or e-mail. We will monitor questions relevant to MESI-STRAT, as detailed in the impact section of our project proposal, by a questionnaire, analyze the data obtained and annually report on the results at the MESI-STRAT meetings. We will be happy to discuss and advise the MESI-STRAT strategic board as well as health care professionals and patient organizations in MESI-STRAT on how to implement the patients' questions into the project, and how to effectively communicate the MESI-STRAT results to the patients. To gain a European perspective, we will invite our partner organizations in The Netherlands, the UK and Norway to participate in this survey.
- informing breast cancer patients with questions on patient stratification in endocrine therapy about the significance of MESI-STRAT and related studies through integrating the information in our internal knowledge data base, which we use to answer enquiries via telephone and e-mail.

We will keep all information confidential that pertains to the structure as well as the technical content of the MESI-STRAT proposal set-up, and we will only disclose said information to third parties upon the coordinator's approval.

We wish MESI-STRAT success and we look forward to a fruitful interaction.

With best regards,



Dr. Susanne Weg-Remers, Head German Cancer Information Service



UniversitätsKlinikum Heidelberg

Koordinierungszentrum für Klinische Studien (KKS) am Universitätsklinikum Heidelberg
Marsilius-Arkaden – Turm West | Im Neuenheimer Feld 130.3 | 69120 Heidelberg

**Coordination Centre
for Clinical Trials (KKS)**

To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Steffen P. Luntz, MD
Head of KKS
Dr. sc. hum. Anja Dietzel
Project Manager

Heidelberg, 24-Mar-17

Letter of Support for the H2020 Research and Innovation Actions proposal “Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer Patient Stratification (MESI-STRAT)”

Dear Prof. Thedieck,

On behalf of the KKS Heidelberg, it is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

As an academic CRO focused on designing and conducting clinical trials and providing professional infrastructure for clinical studies to ensure highest level of scientific quality according to international guidelines and current laws, we endorse your efforts to develop tools that may help predict which patients respond to endocrine therapy or become resistant.

The KKS Heidelberg will provide supporting project management, clinical monitoring, pharmacovigilance and data management according to modern aspects of risk-based quality management.

Therefore, we fully support the MESI-STRAT initiative and we look forward to a productive interaction.

Yours sincerely,

A handwritten signature in blue ink, appearing to read "Anja Dietzel".

Dr. sc. hum. Anja Dietzel
Project Manager



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To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12, Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Groningen, March 17, 2017

**Letter of Support for the
H2020 Research and Innovation Actions proposal
“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast Cancer
Patient Stratification (MESI-STRAT)”**

Dear Prof. Thedieck,

As the head of the Business Generator Groningen (BGG) and the Center for Development and Innovation (CDI) I would like to express my strong support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy (ET) in breast cancer (BC) patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

MESI-STRAT foresees a medical need for better diagnostics and treatment of ER-positive (ER+) BC. Your innovative approach aims at identifying metabolite marker panels, measurable in body fluids, that predict which patients will respond to ET or become resistant, and which ET-resistant patient subgroups respond to which targeted combinatorial therapies. MESI-STRAT may also identify new targets and intermediates in signaling pathways to help ER+BC patients.

The UMCG strongly commits to the development of improved diagnostics (c.f. Biomarker Bay Initiative) to enable early detection and treatment of disease, and MESI-STRAT provides an excellent match with this focus. BGG/CDI promotes the translation of knowledge into problem solving solutions and applications, through providing support in idea evaluation, knowledge protection, licensing, generation of partnerships and entrepreneurship. Our expertise and services are available for researchers of the UMCG and their collaborators to accelerate the value creation process.

If MESI-STRAT is granted, BGG/CDI will fully support you in evaluating opportunities, IP protection and management, setting up additional collaborations including licensing, and assist in establishing possible new industrial engagements.

We specifically will support MESI-STRAT with a feasibility study including a business case study to evaluate the opportunities of translating MESI-STRAT results into a spin-off company, with the intent to increase the impact of the results.

We are looking forward to participate in the ambitious, innovative and interesting program of MESI-STRAT.

Yours sincerely,

Dr. J. Sikkema
Director
Business Generator Groningen

Annex 3.4.4: Institutional commitments

Dr. Ruth Herzog
Head of Office of
Technology Transfer
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
+49 6221 42-2955
r.herzog@dkfz-heidelberg.de

To the
MESI-STRAT Consortium Coordinator
Prof. Dr. Kathrin Thedieck
Lab for Metabolic Signaling
Department of Pediatrics
University Medical Center Groningen (UMCG)
Internal Zip Code EA12
Antonius Deusinglaan 1
9713 AV Groningen
The Netherlands

Heidelberg, 21.03.2017

**Letter of Support for the
H2020 Research and Innovation Actions proposal
“Systems Medicine of Metabolic-Signaling networks: A New Concept for Breast
Cancer Patient Stratification (MESI-STRAT)”**

Dear Prof. Thedieck,

On behalf of the German Cancer Research Center (DKFZ), it is my pleasure to herewith express my support for your H2020 proposal MESI-STRAT that aims to improve the outcome of endocrine therapy in breast cancer patients by developing new, predictive algorithms for patient stratification and combinatorial treatment strategies.

As a Research Institution focused on Cancer Research and Personalized Medicine, we endorse your efforts to develop tools that may help predict which patients respond to endocrine therapy or become resistant.

Therefore, we would like to show our support through this letter.

The Office of Technology Transfer supports DKFZ scientists with patenting and works out the best marketing strategy for each new invention in consultations with them. At the end of 2016, the DKFZ managed a patent portfolio of 232 patent families, comprising 1037 individual national and international patents and patent applications. Another important focus of the Office of Technology Transfer activities is the negotiations of license agreements. The DKFZ has an actively managed portfolio of 119 license agreements.

As the Technology Transfer Office at the DKFZ, we will be happy to advise our participating scientists on how best to exploit any relevant intellectual property arising from the MESI-STRAT project.

Specifically our services include:

- invention disclosures
- patent applications
- license agreements
- confidentiality agreements
- industrial cooperation agreements
- material transfers
- technology marketing
- feasibility studies
- business plans
- spin-offs

Therefore, we fully support the MESI-STRAT initiative and we look forward to a productive interaction.

Yours sincerely,



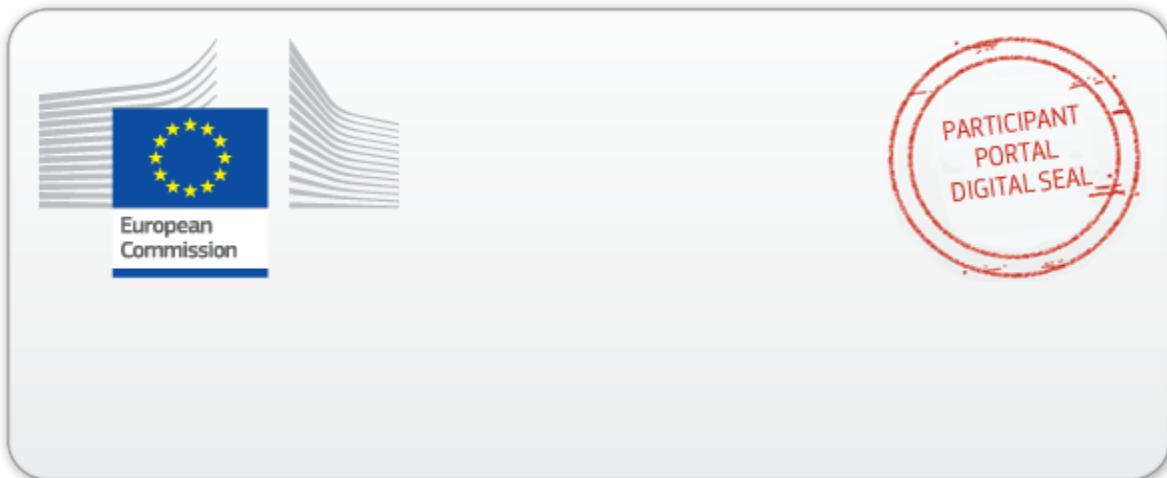
A handwritten signature in blue ink, appearing to read "Ruth Herzog".

Dr. Ruth Herzog

ESTIMATED BUDGET FOR THE ACTION

Estimated eligible ¹ costs (per budget category)											EU contribution			Additional information			
A. Direct personnel costs			B. Direct costs of subcontracting	C. Direct costs of fin. support	D. Other direct costs		E. Indirect costs ²	F. Special unit costs	Total costs	Reimbursement rate %	Maximum EU contribution ³	Maximum grant amount ⁴	Information for indirect costs	Information for auditors	Other information		
A.1 Employees (or equivalent)		A.4 SME owners without salary					D.1 Travel	D.5 Costs of internally invoiced goods and services		F.1 Costs for clinical studies ⁵				Estimated costs of in-kind contributions not used on premises	Declaration of costs under Point D.4	Estimated costs of beneficiaries/ linked third parties not receiving funding/ international partners	
A.2 Natural persons under direct contract		A.5 Beneficiaries that are natural persons without salary					D.2 Equipment										
A.3 Seconded persons		[A.6 Personnel for providing access to research infrastructure]					D.3 Other goods and services										
							D.4 Costs of large research infrastructure										
Form of costs ⁶	Actual	Unit ⁷	Unit ⁸		Actual	Actual	Actual	Unit ⁹	Flat-rate ¹⁰	Unit ¹²							
	a	Total b	No hours	Total c	d	e	f	Total g	h = 0,25 x (a +b+c+f+g +[i1] ¹³ +[i2] ¹³ -n)	Total i1	j = a+b+c+d+[e]+f+g+h+[i1]+[i2]	k	l	m	n	Yes/No	
1. UIBK	970 588.35	0.00	0.00	0.00	0.00	0.00	316 742.15	0.00	321 832.63	0.00	1 609 163.13	100.00	1 609 163.13	1 609 163.13	0.00	No	n/a
2. PATH Biobank	76 800.00	0.00	0.00	0.00	113 300.00	0.00	33 000.00	0.00	27 450.00	0.00	250 550.00	100.00	250 550.00	250 550.00	0.00	No	n/a
3. UKL-HD	218 241.00	0.00	0.00	0.00	0.00	0.00	64 705.00	0.00	70 736.50	0.00	353 682.50	100.00	353 682.50	353 682.50	0.00	No	n/a
4. DKFZ	484 200.00	0.00	0.00	0.00	0.00	0.00	211 880.00	0.00	174 020.00	0.00	870 100.00	100.00	870 100.00	870 100.00	0.00	No	n/a
5. VHIO	63 765.00	0.00	0.00	0.00	0.00	0.00	89 000.00	0.00	38 191.25	0.00	190 956.25	100.00	190 956.25	190 956.25	0.00	No	n/a
6. DDI	163 200.00	0.00	0.00	0.00	0.00	0.00	68 000.00	0.00	57 800.00	0.00	289 000.00	100.00	289 000.00	289 000.00	0.00	No	n/a
7. UiB	491 616.00	0.00	0.00	0.00	0.00	0.00	52 000.00	0.00	135 904.00	0.00	679 520.00	100.00	679 520.00	679 520.00	0.00	No	n/a
8. UiT	279 540.00	0.00	0.00	0.00	0.00	0.00	14 000.00	0.00	73 385.00	0.00	366 925.00	100.00	366 925.00	366 925.00	0.00	No	n/a
9. UNEW	193 950.00	0.00	0.00	0.00	0.00	0.00	13 000.00	0.00	51 737.50	0.00	258 687.50	100.00	258 687.50	258 687.50	0.00	No	n/a
10. Charité	268 965.00	0.00	0.00	0.00	0.00	0.00	50 000.00	0.00	79 741.25	0.00	398 706.25	100.00	398 706.25	398 706.25	0.00	No	n/a
11. UDUR	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	No	n/a
12. Neuroimmun GmbH	72 000.00	0.00	0.00	0.00	0.00	0.00	33 400.00	0.00	26 350.00	0.00	131 750.00	100.00	131 750.00	131 750.00	0.00	No	n/a
13. SysBioSim B.V.	74 169.00	0.00	0.00	0.00	0.00	0.00	8 000.00	0.00	20 542.25	0.00	102 711.25	100.00	102 711.25	102 711.25	0.00	No	n/a
14. HITS	165 750.00	0.00	0.00	0.00	0.00	0.00	14 000.00	0.00	44 937.50	0.00	224 687.50	100.00	224 687.50	224 687.50	0.00	No	n/a
15. UMCG	167 411.65	0.00	0.00	0.00	0.00	0.00	11 407.85	0.00	44 704.87	0.00	223 524.37	100.00	223 524.37	223 524.37	0.00	No	n/a
Σ consortium	3 690 196.00	0.00		0.00	113 300.00	0.00	979 135.00	0.00	1 167 332.75	0.00	5 949 963.75	100.00	5 949 963.75	5 949 963.75	0.00		

¹ See Article 6 for the eligibility conditions.² Indirect costs already covered by an operating grant (received under any EU or Euratom funding programme; see Article 6.5.(b)) are ineligible under the GA. Therefore, a beneficiary/linked third party that receives an operating grant during the action's duration cannot declare indirect costs for the year(s)/reporting period(s) covered by the operating grant, unless it can demonstrate that the operating grant does not cover any costs of the action (see Article 6.2.E).³ This is the theoretical amount of EU contribution that the system calculates automatically (by multiplying all the budgeted costs by the reimbursement rate). This theoretical amount is capped by the 'maximum grant amount' (that the Commission/Agency decided to grant for the action) (see Article 5.1).⁴ The 'maximum grant amount' is the maximum grant amount decided by the Commission/Agency. It normally corresponds to the requested grant, but may be lower.⁵ Depending on its type, this specific cost category will or will not cover indirect costs. Specific unit costs that include indirect costs are: costs for energy efficiency measures in buildings, access costs for providing trans-national access to research infrastructure and costs for clinical studies.⁶ See Article 5 for the forms of costs.⁷ Unit : hours worked on the action; costs per unit (hourly rate) : calculated according to the beneficiary's usual accounting practice.⁸ See Annex 2a 'Additional information on the estimated budget' for the details (costs per hour (hourly rate)).⁹ Unit and costs per unit : calculated according to the beneficiary's usual accounting practice.¹⁰ Flat rate : 25% of eligible direct costs, from which are excluded: direct costs of subcontracting, costs of in-kind contributions not used on premises, direct costs of financial support, and unit costs declared under budget category F if they include indirect costs.¹¹ See Annex 2a 'Additional information on the estimated budget' for the details (units, costs per unit).¹² See Annex 2a 'Additional information on the estimated budget' for the details (units, costs per unit, estimated number of units, etc).¹³ Only specific unit costs that do not include indirect costs.¹⁴ See Article 9 for beneficiaries not receiving funding.¹⁵ Only for linked third parties that receive funding.



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