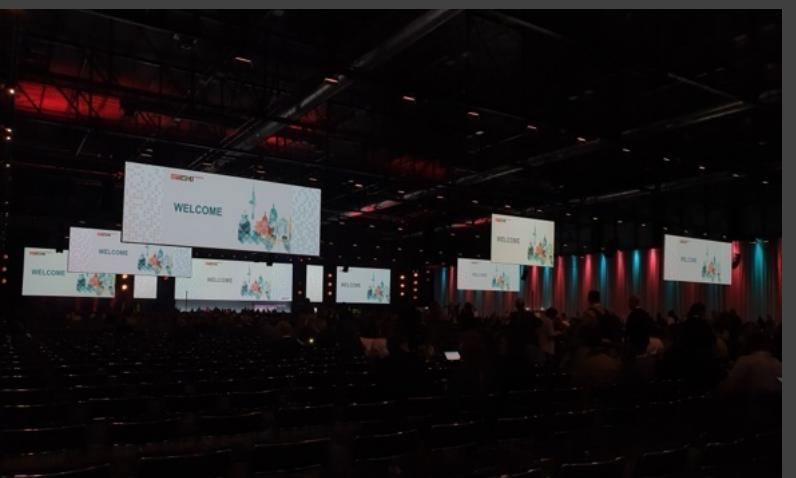
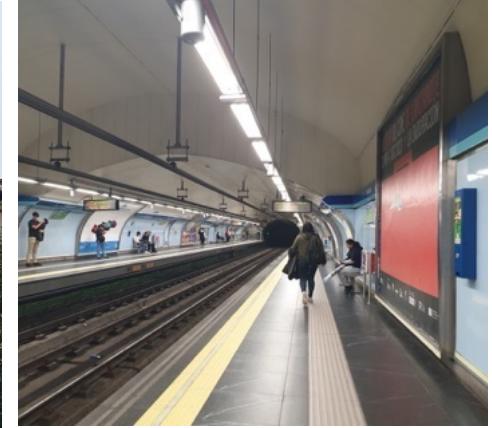
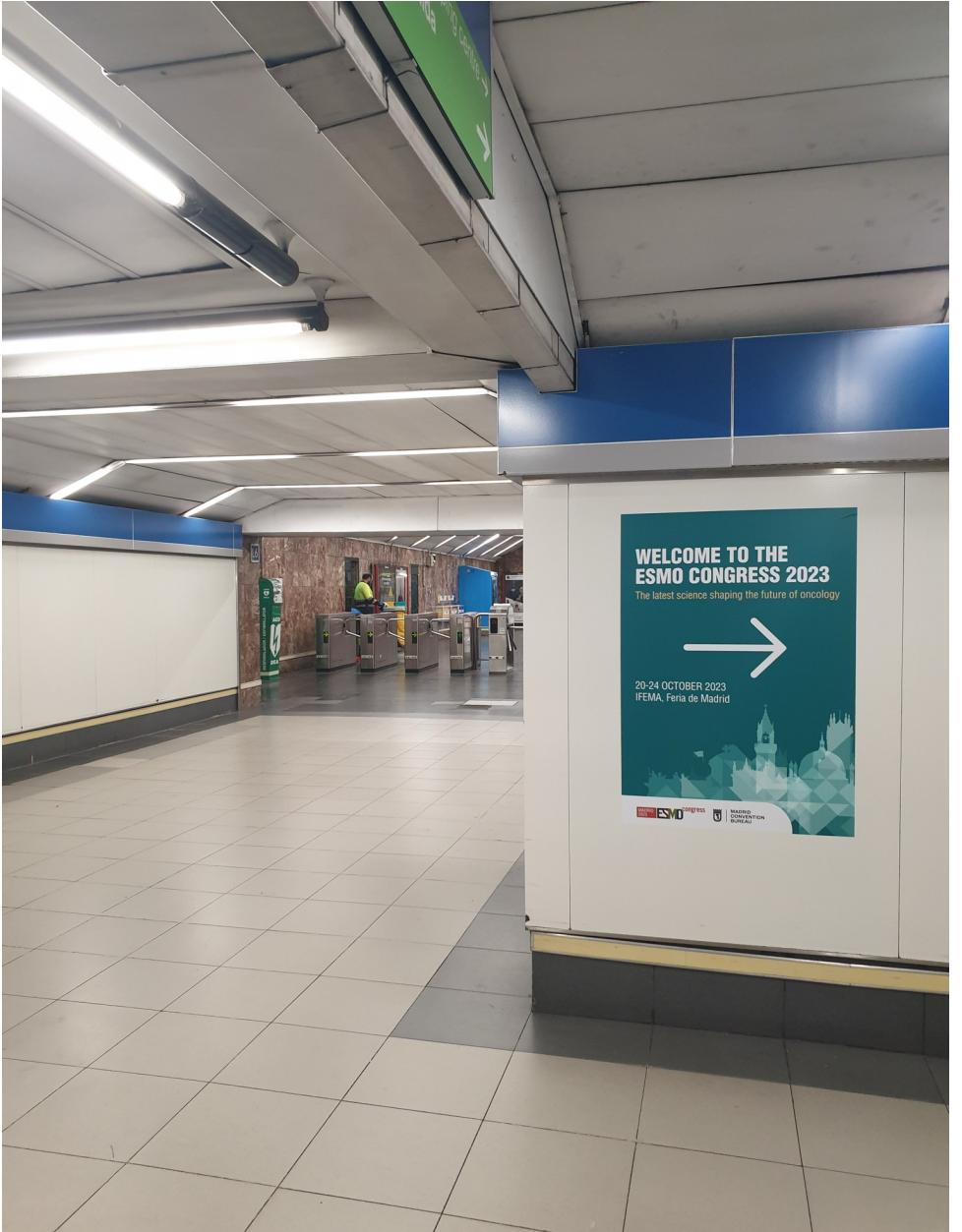


# Highlights from ESMO congress Madrid 2023

Group meeting November  
Synnøve Yndestad



- The ESMO Congress is a highly influential oncology platform for clinicians, researchers, patient advocates, journalists and healthcare industry representatives from all over the world.



**A Lot of presentations in ESMO.**

**In this presentation I decided to focus on:**

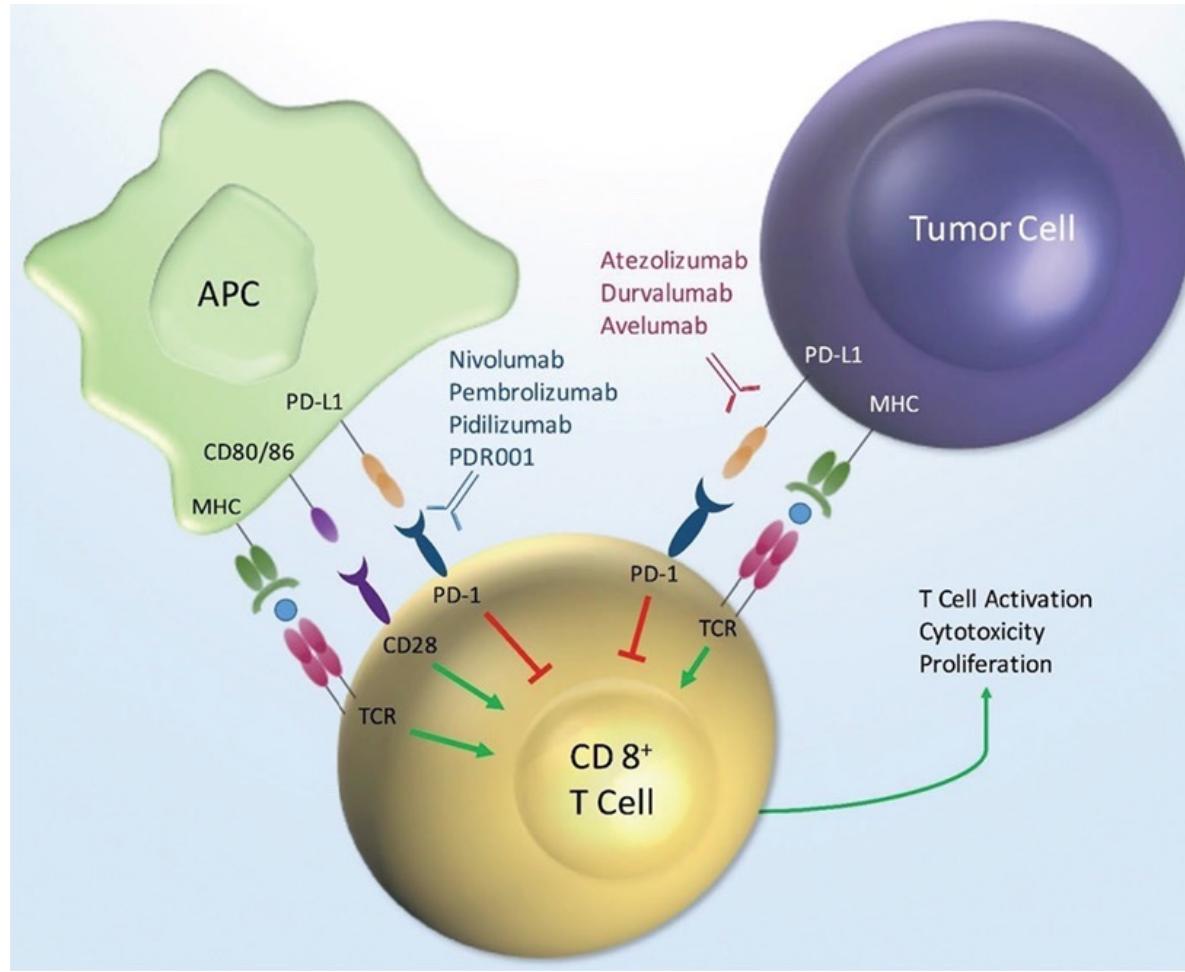
**New drugs and old drugs for a wider audience**

- Immunotherapy in TN and HR+ BC
- ADCs (30 oral presentations on ADCs)

**Basic science**

- ctDNA, Epigenomic liquid biopsy profiling
- Intronic variants
- Where does the discussion on HRD stand?

# Immunotherapy

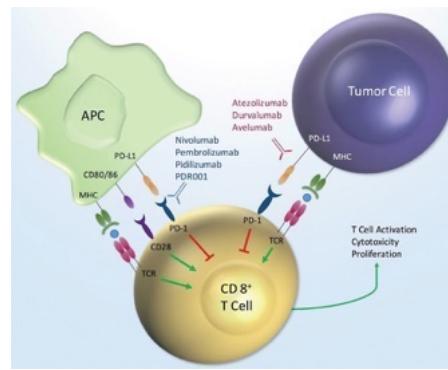


# Follow-up on Immunotherapy in TNBC

## PD-1 targeting

**KEYNOTE-522** - **Pembrolizumab** or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC.

EFS **benefit** with pembro was **consistent across subgroups**, including PD-L1 expression and nodal status.



## PD-L1 targeting

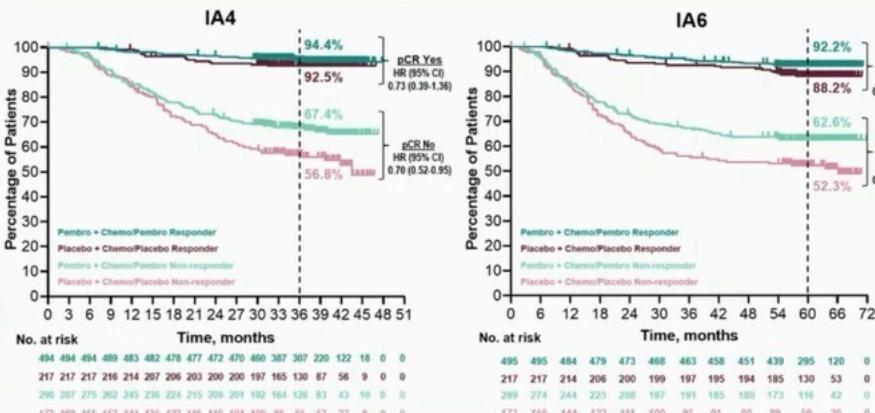
**NeoTRIP** high-risk, early-stage/locally advanced TNBC. Addition of **atezolizumab** to nab-paclitaxel/carboplatin gave minor increase of pCR (Gianni L et al, Annal Oncol 2022) At median follow-up of 54 months it did not improve EFS.

**PD-L1 expression** and higher **sTILs** at baseline were **prognostic** for better EFS, but not predictive of atezolizumab benefit.

14:00 - 15:40 Proffered Paper session - Breast cancer, early stage

### KEYNOTE-522

#### EFS by pCR (ypT0/Tis ypN0)

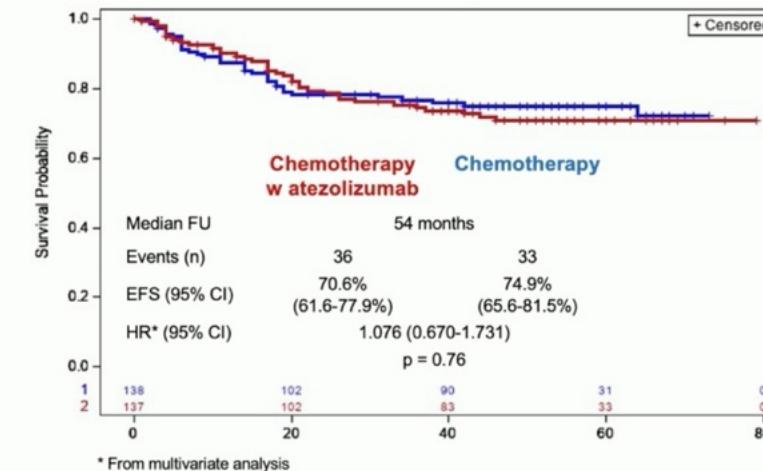


Peter Schmid

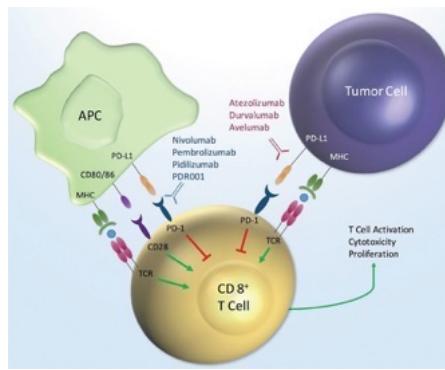
Pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: Updated EFS results from the phase III KEYNOTE-522 study

### NeoTRIP 5-yr Event Free Survival

#### ITT population



# Follow-up on Immunotherapy in TNBC



Negative, why?  
Different population?  
PDL1 inhibitor and not  
PD1 inhibitor?

## PD-1 targeting

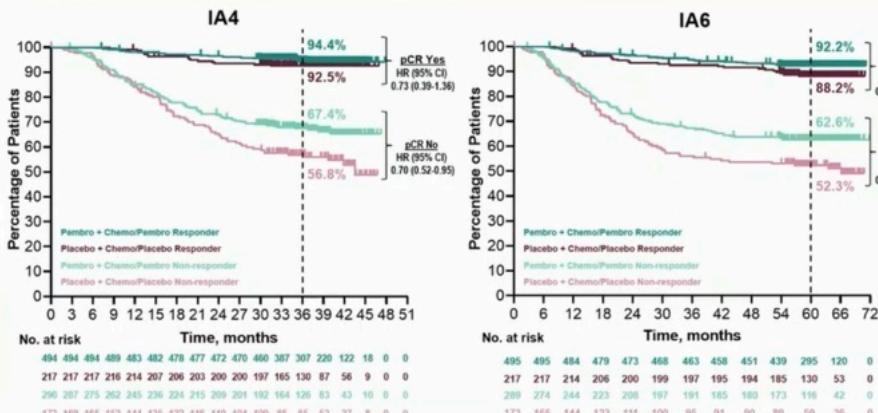
**KEYNOTE-522** - **Pembrolizumab** or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC.

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## KEYNOTE-522

### EFS by pCR (ypT0/Tis ypN0)



Peter Schmid

Pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: Updated EFS results from the phase III KEYNOTE-522 study

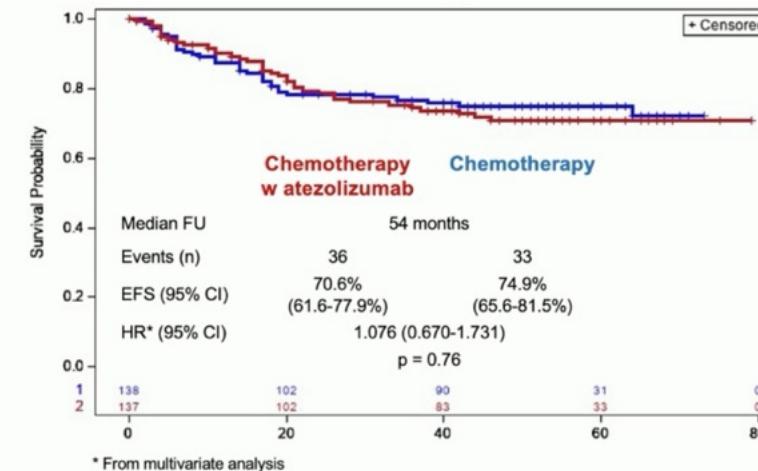
## PD-L1 targeting

**NeoTRIP** high-risk, early-stage/locally advanced TNBC.  
Addition of **atezolizumab** to nab-paclitaxel/carboplatin gave minor increase of pCR (Gianni L et al, Annal Oncol 2022)  
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**PD-L1 expression** and higher **sTILs** at baseline were **prognostic** for better EFS, but not predictive of atezolizumab benefit.

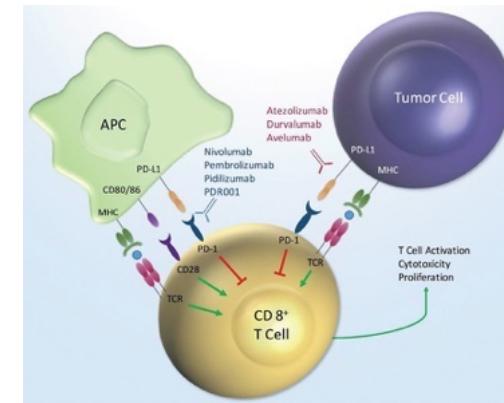
## NeoTRIP 5-yr Event Free Survival

ITT population



# A significant benefit of neoadjuvant immunotherapy in HR-positive early breast cancer shown for the first time

Two different PD-1 targeting mAb



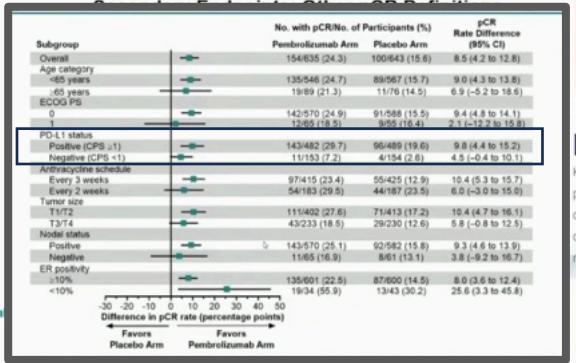
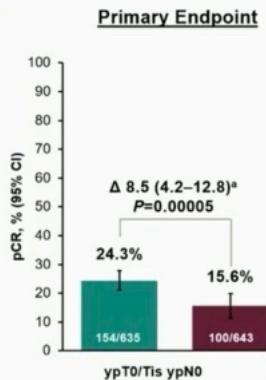
[KEYNOTE756](#) high-risk, early-stage ER+ breast cancer:  
Adding **pembrolizumab** to NAC increased pCR (ypT0/Tis ypNO) 8.5%, regardless of PD-L1 status

[CheckMate7FL](#) high-risk, ER+ early stage breast cancer—  
addition of **NIVOLUMAB** to NACT increased in pCR of 10.5%  
(24.5% in arm A vs 13.8% in arm B) Greatest benefit in PD-L1+

14:00 - 15:40 Proffered Paper session - Breast cancer, early stage

CHAIRS : STEPHEN JOHNSTON, SARA TOLANEY

## Pathological Complete Response at IA1



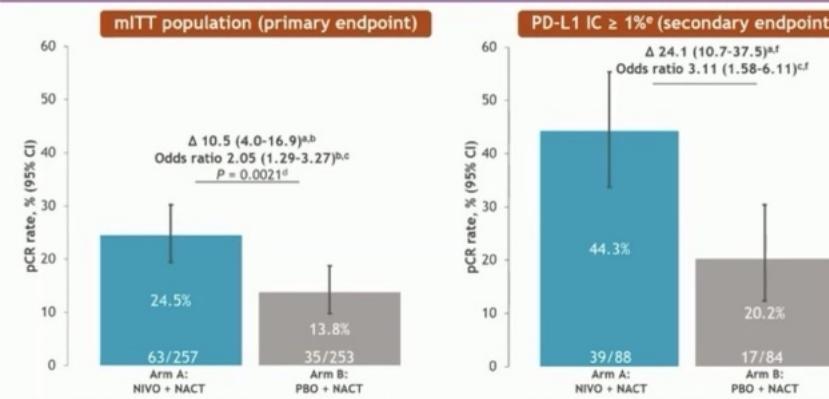
Fatima Cardoso

KEYNOTE-756: Phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2- breast cancer

14:00 - 15:40 Proffered Paper session - Breast cancer, early stage

CHAIRS : STEPHEN JOHNSTON, SARA TOLANEY

## pCR rate in mITT population and by PD-L1 IC ≥ 1%



Sherene Loi

A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER+ HER2- primary breast cancer (BC)

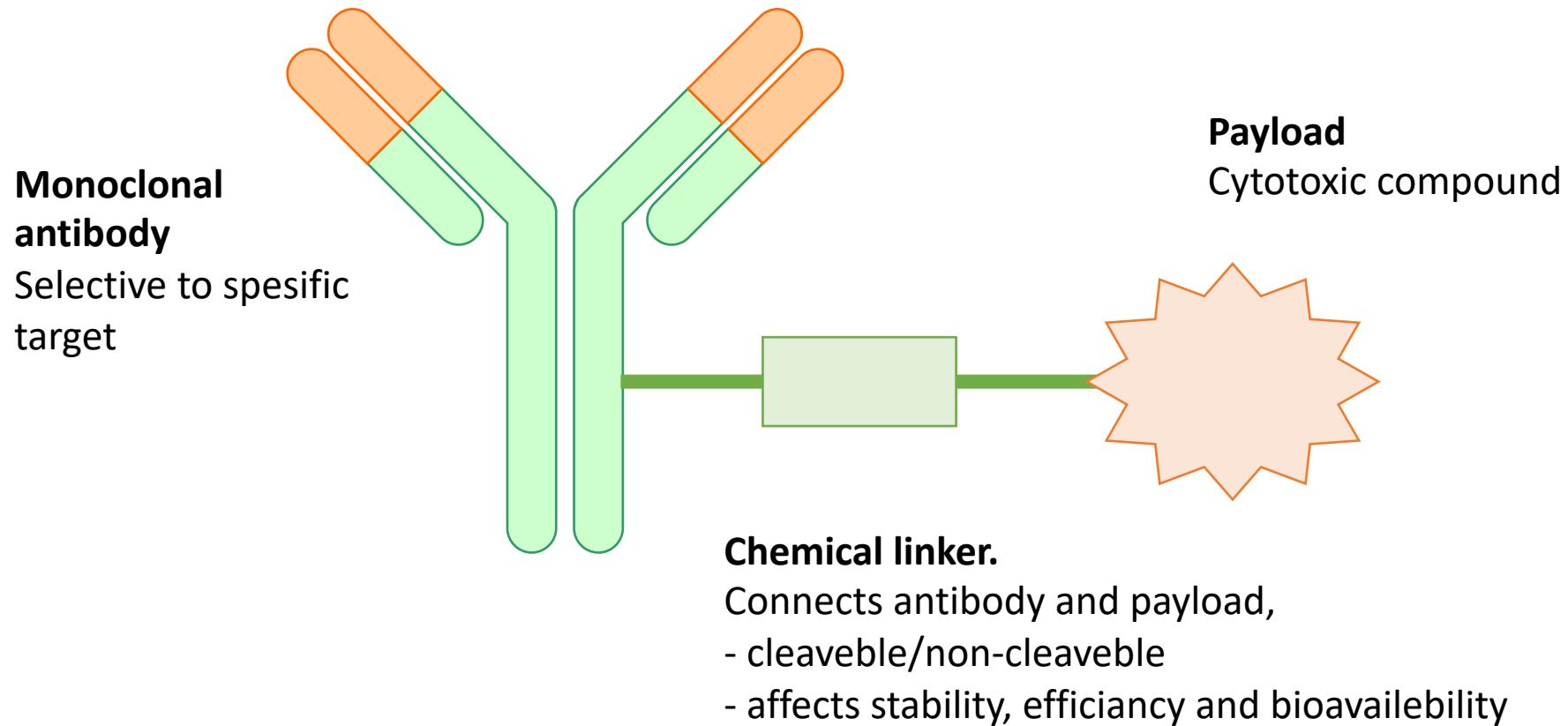
\*Estimated treatment difference based on Miettinen & Nurminen method stratified by the analysis randomization stratification factors. Data cutoff date: May 25, 2023.

<sup>a</sup>Strata-adjusted difference in pCR (Arm A–Arm B) based on Cochran-Mantel-Haenszel method of weighting. <sup>b</sup>Stratified by PD-L1 (≥ 1% vs < 1%) and AC dose-frequency chemotherapy regimen (Q2W vs Q3W) per IRT. <sup>c</sup>Strata-adjusted odds ratio (arm A vs arm B) using Mantel-Haenszel method. <sup>d</sup>Two-sided P value from stratified Cochran-Mantel-Haenszel test. <sup>e</sup>PD-L1 ICs and PD-L1-expressing tumor-infiltrating ICs as percentage of tumor area using the VENTANA SP142 assay. <sup>f</sup>Stratified by AC dose-frequency chemotherapy regimen.

AC, anthracycline + cyclophosphamide; CI, confidence interval; IC, immune cell; IRT, interactive response technology; mITT, modified intent-to-treat; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death ligand 1; Q3W, every 3 weeks.

10

# ADC: Antibody Drug Conjugates



## 10:15 - 11:45 AstraZeneca - Evolving Paradigms in Hormone Receptor-Positive Breast Cancer: The Rise of Antibody-Drug Conjugates

CHAIR : JAVIER CORTÉS

### New ADCs

- Antibody Characteristics:**
- High-affinity antibody
  - Chimeric/humanized lowers immunogenicity
  - Long half-life (affected by optimal DAR)
  - High molecular weight

mAb targets tumor-specific antigens

Tumor antigen internalized upon ADC binding

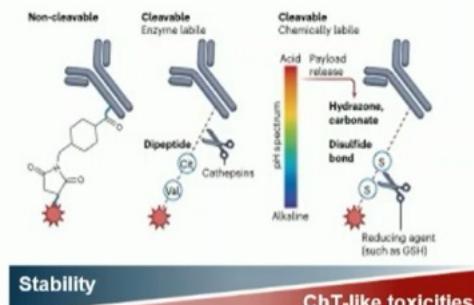
- Cytotoxic payloads:**
- Highly potent cytotoxics ( $IC_{50} < 1$  nmol)
  - Current payload class
  - DNA targeting (Topo I inhibitor)
  - Tubulin targeting (eg, MMAE, DM1)
  - Amenable to conjugation



Potent cytotoxic payload

Stable linker releases payload only in target cell

- Target Antigens:**
- Oncogenic driver (historic)
  - Antigens expressed on cancer cells
  - Antigens on tumor vasculature
  - Antigens in tumor stroma



**Linker characteristics:**

- Stable in circulation
- Efficient payload release at target site
- Cleavable vs noncleavable linker
- Site of conjugation (affects drug distribution)

DAR, drug to antibody ratio;  $IC_{50}$ , half-maximal inhibitory concentration; MMAE, monomethyl auristatin E; Topo I, topoisomerase I. Chau CH, et al. Lancet. 2019;394:793-804; Fu Z, et al. Signal Transduct Target Ther. 2022;7:93; Tarantino P, et al. Nat Rev Clin Oncol. 2023;20:558-576.

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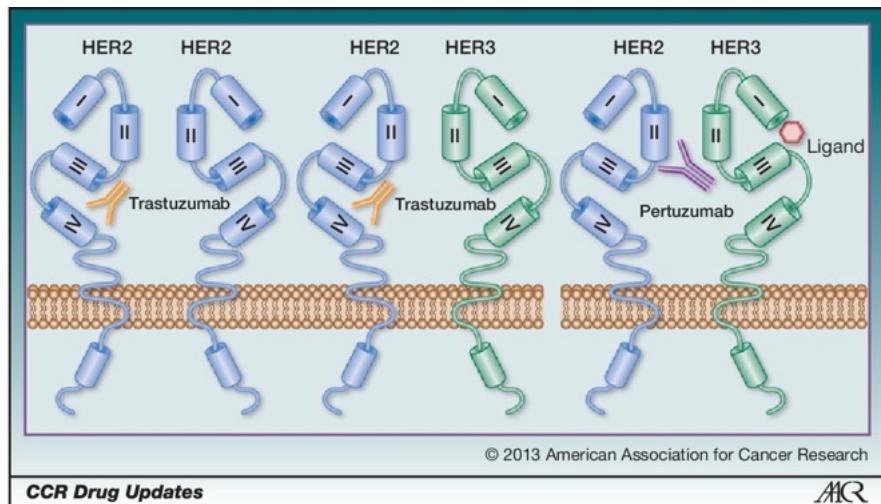
### Peter Schmid

New Antibody-Drug Conjugates on the Horizon

## Old mAb :

Inhibit dimerization of HER2:HER2 or HER2:Her3 to stop downstream Pi3K-Akt signalling

Targets oncogen



## New Antibody Drug Conjugates:

Bind to their target antigens and are internalized through receptor-mediated endocytosis.

Release of cytotoxins inside cell kill cancer cell

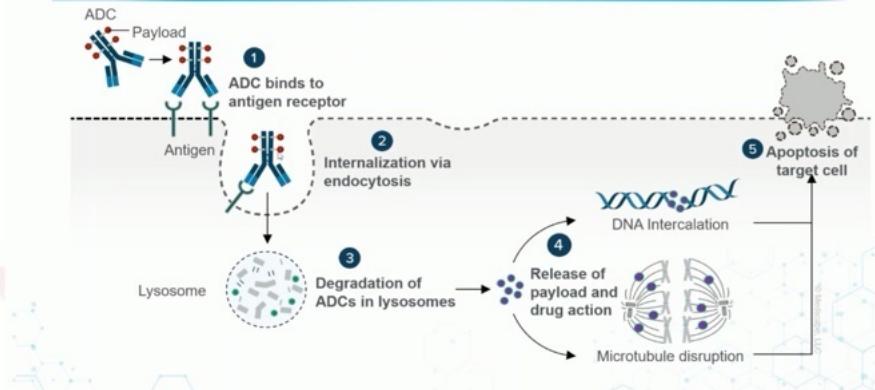
- Less toxic

- Targets antigens expressed on tumor cell/stroma/vasculature

18:30 - 20:00 Daiichi Sankyo - The Multi-Tumor Toolkit: ADCs in Cancer Therapy

CHAIR : BENJAMIN LEVY

### ADC Mechanism 1: mAb Engagement of Cell Surface Antigen

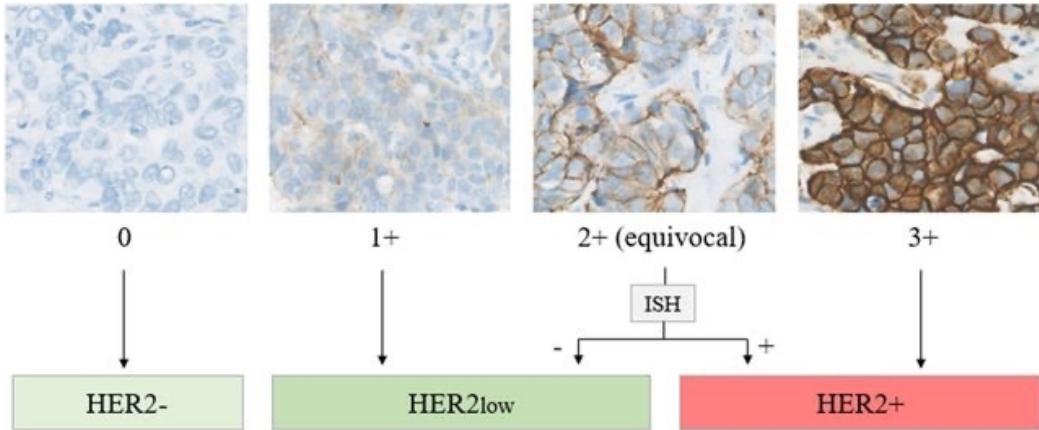


**Benjamin Levy**  
ADC technology in cancer therapy

### Select list of ADC payloads

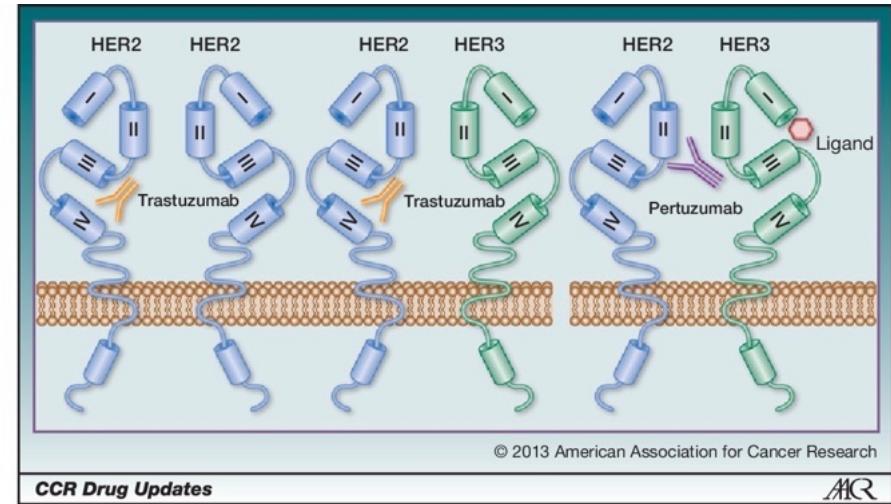
Payload class	Mechanism of action	Payload	Drug
Auristatin	Microtubule destabilizers	Vedotin (MMAE)	Telisotuzumab vedotin
Calicheamicin	Double-stranded DNA breaks	Ozogamicin	Gemtuzumab ozogamicin
Maytansinoid	Microtubule destabilizers	DM1	Trastuzumab emtansine (T-DM1)
Camptothecin	Topoisomerase 1 inhibitors	DXd	Trastuzumab deruxtecan (T-DXd)

# Who is eligible for HER2 targeted treatment?



Before: HER2+ only

Figure 1. The mechanism of action of pertuzumab and trastuzumab. Trastuzumab binds to the ECD IV of the HER2 receptor, preventing the spontaneous formation of homodimers (HER2-HER2) and ligand-independent heterodimers (HER2-HER3 and also HER2-HER1 and HER2-HER4). Pertuzumab binds to the dimerization domain of the HER2 receptor (ECD II), preventing the formation of ligand-induced HER2 heterodimers.



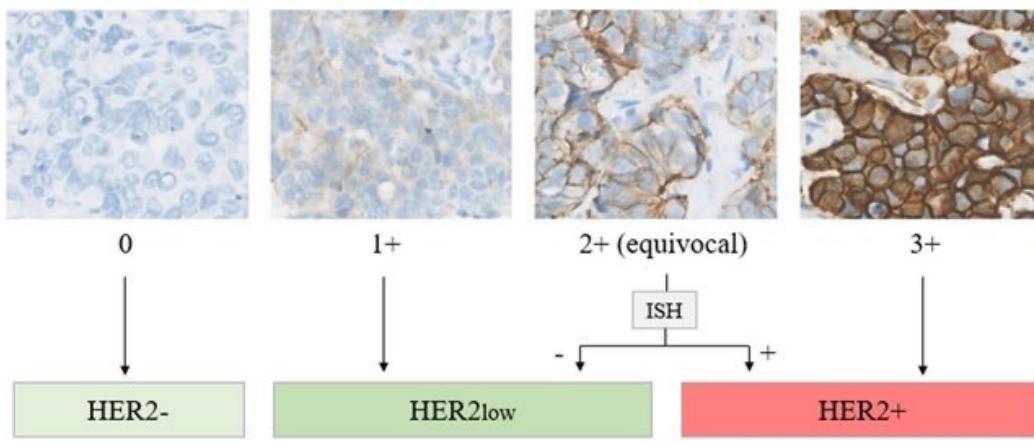
© 2013 American Association for Cancer Research

CCR Drug Updates

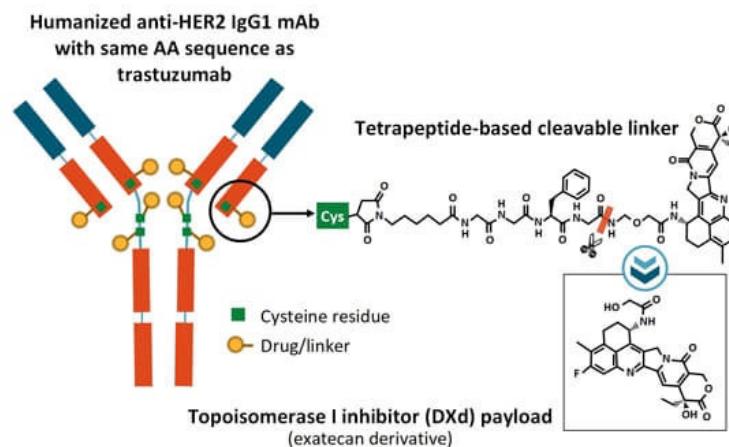


Clinical Cancer Research 19 (2013): 5552 - 5556.

Like in the PETREMAC study



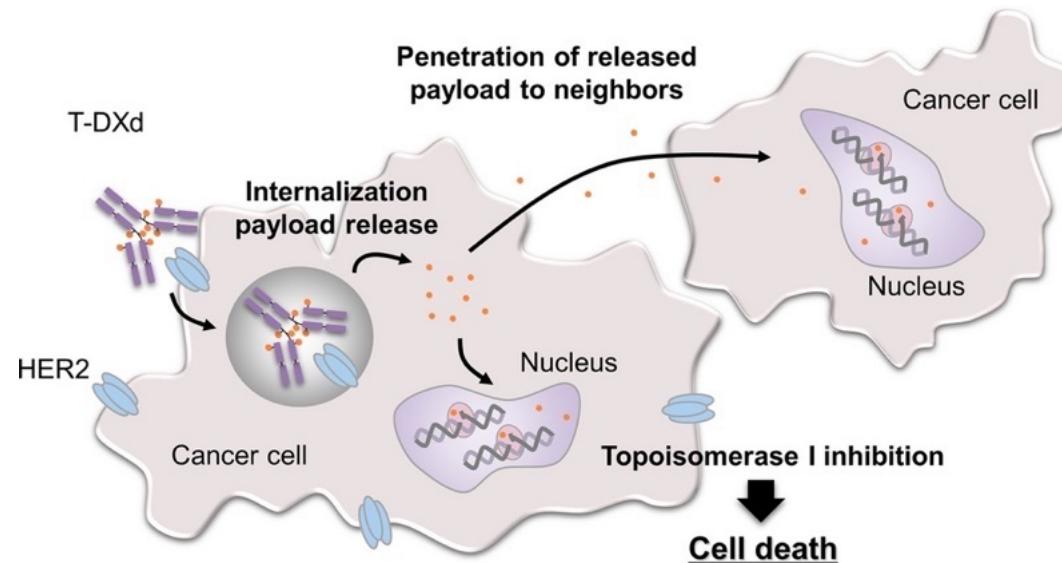
## HER2-Targeted ADC: Trastuzumab Deruxtecan



- High drug:antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

Can we also treat HER2-Low expressing tumors using HER2-targeting ADC??

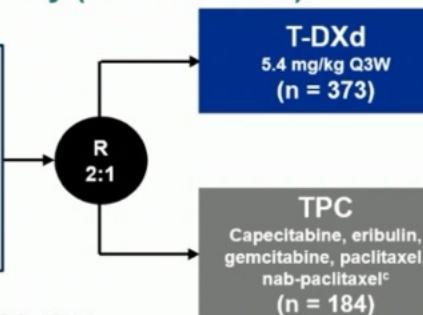


# DESTINY-Breast04 Study Design:

An open-label, multicenter study (NCT03734029)<sup>1-3</sup>

**Patients<sup>a</sup>**

- HER2-low (IHC 1+ or IHC 2+/ISH-), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

**Stratification factors**

- Centrally assessed HER2 status<sup>b</sup> (IHC 1+ vs IHC 2+/ISH-)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR-

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

**Primary endpoint**

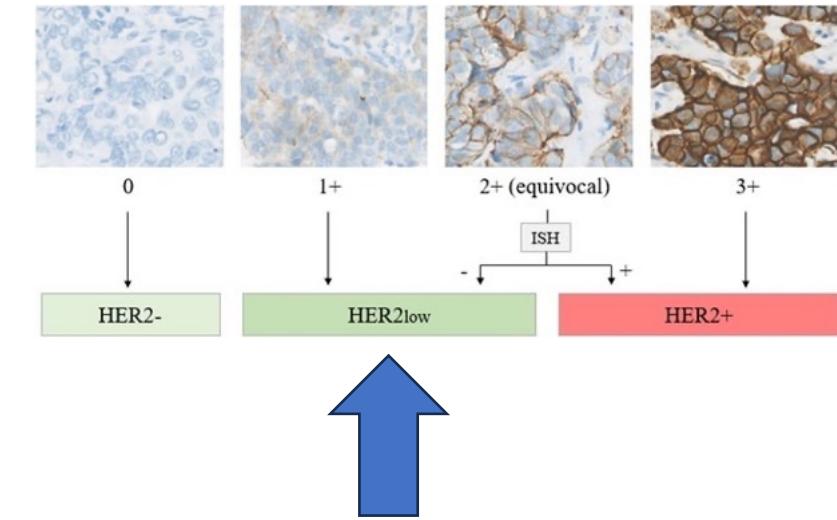
- PFS by BICR (HR+)

**Key secondary endpoints<sup>d</sup>**

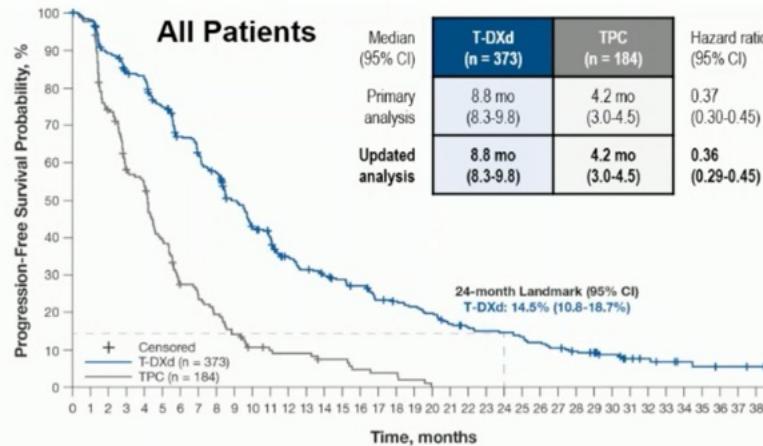
- PFS by BICR (all patients)
- OS (HR+ and all patients)

**Secondary endpoints<sup>d</sup>**

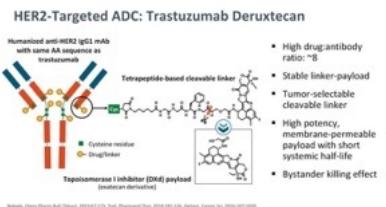
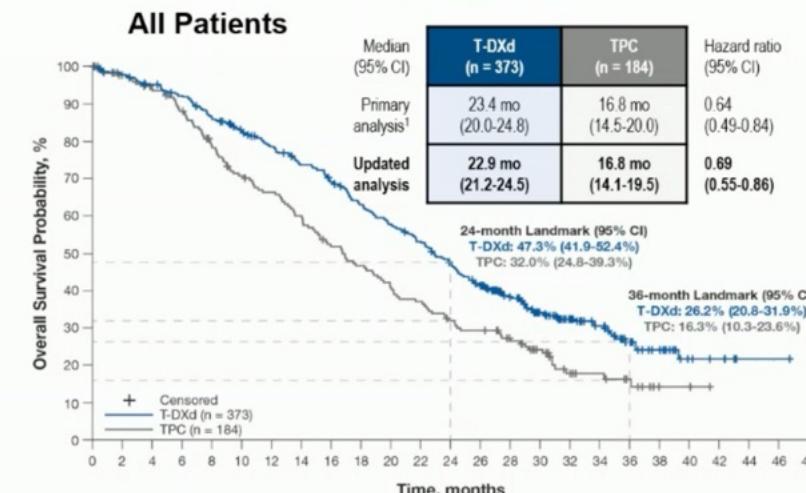
- PFS by investigator
- ORR by BICR and investigator
- DOOR by BICR
- Safety
- Patient-reported outcomes (HR+)<sup>e</sup>



## Progression-Free Survival



## Overall Survival



Trastuzumab deruxtecan  
= Enhertu  
Approved EU Jan 2023 for  
HER2-low

## Patients still at risk:

T-DXd (n = 373): 373 364 357 350 297 297 254 210 190 160 140 130 127 97 90 85 79 77 64 40 39 38 31 27 23 21 10 11 7 5 4 3 2 0

TPC (n = 184): 184 170 165 160 156 152 145 137 127 119 113 107 105 100 96 86 81 79 73 69 64 59 53 49 45 44 37 33 27 19 15 12 10 6 5 2 2 1 0

## Patients still at risk:

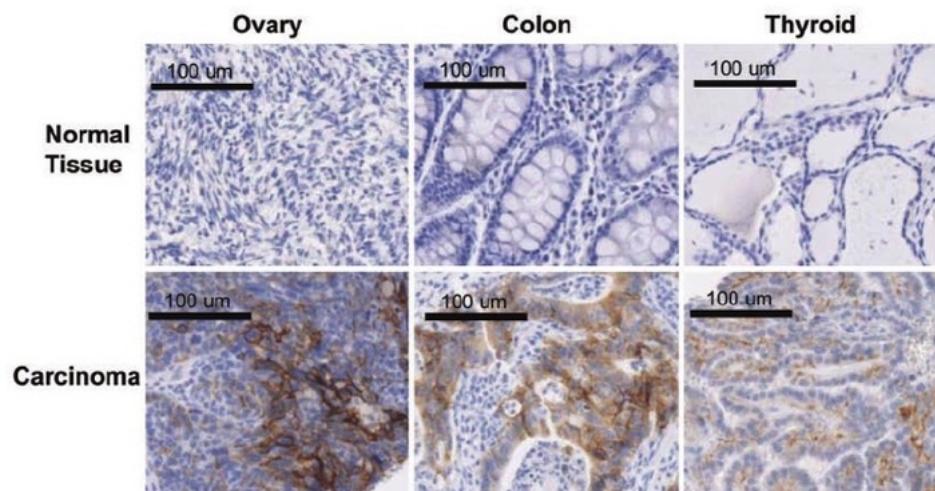
T-DXd (n = 373): 373 346 343 309 300 342 337 326 314 309 306 289 276 269 257 254 240 231 217 209 199 191 182 186 180 148 137 122 107 94 81 75 72 62 48 39 28 21 19 11 7 6 5 3 1 1 0

TPC (n = 184): 184 170 165 160 156 152 145 137 127 119 113 107 105 100 96 86 81 79 73 69 64 59 53 49 45 44 37 33 27 19 15 12 10 6 5 2 2 1 0

Results from the 32-month median follow-up for DESTINY-Breast04 confirm the sustained clinically meaningful improvement for T-DXd vs TPC previously demonstrated in HER2-low (IHC 1+, IHC 2+/ISH-) mBC, regardless of HR status

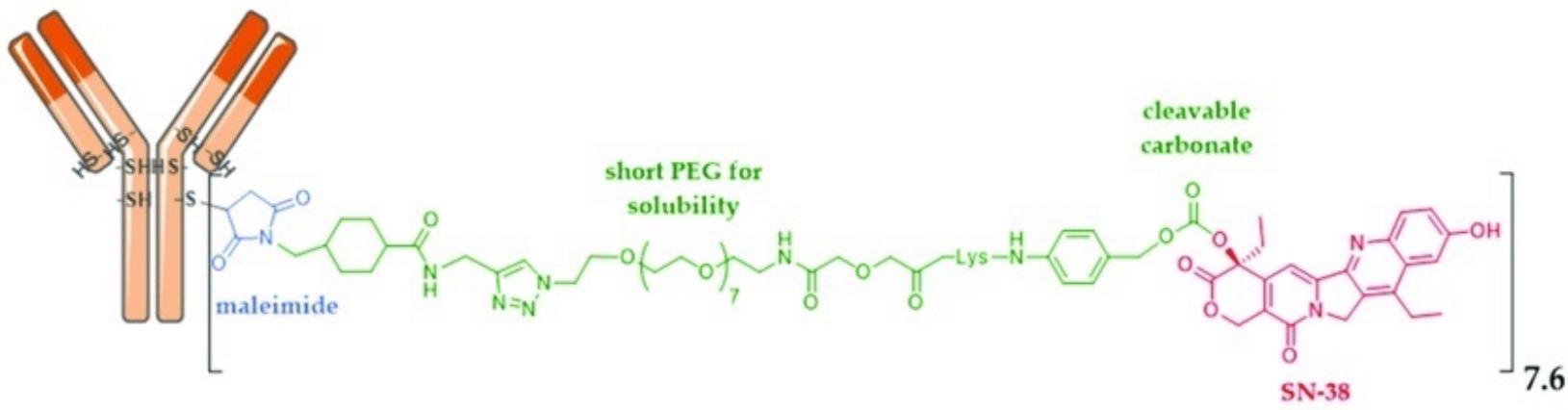
# New(er) target: TROP2

- Cell-surface glycoprotein
- Highly expressed in cancer cells
- Low expression in normal tissue
- Not an oncogenic driver



Trop2 is highly expressed on human ovarian, colonic and thyroid carcinomas, but is not detected on the corresponding normal tissues.

DOI:10.1369/0022155411410430



anti-TROP2 Trodelvy® (sacituzumab govitecan or IMMU-132)

April 23, 2020, [Trodelvy \(Sacituzumab govitecan\)](#), the first ADC drug targeting Trop-2, received accelerated approval from the FDA for the treatment of unresectable locally advanced or metastatic TNBC

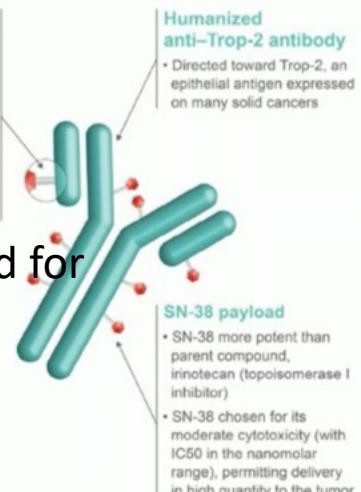
CHAIRS : FABRICE ANDRÉ, SILKE GILLESSEN

## ADCs anti-Trop2 in HR+/HER2- mBC

	Sacituzumab-gov. (n=272)	Datopotamab-DXd (n=365)	SKB264 (MK-2870) (n=38)
Payload	Anti-TOPO1	Anti-TOPO1	Anti-TOPO1
DAR	7.6	4	7.8
Trial	Ph3 RCT (TROPiCS-02)	Ph3 RCT (TROPION-Breast01)	Single arm Ph1-2

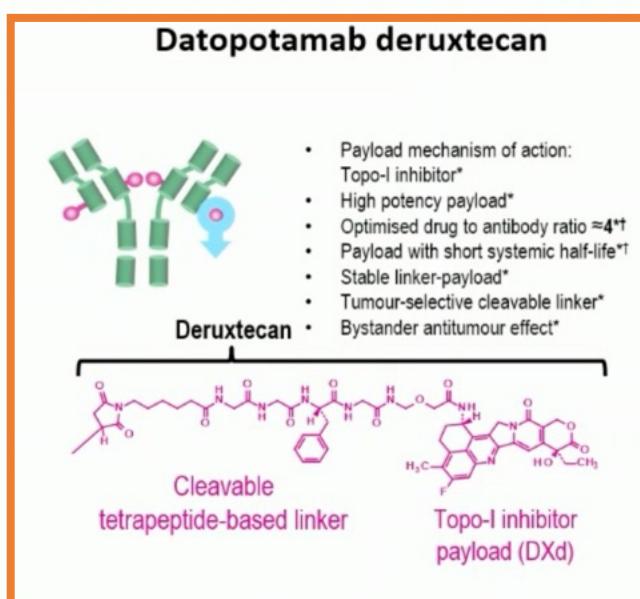
### Sacituzumab govitecan

- Linker for SN-38
- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)

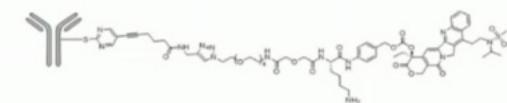


Approved for  
mTNBC

Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody



### SKB264 (MK-2870)



- anti-TROP2 ADC
- Sulfonyl pyrimidine-CL2A-carbonate linker
- Payload:** belotecan-derivative topoisomerase I inhibitor
- DAR:** 7.4



**Giuseppe Curigliano**

Breast cancer, metastatic

**LBA11 - Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer (BC): Primary results from the randomised phase III TROPION-Breast01 trial**

Aditya Bardia (Boston, United States of America)

## TROPION-Breast01 Study Design<sup>1</sup>

Randomised, phase 3, open-label, global study (NCT05104866)

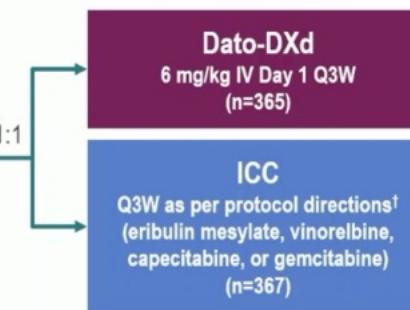
### Key inclusion criteria

Patients with HR+/HER2- breast cancer\* (HER2- defined as IHC 0/1+/2+; ISH negative)

Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)

Experienced progression on ET and for whom ET was unsuitable

ECOG PS 0 or 1



1:1

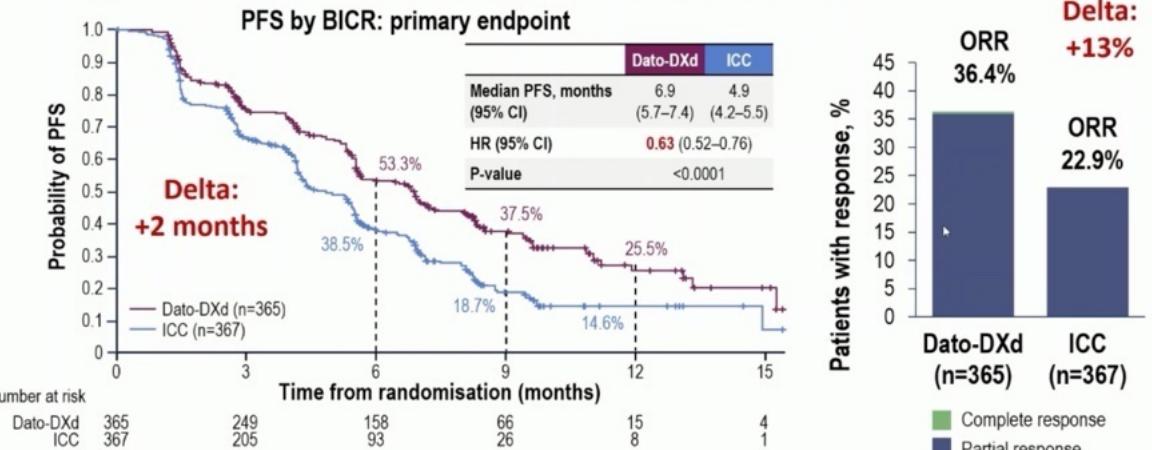
### Endpoints:

- Dual primary:** PFS by BICR per RECIST v1.1, and OS
- Key secondary:** ORR, PFS (investigator assessed) and safety

### Randomisation stratified by:

- Lines of chemotherapy in unresectable/metastatic setting (1 vs 2)
- Geographic location (US/Canada/Europe vs ROW)
- Previous CDK4/6 inhibitor (yes vs no)
- Treatment continued until investigator-assessed PD (RECIST v1.1), unacceptable tolerability, or other discontinuation criteria
- At this data cut-off, the criteria for performing the primary PFS analysis were met (~419 events)

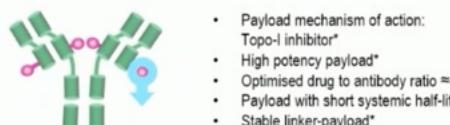
## Progression-Free Survival and Response Rate



OS data were not mature: a trend favouring Dato-DXd was observed, HR 0.84 (95% CI 0.62–1.14)

## Datopotamab deruxtecan

### Anti-TROP2



- Payload mechanism of action: Topo-I inhibitor\*
- High potency payload\*
- Optimised drug to antibody ratio ≈4†
- Payload with short systemic half-life\*†
- Stable linker-payload\*
- Tumour-selective cleavable linker\*
- Bystander antitumour effect\*

Practice changing results for metastatic ER+ BC

## ADCs anti-Trop2 in HR+/HER2- mBC

	Sacituzumab-gov. (n=272)	Datopotamab-DXd (n=365)	SKB264 (MK-2870) (n=38)
Payload	Anti-TOPO1	Anti-TOPO1	Anti-TOPO1
DAR	7.6	4	7.8
Trial	Ph3 RCT (TROPICS-02)	Ph3 RCT (TROPION-Breast01)	Single arm Ph1-2
Age, median (range), years	57 (29-86)	56 (29-86)	50 (34-66)
ECOG PS 0, %	43%	54%	40%
Prior lines of chemotherapy, median	3	1	2
Prior CDK4/6 inhibitor, %	98%	82%	66%
Prior taxane and/or anthracycline, %	64%	65%	100%
ORR, %	21%	36%	37%
Median PFS, months - HR	5.5 vs. 4.0 HR: 0.65 (95% CI 0.53-0.81)	6.9 vs. 4.9 HR: 0.63 (95% CI 0.52-0.76)	11.1
Median OS, months - HR	14.5 vs. 11.2 HR 0.79 (0.65-0.95)	Not mature	NR
Median FUP, months	12.7	10.8	8.2
Treatment discontinuation due to TRAE, %	6%	3%	0%
Oral mucositis/stomatitis - all grades   G3, %	NA	59%   7%	46%   2%
Drug-related ILD - all grades   G3, %	NA	3%   1%	0%   0%

ESMO congress

Giuseppe Curigliano, MD PhD

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Giuseppe Curigliano

Breast cancer, metastatic

Barcelona Auditorium - Hall 9

MADRID SPAIN 20-24 OCTOBER 2023

## My thoughts about ADCs in HR+/HER2- mBC

- Longer T-DXd exposure does not increase toxicity!
- ADCs anti-Trop2 demonstrated to improve clinical outcomes after 3 lines of CT (Sacituzumab govitecan) and in less pre-treated patients, i.e. after 1 line of CT (Datopotamab deruxtecan)
- In pts with HR+/HER2low mBC after 1 line of CT:
  - T-DXd provides a higher magnitude of clinical benefit than Dato-DXd, in terms of PFS (PFS  $\Delta$ : 4 vs. 2 months) and ORR (ORR  $\Delta$ : 36% vs. 13%) across similar patient population
  - T-DXd remains the standard of care in HR+/HER2low mBC after 1 line of CT
- After T-DXd or in HER2-zero disease, anti-Trop2 ADCs are my first choice:
  - Which is the best option after T-DXd between Dato-DXd (same payload) or Sacituzumab govitecan (different payload but same mechanism of action, anti-TOPO1)?

ESMO congress

Giuseppe Curigliano, MD PhD

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Giuseppe Curigliano

Breast cancer, metastatic

Barcelona Auditorium - Hall 9

MADRID SPAIN 20-24 OCTOBER 2023

## My thoughts about ADCs in HR+/HER2- mBC

**Patients with ER+/HER2- MBC**  
PD on CDK4/6i and 2L oral combinations

ChT (capecitabine is my 1<sup>st</sup> choice)

PD

If HER2-0

Sacituzumab govitecan  
[I, A; MCBS 3]  
Datopotamab deruxtecan  
[I, NA; MCBS @@]

Trastuzumab deruxtecan  
[I, B; MCBS 4]

Sacituzumab govitecan  
[I, A; MCBS 3]  
Datopotamab deruxtecan  
[I, NA; MCBS @@]

ChT

If HER2low

Sacituzumab govitecan  
[I, A; MCBS 3]  
Datopotamab deruxtecan  
[I, NA; MCBS @@]

ChT

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ESMO congress

Giuseppe Curigliano, MD PhD

ESMO congress

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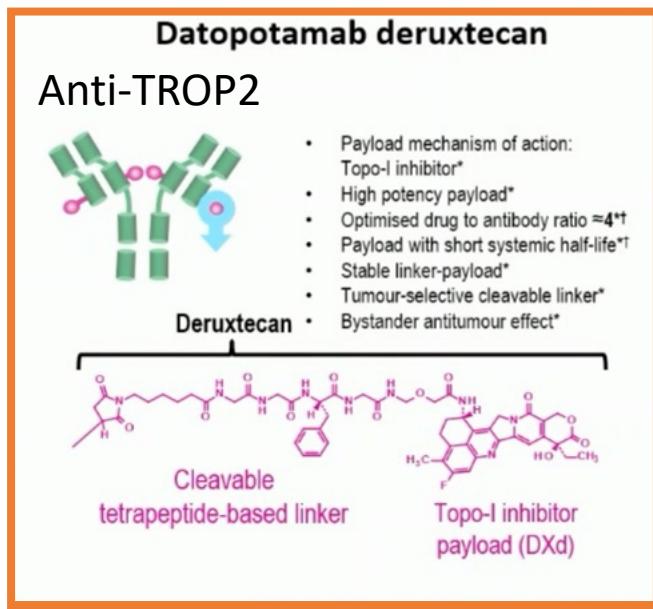
Giuseppe Curigliano

Breast cancer, metastatic

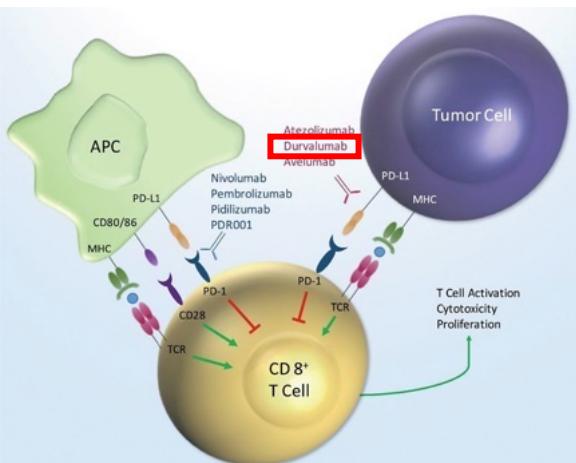
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MADRID SPAIN 20-24 OCTOBER 2023

# ADC + immunotherapy in mTNBC



Durvalumab = anti-PD-L1



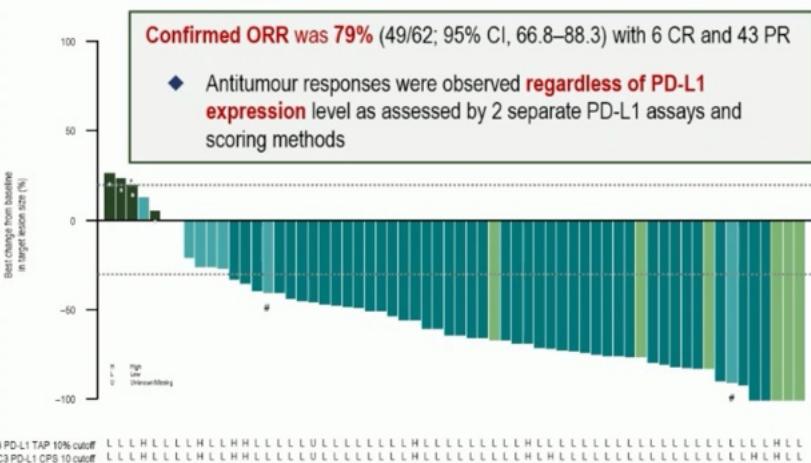
379MO - **Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC):**

**Updated results from BEGONIA, a phase Ib/II study**

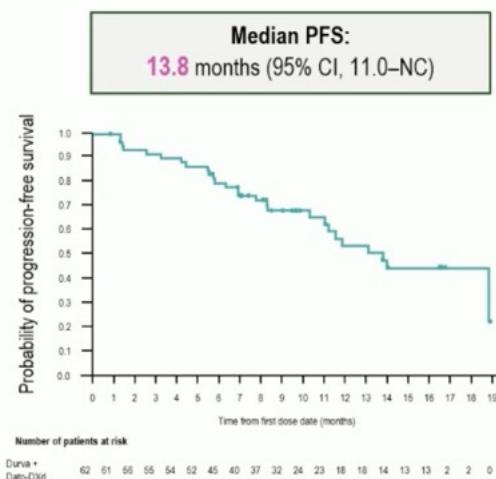
Peter Schmid (London, United Kingdom)

## BEGONIA Arm 7: Dato-DXd + Durvalumab

### Antitumour Responses in 1L a/mTNBC



### Progression-Free Survival



**Dato-DXd + durvalumab continues to demonstrate robust, durable responses in first-line a/mTNBC in a biomarker-unselected population with median 11.7 months of follow-up**

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2023 ESMO Congress

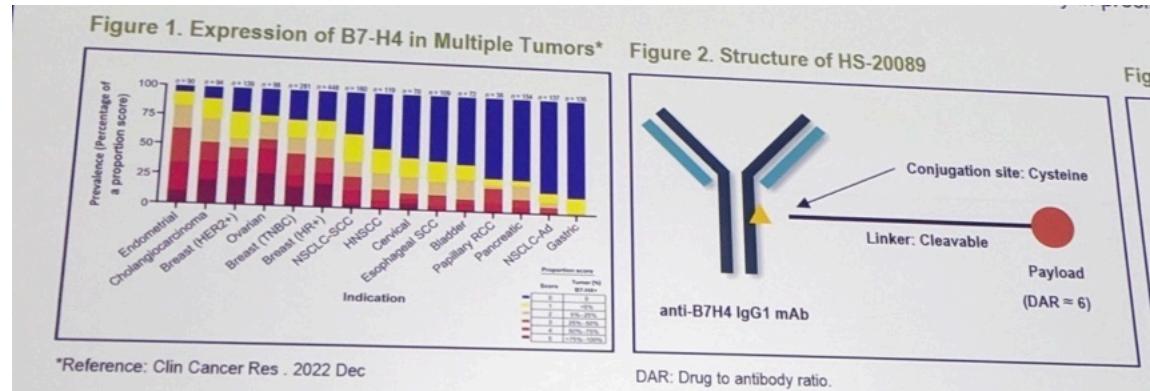
Giuseppe Curigliano, MD PhD

Data cutoff: 02 Feb 2023

# 3810 - First-in-human/phase I trial of HS-20089, a B7-H4 ADC, in patients with advanced solid tumors Jian Zhang (Shanghai, China)

Patients failed on PARPi and/or PDL1/PD1 inhibitors

- B7 homolog 4 protein (B7-H4), a transmembrane glycoprotein highly expressed in various solid tumors (highest in TNBC, Endometrial and Ovarian Cancer ) and low expression in normal tissue
- HS-20089 is a novel B7-H4 targeting ADC.
- Payload: Topoisomerase inhibitor via a protease-cleavable linker.
- Drug was safe and tolerable
- 27% ORR in advanced TNBC at dose 5.8mg/kg



DAR: Drug to antibody ratio.

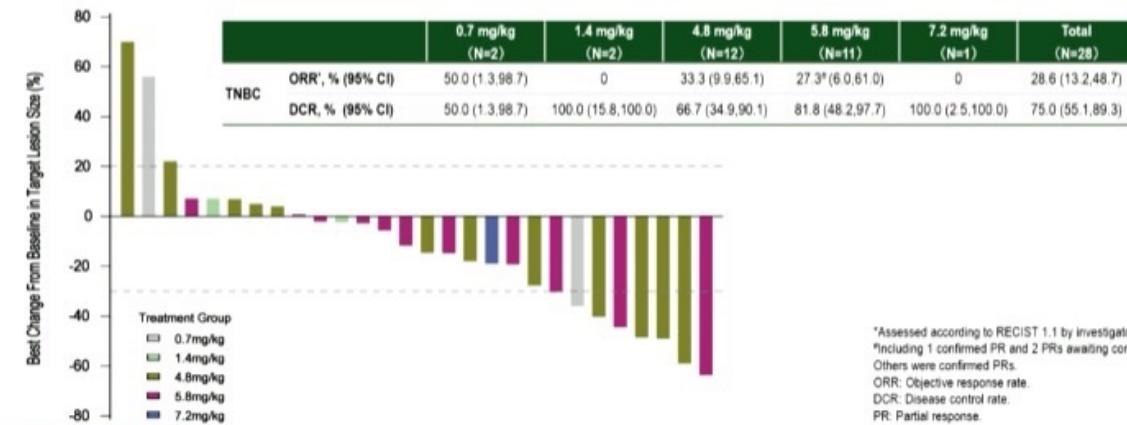
MADRID ESMO congress

B7-H4 targeting ADC

## Efficacy - TNBC

- HS-20089 showed promising anti-tumor activity in triple-negative breast cancer (TNBC).
- At potential target therapeutic doses of 4.8 and 5.8 mg/kg, the ORR were 33.3% and 27.3%, respectively.

Figure 5. Best Percent Change of Target Lesions in TNBC



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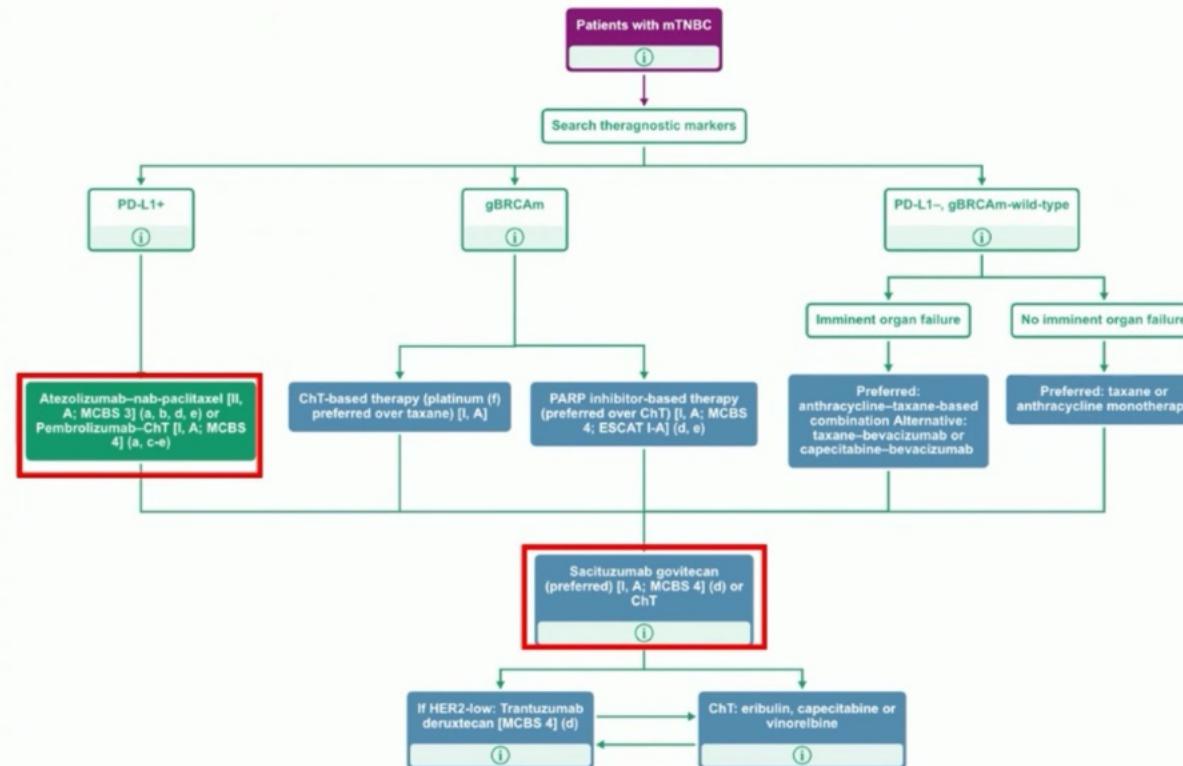
Clinical cutoff: August 17, 2023

## Triple-negative Metastatic Breast Cancer

Novel agents which provides an OS benefit:

- Anti-PD-(L)1
- Sacituzumab govitecan

B7H4 ADC only phase I

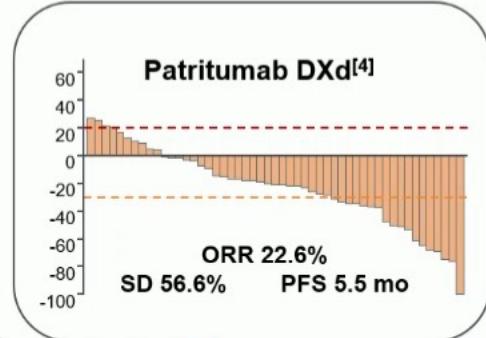
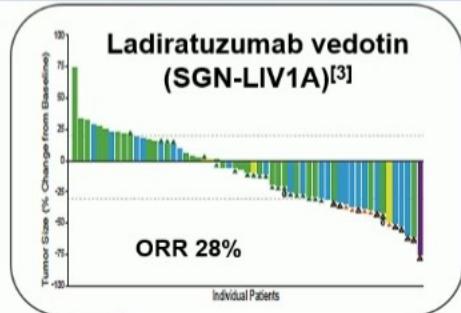
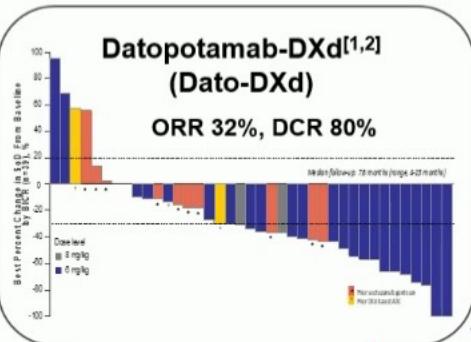


G Curigliano, Living Guidelines, ESMO Breast 2023

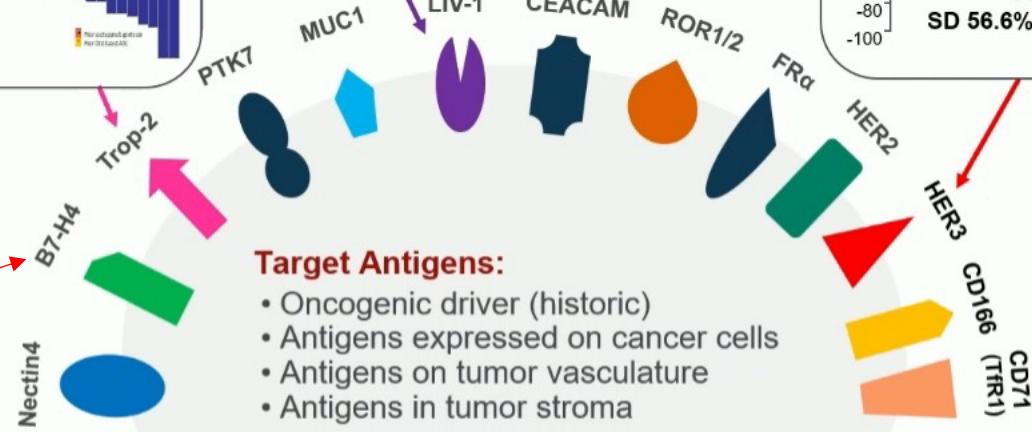


**Giuseppe Curigliano**  
Breast cancer, metastatic

# Targets for ADCs in Breast Cancer



HS-20089



1. Bardia A, et al. Cancer Res. 2023;83(5\_Supplement):P6-10-03; 2. Krop I, et al. Cancer Res. 2022;82(4 suppl):GS1-05; 3. Tsai M, et al. Ann Oncol. 2021;32(suppl 5):S457-S515; 4. Krop I, et al. J Clin Oncol. 2022;40(16 suppl):1002.

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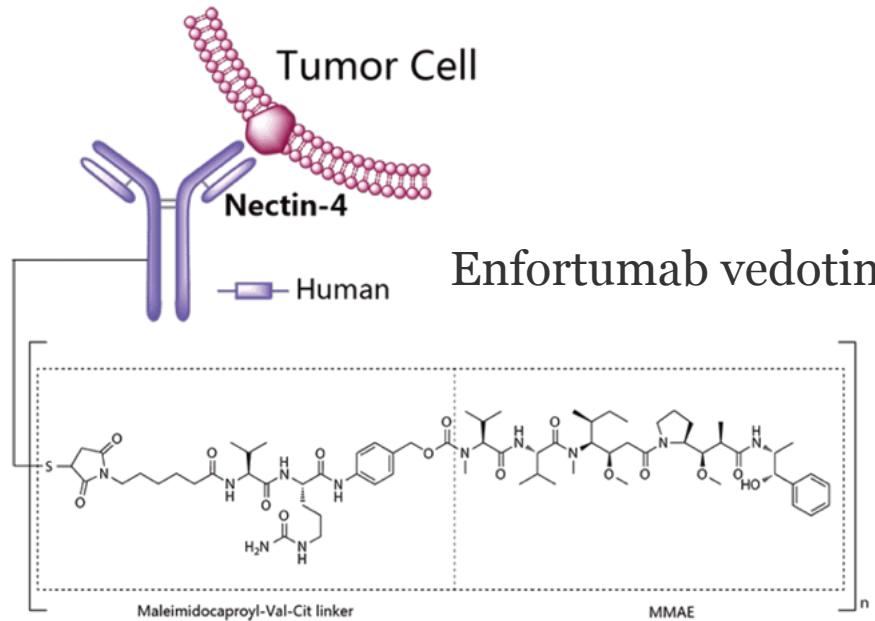


**Peter Schmid**

New Antibody-Drug Conjugates on the Horizon

EV-302/KEYNOTE-A39: Open-label, randomized phase 3 study of **enfortumab vedotin** in combination with **pembrolizumab (EV+P)** vs chemotherapy (chemo) in previously untreated locally advanced **metastatic urothelial carcinoma (la/mUC)**.

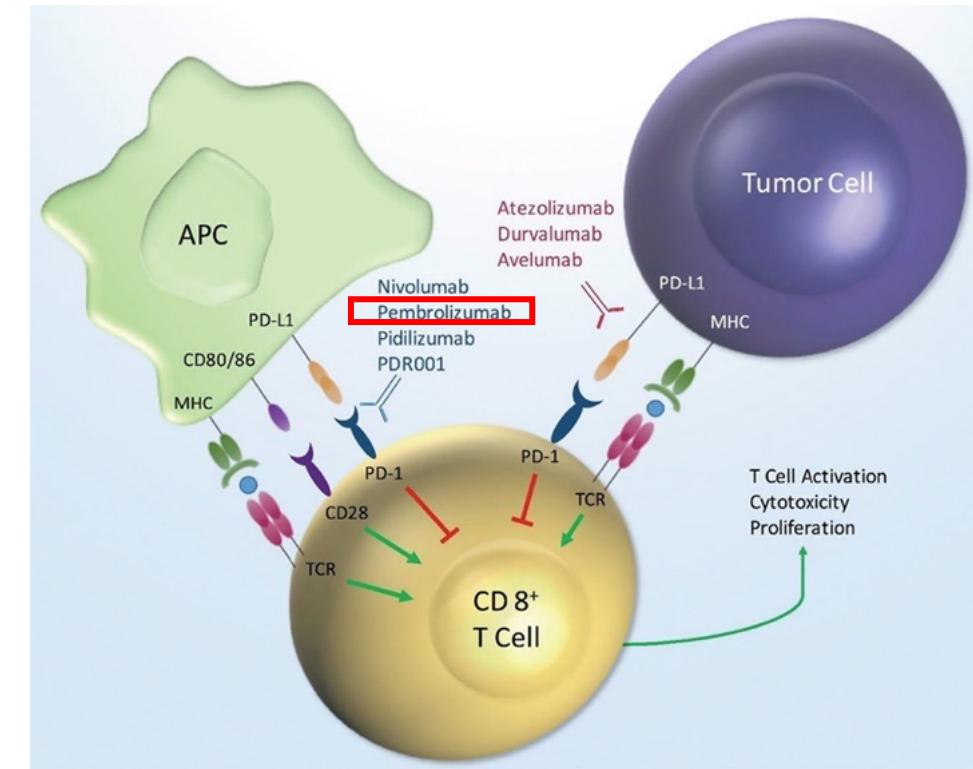
Powles TB, et al.



### Nectin-4 mAB

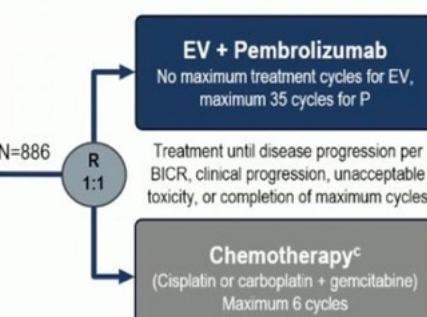
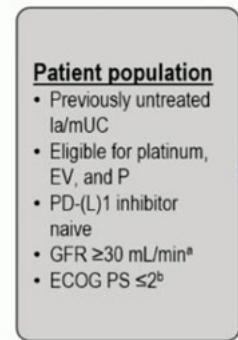
#### Payload:

Microtubule-disrupting chemotherapeutic agent, monomethyl auristatin E (MMAE), joined by a protease-cleavable link.



Pembrolizumab =  
PD-1 targeting

# EV-302/KEYNOTE-A39 (NCT04223856)



**Dual primary endpoints:**

- PFS by BICR
- OS

**Select secondary endpoints:**

- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

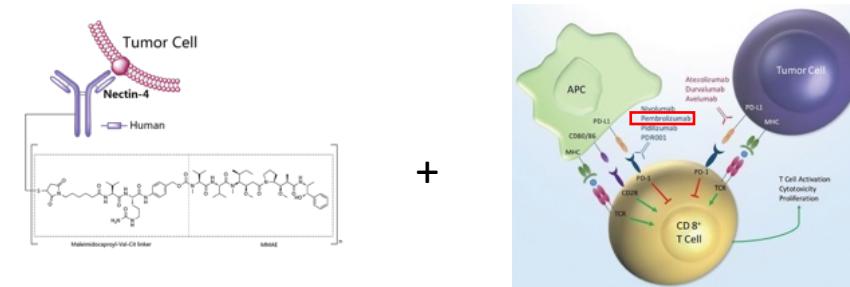
Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

The first trials to challenge the standard of first-line platinum-based chemotherapy for patients with advanced/metastatic urothelial carcinoma.

**"This combination will clearly become the new standard of cancer care for this cohort of patients"**

Dr. A. Apolo.



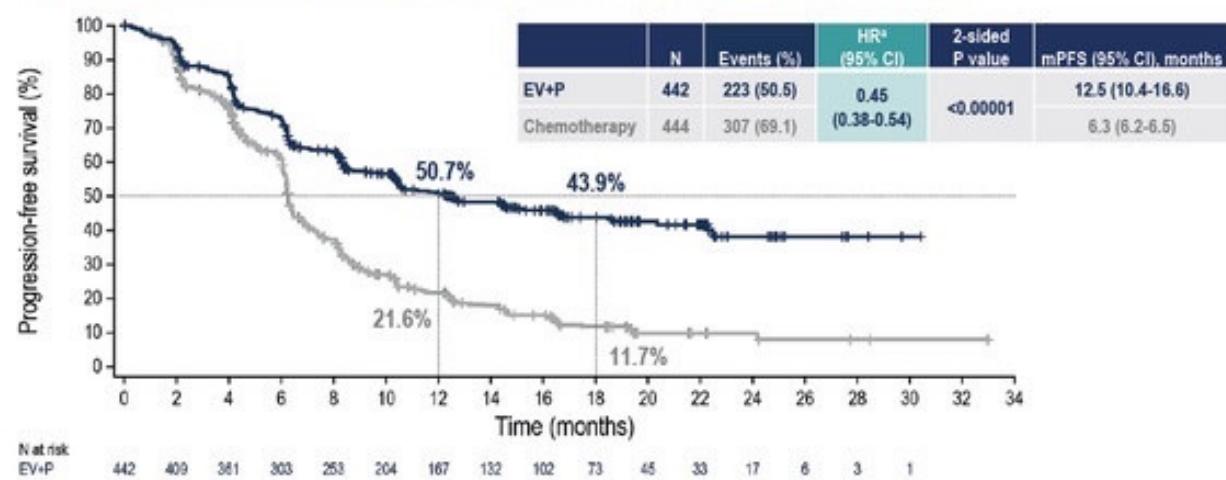
+

## Enfortumab vedotin + pembrolizumab

- almost doubled median progression-free survival (PFS) (12.5 months versus 6.3 months)
- significant increase in the overall response rate compared with chemotherapy (67.7% versus 44.4%)
- Response regardless of PD-L1 status High/low

## Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P



## What is Next for ADCs?

### Main features of novel ADCs and their possible implications for future drug development

First-generation ADCs



Next-generation ADCs



- New linker technologies ( $\uparrow$ DAR)
- Improved conjugation chemistry
- Membrane-permeable payloads



- $\uparrow$  Therapeutic index
- Bystander antitumor effect
- $\uparrow$  Tissue agnostic profile

#### Future perspectives

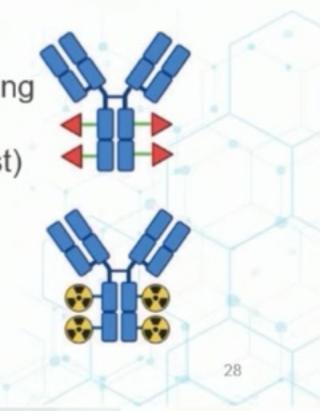


- Bispecific ADCs



- Dual-payload ADCs

- ADCs with immune-stimulating payloads (eg, TLR8 agonist)



- Radionuclide ADCs



**Benjamin Levy**  
ADC technology in cancer therapy

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TLR8, Toll-like receptor 8

Tarantino et al. CA Cancer J Clin 2022;72(2) 165-182. Fu Z, et al. Signal Transduct Target Ther. 2022;7(1):93.

CHAIR : BENJAMIN LEVY

## What is Next for ADCs?

### Main features of novel ADCs and the

-> Adapt payload to tumor-specific alterations

#### First-generation ADCs



- New linker technologies ( $\uparrow$ DAR)
- Improved conjugation chemistry
- Membrane-permeable payloads

#### Next-generation ADCs



- $\uparrow$  Therapeutic index
- Bystander antitumor effect
- $\uparrow$  Tissue agnostic profile

#### Future perspectives

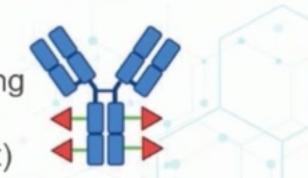
- Bispecific ADCs



- Dual-payload ADCs



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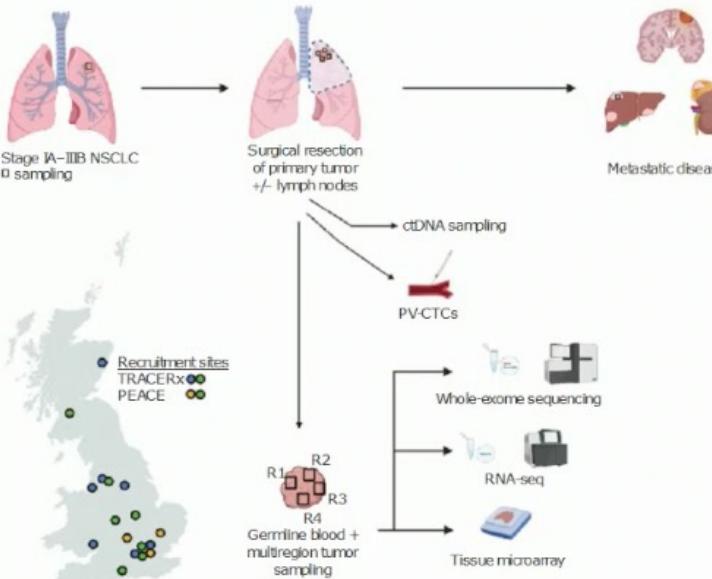
The TRACERx study showed previously that you can predict overall survival by tracking the presence of ctDNA in plasma

## An ultra-sensitive and specific ctDNA assay provides novel pre-operative disease stratification in early stage lung cancer

**TRACERx: NCT01888601**

TRacking Cancer Evolution through therapy (Rx)  
a longitudinal study tracking the evolution of early-stage NSCLC through space and time

### ctDNA in TRACERx lung



How much clinical performance is lost due to assay sensitivity?

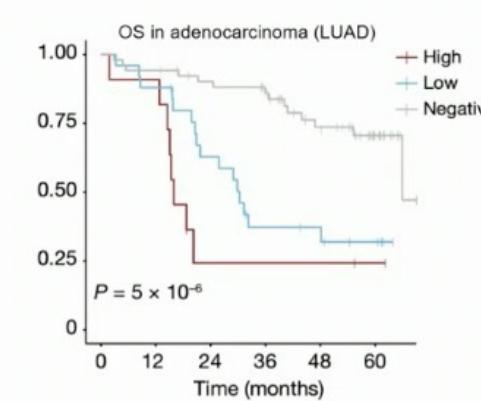
#### First generation tumour-informed ctDNA assays

##### Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution

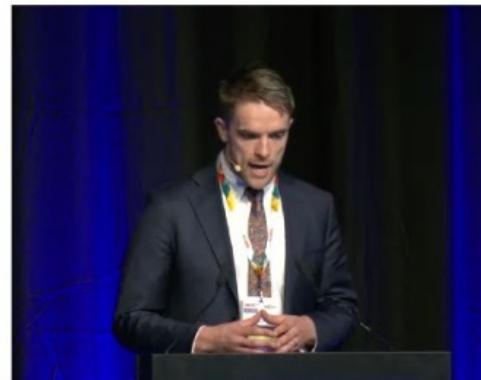
Christopher Abbosh, Nicolai J. Brkljacic, Gareth A. Wilson, Mariam Jamal-Hanjani, Tudor Constantinescu, Reheleh Soltani, John Le Quemo, David A. Morris, Selvaraju Veeriah, Rachel Reesenthal, Teresa Marafioti, Eser Kiskila, Thomas B. Watkins, Nicholas McGranahan, Soochie Ward, Luke Mackintosh, Joen Blew, Francesco Friedl, Mese Al Bakir, Eva Orlinares, Francisco Zambrano, Raymundo Endrizo, Werner Linde, Flora M. Fennelly, The TRACERx consortium, The PEACE consortium & Charles Swanton

Nature 545, 446–451 (2017) | [Cite this article](#)

16 variant personalised panel: LOD95\*  
~0.01% VAF (100 PPM)



- Abbosh et al., 2017, *Nature*  
 Sethi et al., 2018, AACR  
 Bailey, Black et al., 2021, *Cancer Discov.*  
 Zhou et al., 2023, *Mol Diagn Ther.*  
 Abbosh et al., 2023, *Nature*



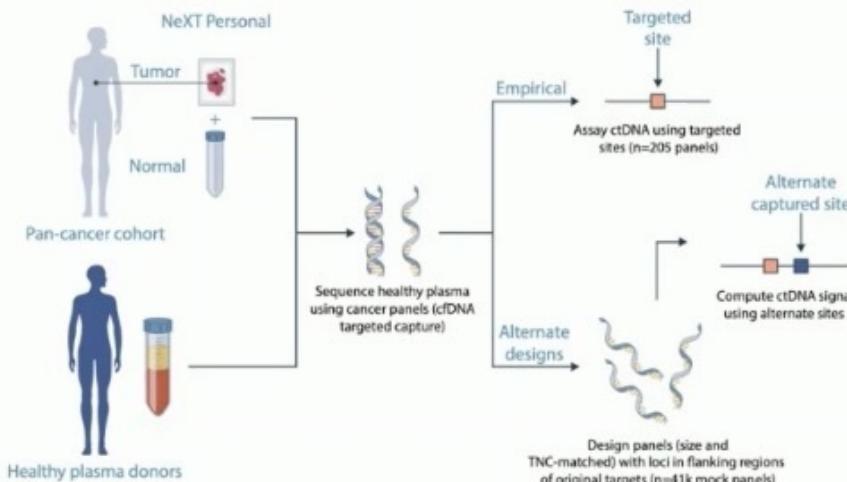
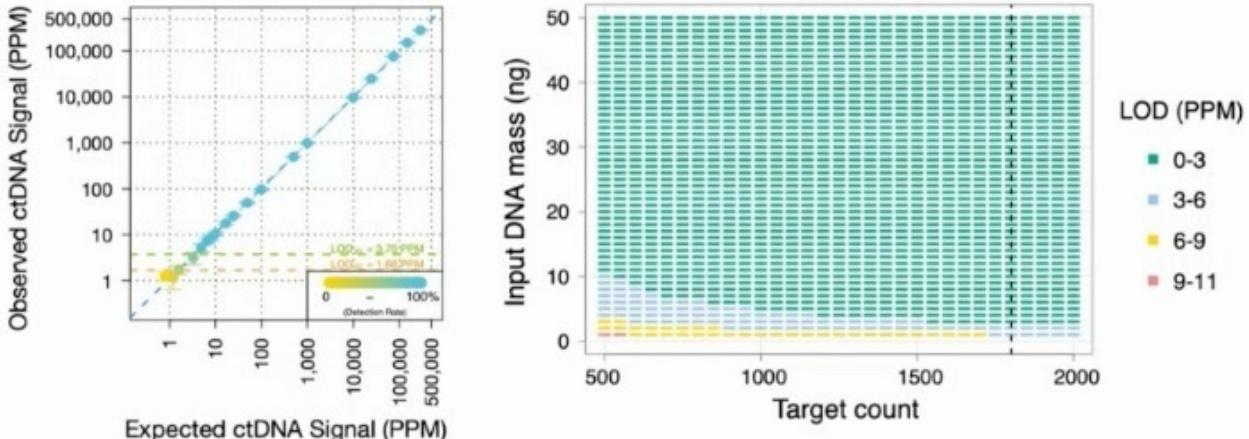
### James Black

An ultra-sensitive and specific ctDNA assay provides novel pre-operative disease stratification in early stage lung cancer

\*LOD95: estimated ctDNA fraction which would be detected in 95% of replicates

# NeXT Personal: ultra-sensitive ctDNA detection

- Tracks ~1,800 mutations per patient
- LOD95\* of 3.76 PPM (0.00037% ctDNA fraction)
- Simulations suggest LOD < 10 PPM (0.001% ctDNA fraction) with 1ng DNA input
- Estimated specificity 99.98%



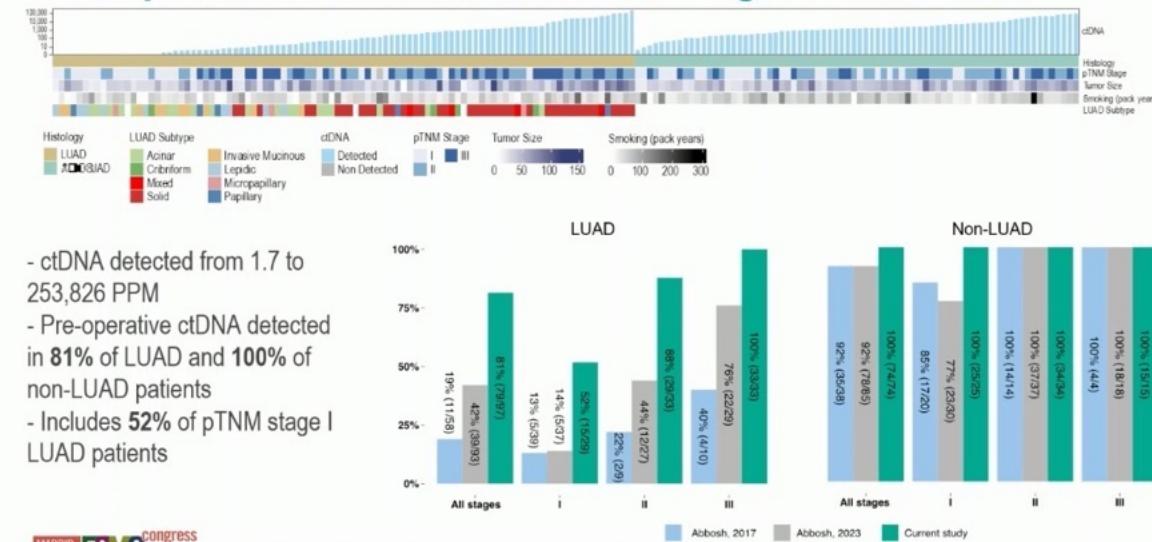
Number of Patient-Specific Panels	True Negative ctDNA Detections	False Positive ctDNA Detections	Specificity (95% CI)
205	205	0	100% (98.22-100%)
Number of Simulated Mock Panels	True Negative ctDNA Detections	False Positive ctDNA Detections	<i>in silico</i> Specificity (95% CI)
40,600	40,593	7	99.98% (99.96-99.99%)

\*LOD95: estimated ctDNA fraction which would be detected in 95% of replicates

NeXT Personal: a whole genome based, tumour-informed platform for ultra-sensitive ctDNA detection, and analytically validated detection thresholds consistently within 1-3 parts per million (PPM) of ctDNA with >99.95% specificity.

ctCDA identified in 81% of LUAD (low-shedding tumours ) patients

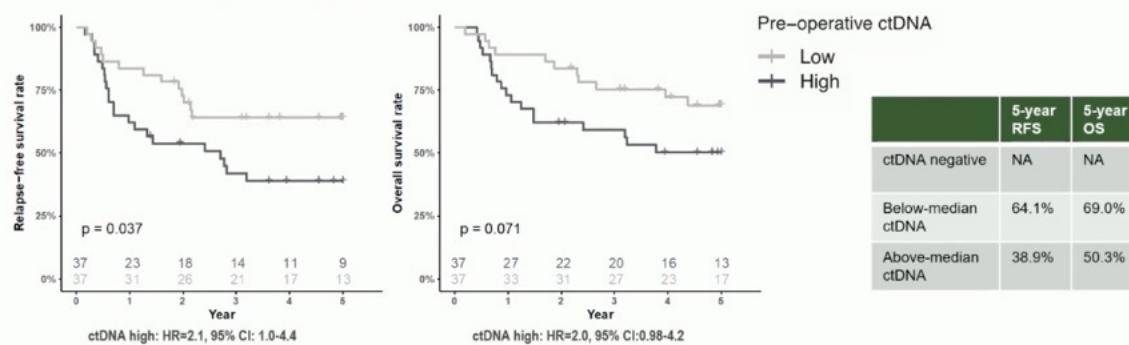
## Pre-operative detection of ctDNA using NeXT Personal



## Survival by old assay:

## Patient stratification with pre-operative ctDNA: non-adenocarcinomas

ctDNA status independently predicts RFS



HRs adjusted in multivariable Cox regression model containing cDNA level (low, high), histology (squamous cell, non-squamous cell), treatment status (adjuvant treatment, no adjuvant treatment), smoking (never, ever), T stage (T1-2, T3-4) and N stage (N0-1, N2-3).

status (per 10 pack years), pTNM stage (I, II, III) and age (per 10 years).

## Does a more sensitive assay add clinical benefit?

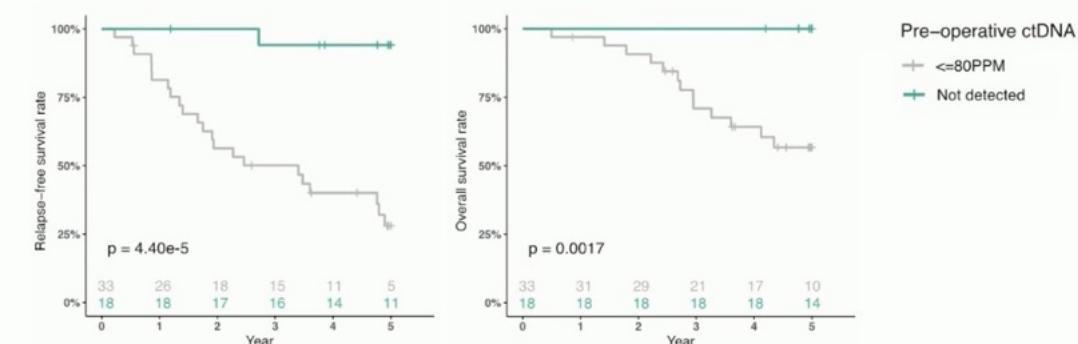
**YES it does!**

-> increased Technical sensitivity gave a clinical meaningful benefit

## Survival by NEW assay NeXT Personal:

## Adenocarcinoma with ultra-low pre-operative ctDNA levels

Patients below 95LOD of assay used in Abbosh et al. 2023 (80 PPM ctDNA) stratified for RFS and OS by NeXT Personal



#### NeXT Personal identifies ultra low-risk group of adenocarcinomas

# Future plans in TRACERx

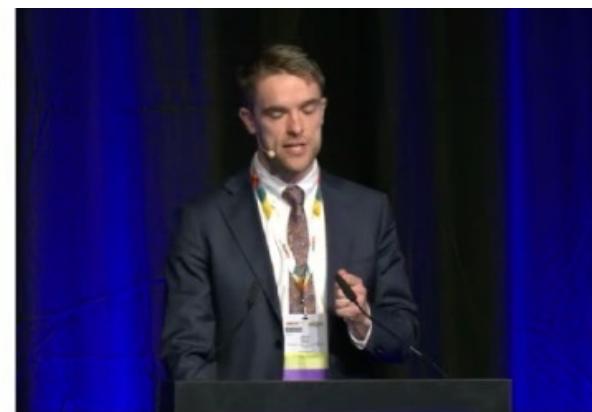
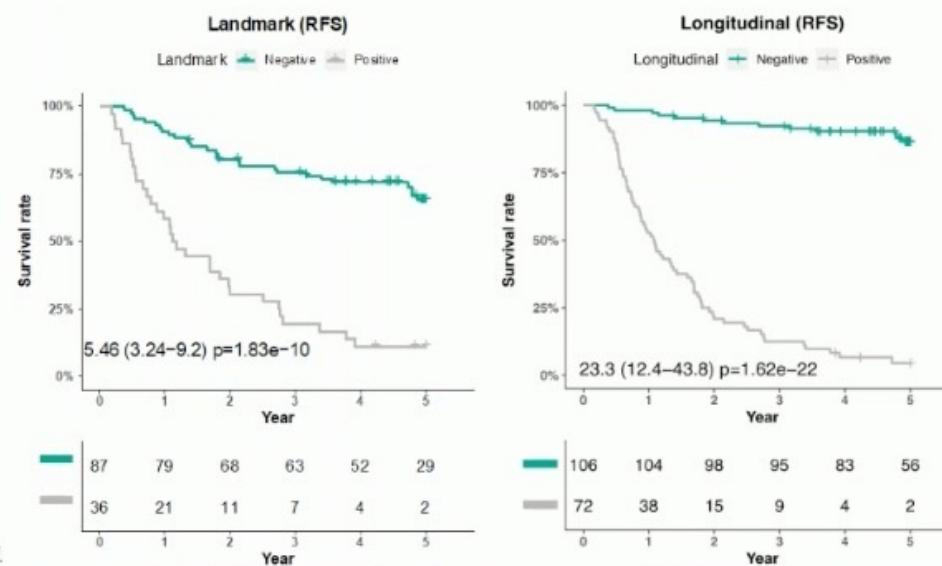
- Planned analysis of ~450 TRACERx patients ongoing
- Approximately 4200 plasma samples being analysed
- 350 tumour-specific subclonal mutations tracked in each patient
- Future expanded analyses will focus on clinical performance, clonal evolution through treatment, acquisition of treatment resistance and factors governing ctDNA shedding

	Lead time (days)
All tumours	173
LUAD	145
Non-LUAD	213
Landmark positive	331
Positive detection pre-recurrence*	225

PPM: parts per million ctDNA. Landmark positive: ctDNA detection within first 120 days of follow up. After adj. treatment: following completion of final treatment with curative intent. Minimum follow-up to be considered relapse-free: 3 years. Median follow-up: 5 years (range 89-2927 days). Landmark lead times were calculated for landmark positive patients, longitudinal lead time includes all patients. Median time to relapse LUAD: 391 days (range 82-1782); Non-LUAD: 443 days (range 59-1747). \*Positive detection pre-recurrence: lead times calculated as in Gale et al., 2022.

## Preliminary data from post-operative timepoints

	PPV	NPV	Sensitivity	Specificity	ctDNA PPM (IQR)
Landmark (n=123)	89%	69%	54%	94%	239 (21-1547)
Landmark (n=74, LUAD only)	90%	58%	46%	94%	159 (21-1166)
Landmark (n=49, Non-LUAD only)	87%	85%	72%	94%	358 (25-1830)
Landmark (from end of curative treatment, n=110)	94%	73%	58%	97%	152 (14-1332)
Longitudinal (n=178)	94%	89%	85%	96%	



## James Black

An ultra-sensitive and specific ctDNA assay provides novel pre-operative disease stratification in early stage lung cancer

## Clinical subtyping of cancer from plasma based on comprehensive epigenomic profiling

Sylvan C. Baca, Ji-Heui Seo, Karl Semaan, Jacob Berchuck, Talal El Zarif, Renee Maria Salby, Brad Fortunato, Mark Awad, Cindy Chau, James DeCaprio, William Douglas Figg, Aaron Hata, Stephen Hodis, Keith Ligon, Kimmie Ng, Matthew Oser, Sara Tolane, Patrick Wen, Matthew L. Freedman, and Toni K. Choueiri



Speaker: Sylvan C. Baca, M.D., Ph.D.

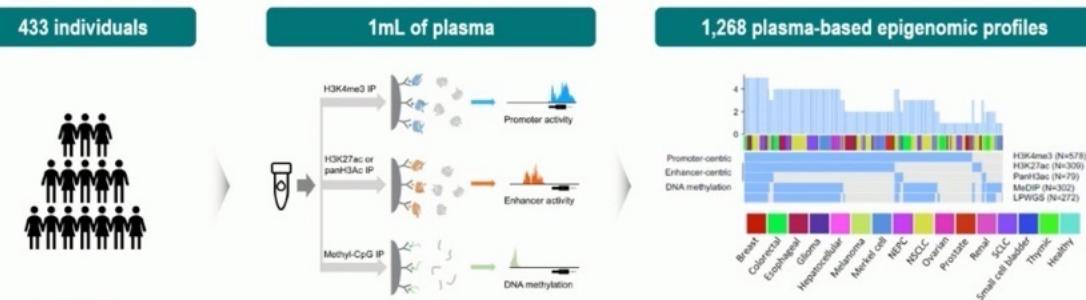
Dana-Farber Cancer Institute, Boston, USA

## Profiling multiple aspects of gene regulation from plasma

Genome-wide profiles of DNA methylation, active enhancers, and active promoters

- Immunoprecipitation-based assay requiring 1mL of plasma
- 1,268 plasma-based epigenomic profiles
- 433 individuals
- 15 advanced cancers including breast, colorectal, lung, and prostate

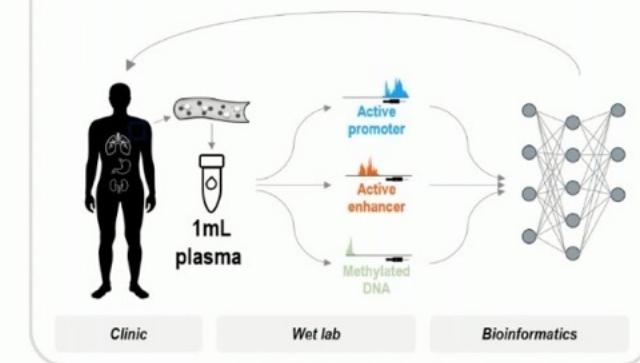
1ml plasma!



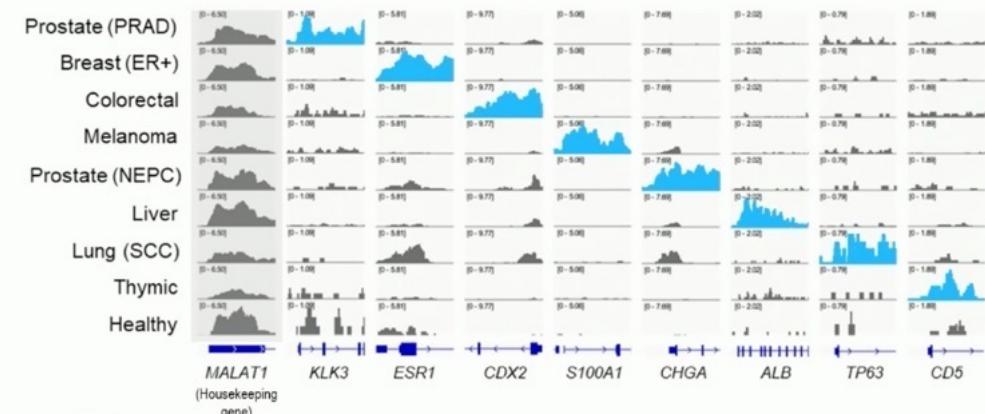
## Epigenomic liquid biopsy technologies could advance precision oncology

- Liquid biopsies address issues of biopsy morbidity, tissue insufficiency, and heterogeneity across metastatic sites
- Current assays focus mainly on somatic genomic alterations
- Epigenomic re-programming of gene regulation is a hallmark of cancer<sup>1</sup>
- Blood-based measurements of gene regulation could aid clinical diagnoses, therapeutic decision-making, and drug development

We developed a plasma-based epigenomic assay that provides a functional, dynamic readout of gene regulation

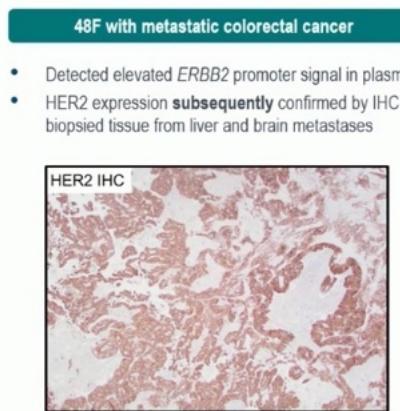
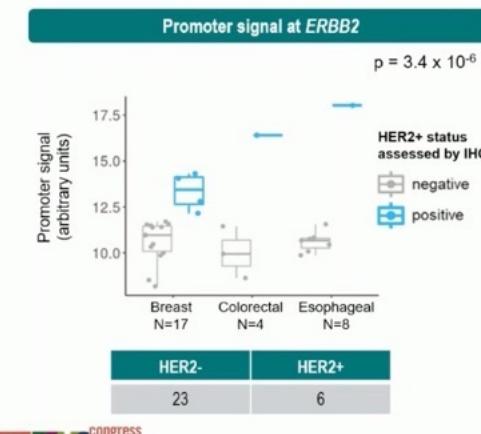


## Plasma Promoter profiling infers expression of tissue-specific diagnostic genes



High signal at cancer site spesific typical areas, expected for the cancer type

## Plasma Promoter profiling identifies patients with targetable HER2+ cancers



## Detection of Enhancer-driven resistance in prostate cancer plasma

### Activation of AR gene enhancer drives treatment-resistant CRPC<sup>1,2</sup>

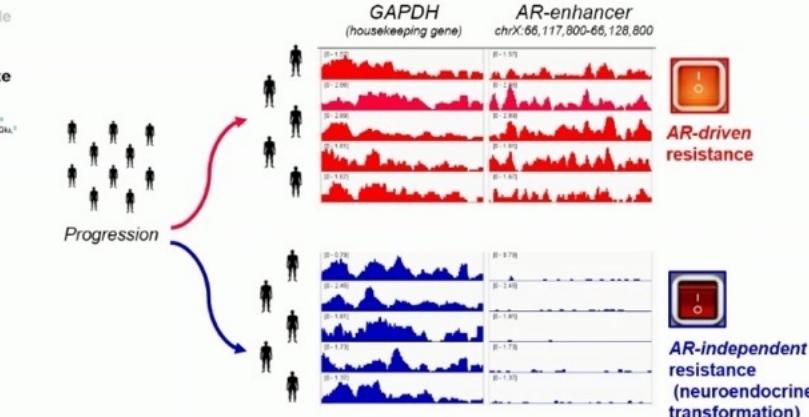
Cell

#### A Somatically Acquired Enhancer of the Androgen Receptor Is a Noncoding Driver in Advanced Prostate Cancer

David Y. Takeda,<sup>1,10</sup> Sándor Spolský,<sup>1,2,10</sup> Ji-Heuk Seo,<sup>1,2</sup> Connor Bell,<sup>1,2</sup> Edward O'Connor,<sup>1</sup> Keegan Korfhage,<sup>1,2</sup> Dézso Riba,<sup>1</sup> Iván Csaba,<sup>1</sup> Norbert Solymosi,<sup>1,2,10</sup> Zoltán Szálasi,<sup>1,2,10</sup> David R. Stillman,<sup>1</sup> Paloma Crops,<sup>1</sup> Xintao Gu,<sup>1</sup> Henry W. Long,<sup>1</sup> Viktória Tótsza,<sup>1,2</sup> Péter Vitai Náray,<sup>2,11</sup> Manséchéh Rohanzadegan,<sup>1,2,10</sup> Mark M. Pomerantz,<sup>1</sup> William C. Hahn,<sup>1,2</sup> and Matthew L. Freedman,<sup>1,2,10</sup>

- AR enhancer activation is not detectable by profiling DNA methylation

### Activation of AR enhancer in plasma of patients with AR-dependent resistance



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1. Takeda et al., Cell 2018  
2. Image from Epstein, Modern Pathology 2004

## Conclusion

- We demonstrate a proof-of-concept for **comprehensive epigenomic profiling of gene regulation from plasma** to inform diagnosis, therapy selection, and resistance monitoring
- This assay provides a **functional readout** of gene regulation and enables **longitudinal dynamic profiling**
- This method **requires only ~1mL of plasma** from standard clinical collection tubes
- Work is ongoing to further demonstrate clinical utility and discover epigenetic resistance mechanisms
- This approach is **extensible across oncology and to non-oncologic conditions**

# Does intronic variants have clinical significance and should they be reported in NGS panels?

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## Pan-Cancer Assessment of the Impact of Intronic Variants on Cancer Development and Progression

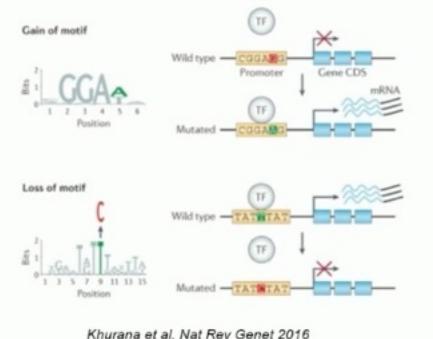


Anton Safonov, MD  
Assistant Attending, Breast Medicine Service  
Memorial Sloan Kettering Cancer Center  
New York City, USA  
October 21, 2023

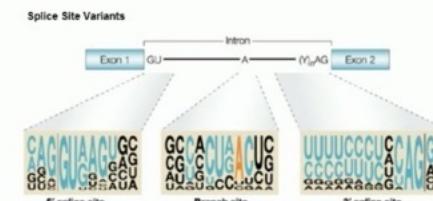
## Introduction

### Implication of intronic variants in cancer

- Clinical next-generation panel-based sequencing traditionally involves exonic regions
- The oncogenic role and clinical implications of **intronic variants** remain to be fully explored.
  - Intronic variants beyond canonical splice variants**  
1-2 bp into the intron are not routinely reported by somatic NGS panels



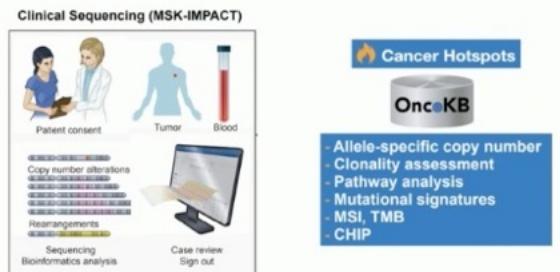
Khurana et al, Nat Rev Genet 2016



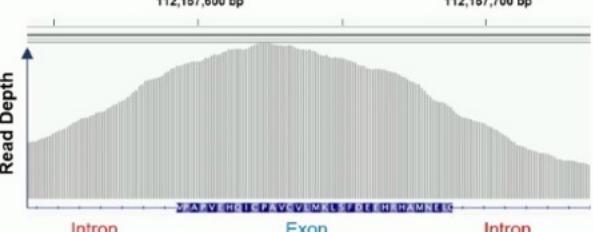
Cartegni et al, Nat Rev Genet 2002

## Aims

To systematically evaluate the genomic and clinical implications of somatic intronic variants in a pan-cancer cohort



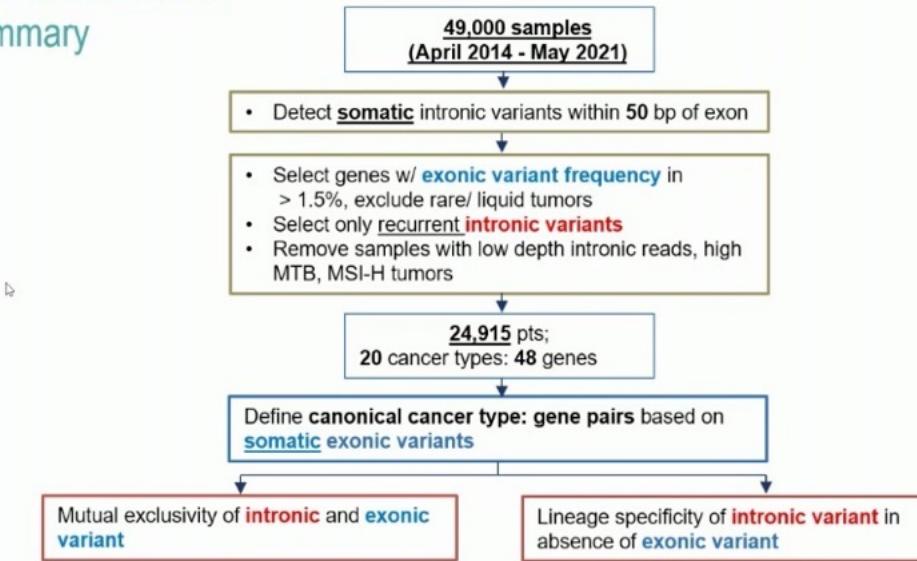
- Are **intronic variants** seen in the **same genomic contexts** as functional exonic variants?
- Do cancers with **intronic variants** follow similar **clinical courses** as functional exonic variants?



Roles of intronic variants  
are mostly unknown

# Methods Overview

## Analysis Summary

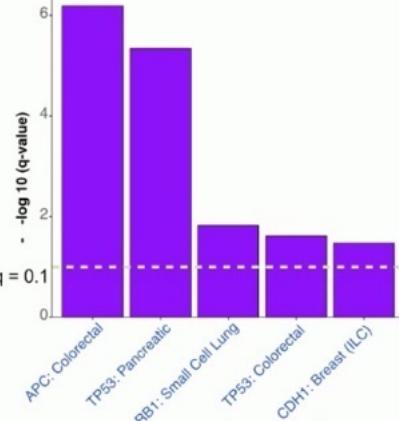


Firth-penalized logistic regression

Hypergeometric test

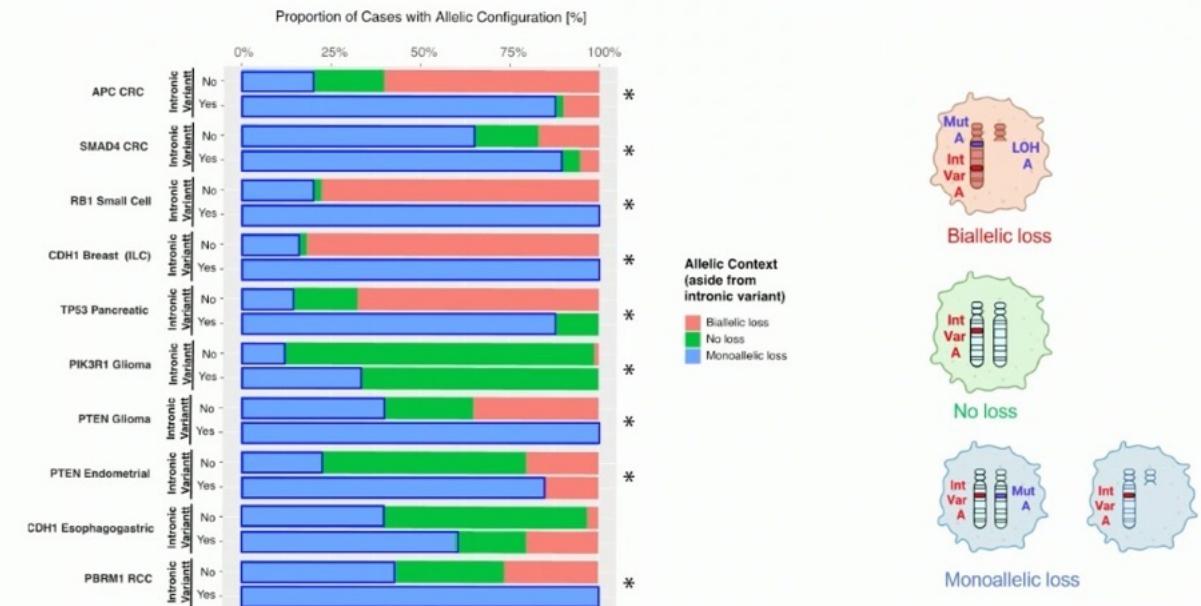
## Results

Exonic variants are mutually exclusive with intronic variants, particularly in canonical TSG



Mutual exclusivity more often with canonical Tumor suppressor genes than oncogenes

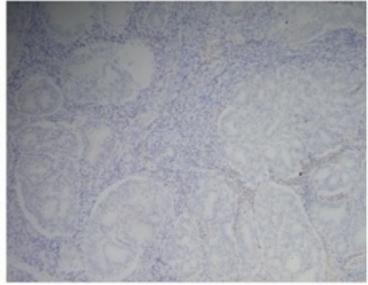
## Intronic variants in TSGs occur in expected allelic configurations



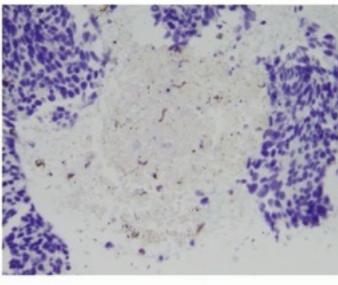
Only significant ( $q < 0.1$ ) pairs are shown

## Effect of intronic variants:

### IHC staining of select cases demonstrates loss of protein



**RB1** in Small Cell Lung Cancer  
c.2490-26A>G



**PTEN** in Endometrial Carcinoma  
c.209+5G>A

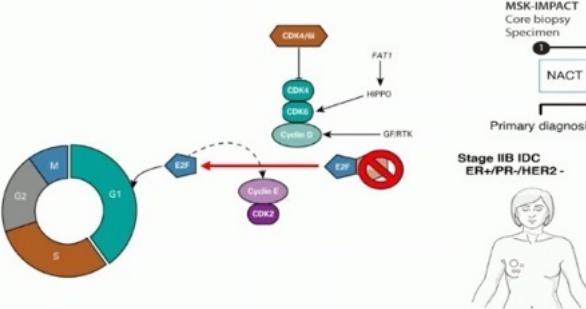
Lost in 7/7 evaluable cases

Lost in 6/6 evaluable cases

IHC staining  
in process on  
*CDH1, APC*

### Intronic variants may play a role in treatment resistance

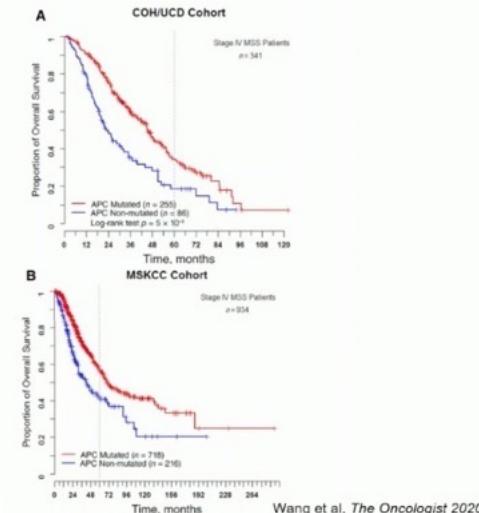
*RB1* loss is a known mechanism of resistance to CDK4/6i in ER+ breast cancer



**RB loss and CDK4/6i resistance**

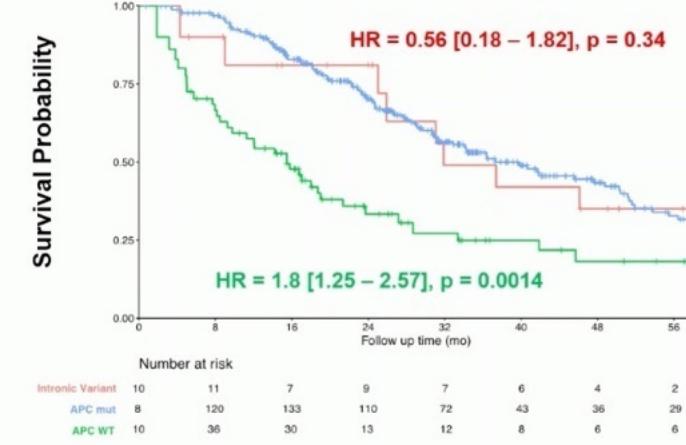
### Clinical Implications of Intronic Variants

*APC-mut* vs *APC-WT* in colorectal cancer



MADRID ESMO congress  
2023

Anton Safonov, MD



\* Left truncated overall survival, adjusted for side of CRC (L vs R)

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### Conclusion

- Further studies needed
  - Confirmation in an additional dataset
  - Expansion of clinical cohorts
- **Intronic variants :**
  - Appear to have **functional consequences** (confer a needed “hit” for complete TSG loss)
  - Harbor **clinical significance** (prognostic biomarker and disease progression).
  - These biologically/ clinically significant events may be missed by “exon-only” assays
- Inclusion of intronic variant calls to currently employed NGS panel output
  - Inclusion in ESCAT framework as “hypothetical target”?
  - Functional annotation using existing sources (Clinvar?)

How to implement this in clinical setting?  
Proper identification/  
classification of the variants is challenging

## Conclusions: What defines actionability?

"Actionable" genes defined as having deleterious mutation(s) whose penetrance would result in specific, defined medical recommendation(s) both supported by evidence and, when implemented, **expected to improve an outcome(s) in terms of mortality or the avoidance of significant morbidity.** Dorschner et al. Am J Hum Genet 2013

Sosinsky et al have a broader definition of Actionability : as

*variants associated with therapeutic response, diagnostic or prognostic classification or clinical trial eligibility- include germline variants, structural and SCNAs*



Majority of NGS panels do not sequence germline hence cannot define germline variants

## Conclusions: Challenges of NGS

- Accurate variant calling crucial
- Identifying bi-allelic alterations in TSGs notoriously difficult
  - Requires outstanding copy number pipelines and adequate coverage
  - Most TSGs require two hits to inactivate them- few NGS reports report status of other allele
- Some tumours are very impure- how many tumours had insufficient purity for NGS?
  - How many failed NGS- intention to sequence

Requires a team of bioinformatics with domain knowledge!



Charles Swanton

Invited Discussant 12070 and 22310

## Conclusions

- Need for clinical validation studies to demonstrate prognostic or predictive capability of WGS vs SOC
  - Price
  - Turnaround times
- Genomics is one part of the MDT process- unlikely to replace all tests.
- Oncology training to keep up with developments in genomics: How many MDTs have physician scientists capable of interpreting WGS data ?
- Interpretation of WGS data is not a one off process: knowledge is evolving
  - A VUS today may be pathogenic tomorrow- what processes are in place to inform patients as knowledge base improves

Interpretation of variants is a continuous discussion

Charles Swanton

ESMO2023:

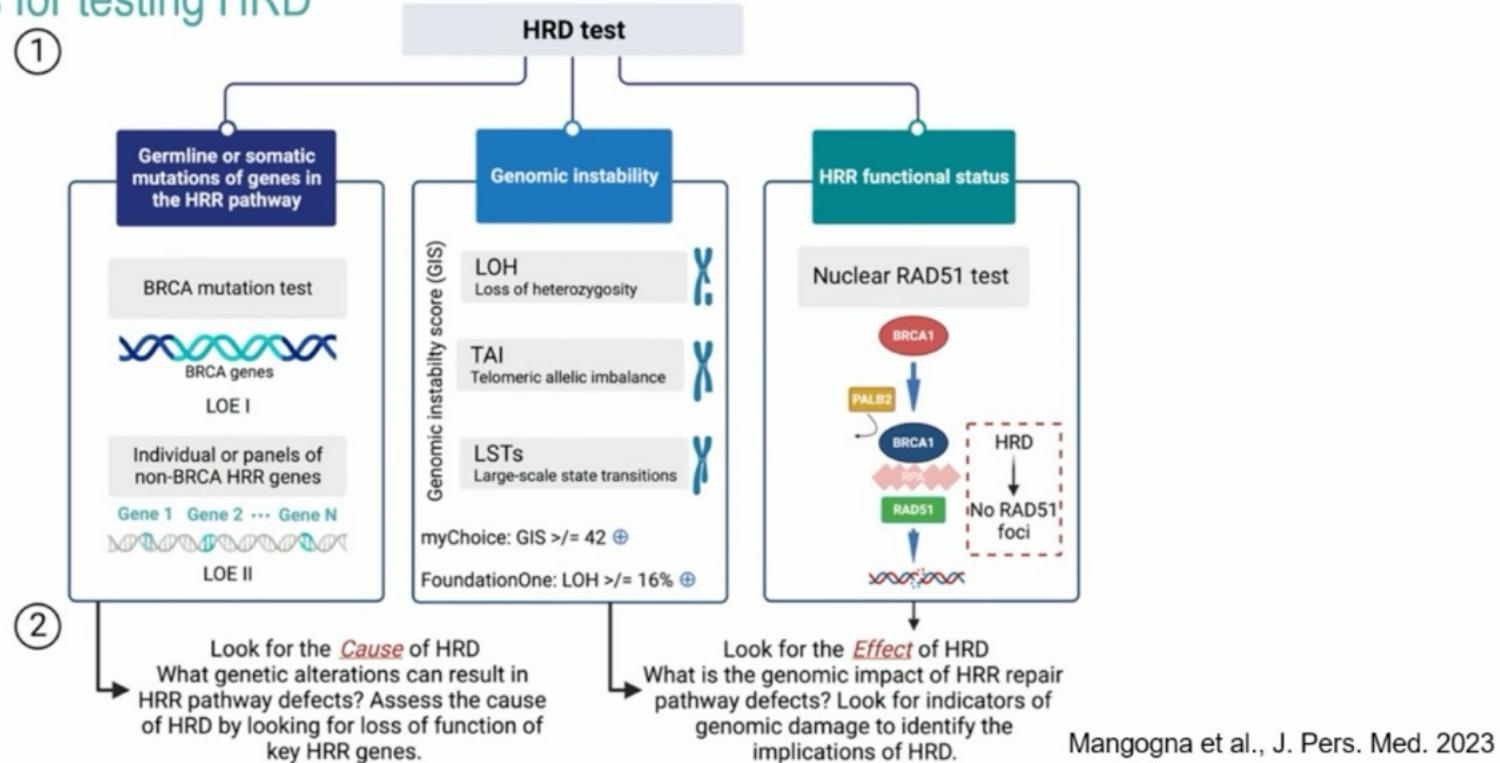
"A VUS today may be pathogenic tomorrow"



# One Big Question everyone is asking: How do we measure HRD?

## Need for extended biomarkers of response to PARP inhibitors

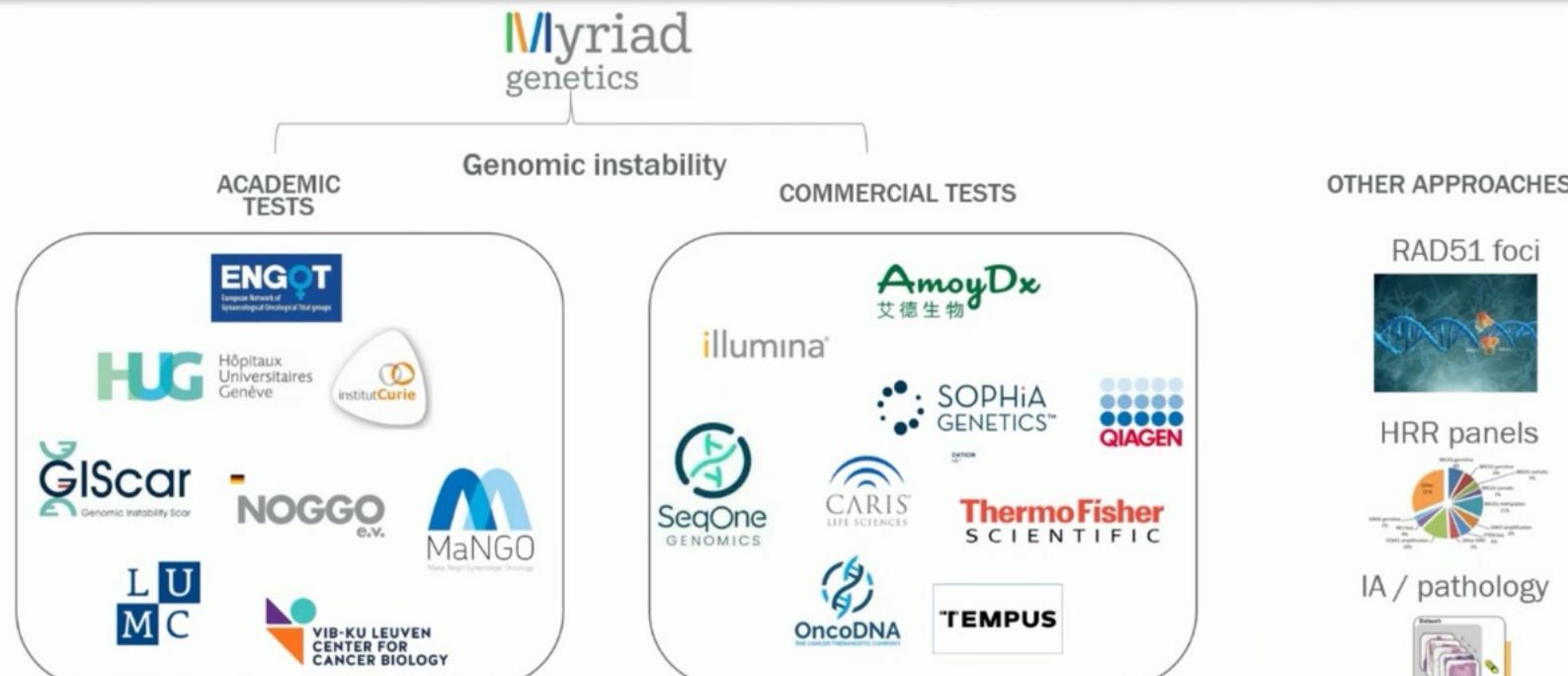
### Approaches for testing HRD



**Elin Gray**  
Invited Discussant 1310 and 10

CHAIRS : CARSTEN DENKERT, PASCAL PUJOL

## HRD tests development



**Pascal Pujol**  
HRD round table

## HR Deficiency (HRD) is widely present in TNBC?

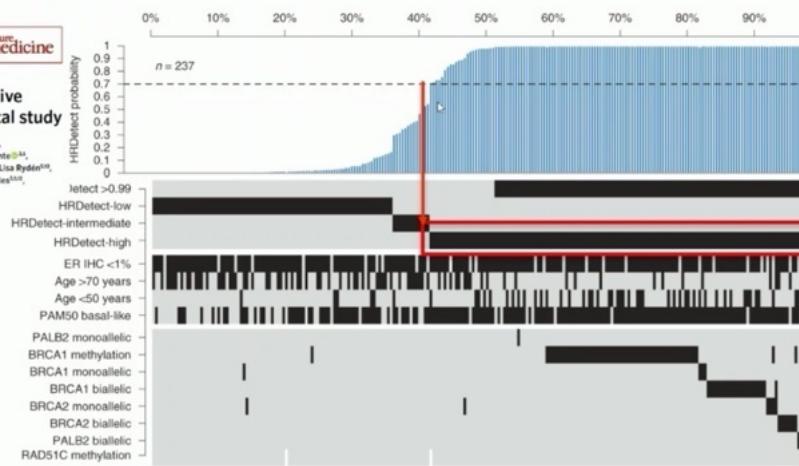


Just looking at scar is not sufficient for accurately identify tumors with HRD

LETTERS  
https://doi.org/10.1038/s41591-019-0582-4

Whole-genome sequencing of triple-negative breast cancers in a population-based clinical study

Johan Staaf<sup>1,2\*</sup>, Dominik Glodzik<sup>1,2,3,4</sup>, Ana Basco<sup>1,5</sup>, Jonas Vallon-Christensen<sup>3,5</sup>, Christel Reuter<sup>1,6</sup>, Jari Hakkila<sup>1,7</sup>, Andrea Desparri<sup>1,8</sup>, Tassanne Díaz Amorante<sup>1,9</sup>, Lao H. Saal<sup>1,2</sup>, Cecilia Hegardt<sup>1</sup>, Hilary Stobart<sup>1</sup>, Anna Chingorai<sup>1,2</sup>, Christer Larsson<sup>1</sup>, Lisa Rydén<sup>10</sup>, Niklas Loman<sup>1,2</sup>, Martin Malmberg<sup>1,2</sup>, Anders Kvist<sup>1</sup>, Hans Ehvrezena<sup>11</sup>, Helen R. Davies<sup>1,2,12</sup>, Åke Borg<sup>12</sup> and Serena Nil Zainal<sup>1,2,13</sup>



Andrew Tutt  
Targeting DNA damage response

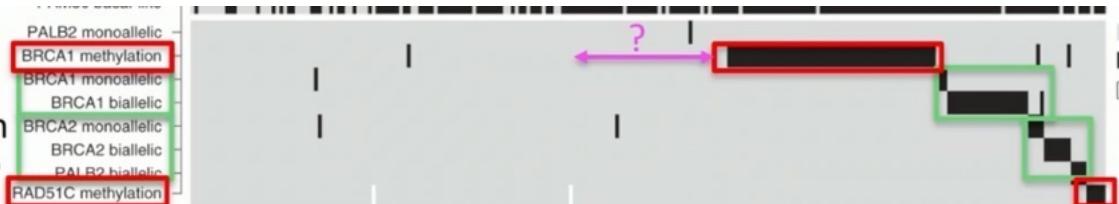
Staaf et al Nature Medicine - <https://doi.org/10.1038/s41591-019-0582-4>

MADRID ESMO congress  
2023

Barcelona Auditorium - Hall 9

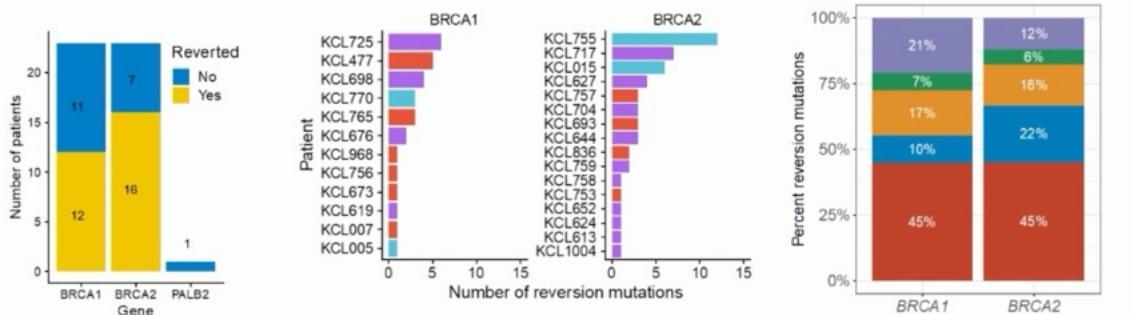
MADRID SPAIN 20-24 OCTOBER 2023

BRCA1/RAD51C methylation more frequent than mutation  
Are these new +ves in TNBC?



Andrew Tutt commented on BRCA methylation and plasticity during treatment. Methylation may be reduced over time. (Shown in ovarian cancer)

# “Reversion” of pathogenic mutation in BRCA1/2 is commonest resistance mechanism – driven by MMEJ



- 60 % of patients have evidence of reversions

- Up to 14 different reversion mutations per patient detected

- Evidence of microhomology use
- Consistent with Microhomology Mediated Endjoining (MMEJ)

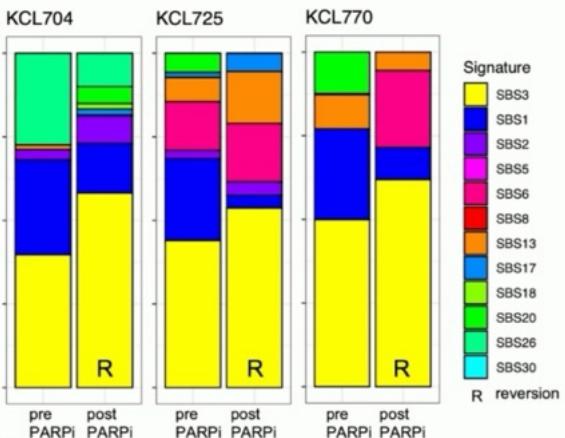


Reversion mutations are very common, 60%!  
-> HRR capacity restored

Harvey-Jones, Raghunandan, Robbez-Masson Abstract 6094 AACR 2023 – in revision Annals of Oncology

## HRD mutational signatures still present despite regain of RAD51 foci after development of resistance

Tumour tissue WES HRD Signature 3  
Before and after PARPi resistance

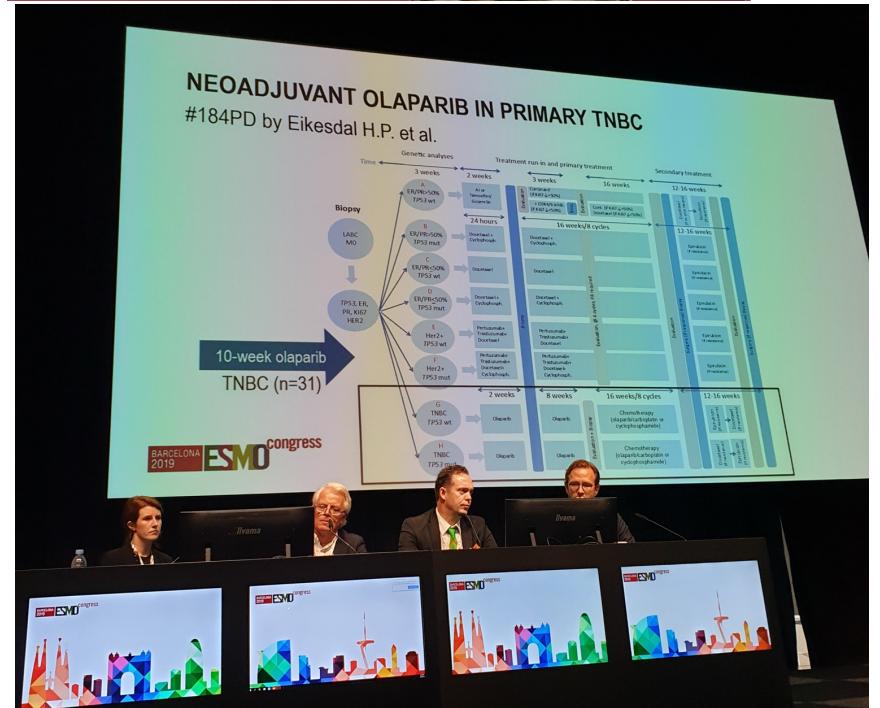
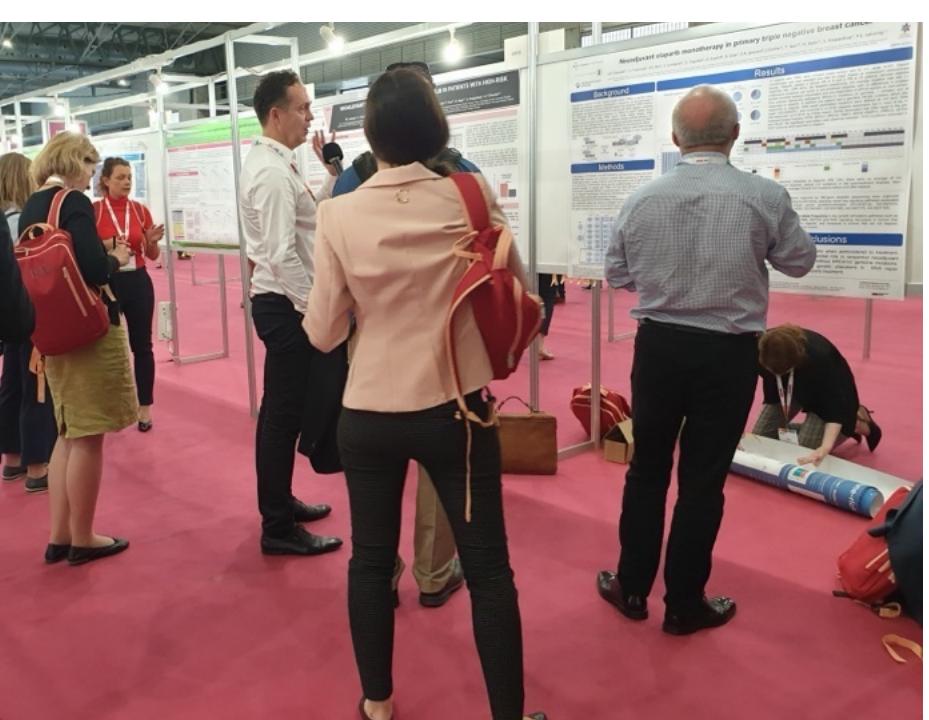
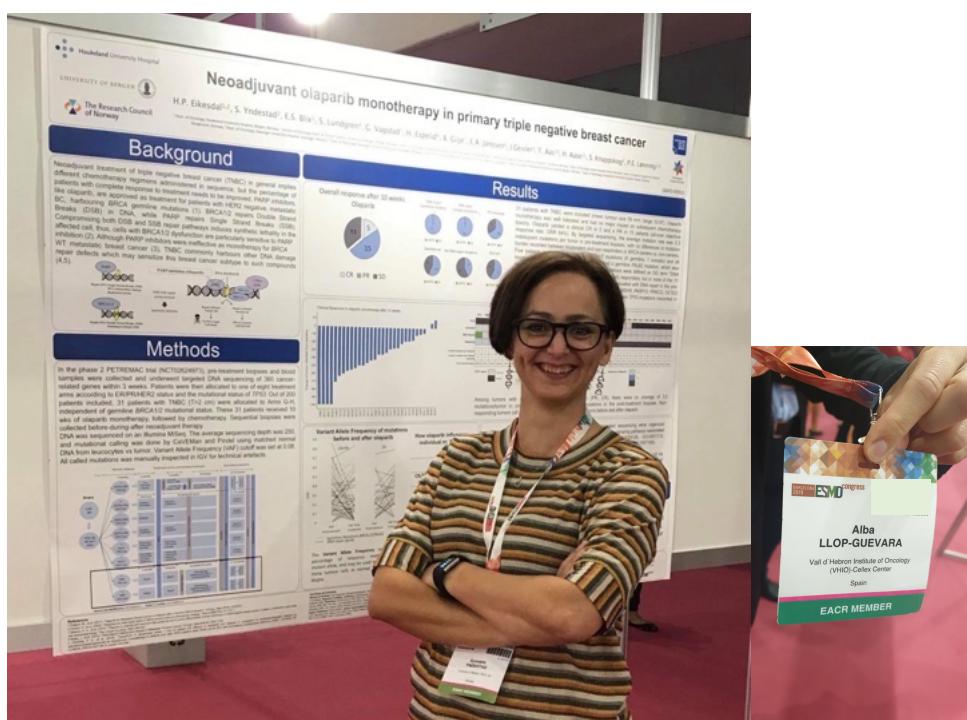


Mutational signature does not change after reversion mutations or loss of methylation.

But RAD51 test will show if there is a functional HRD



Harvey-Jones, Raghunandan, Robbez-Masson Abstract 6094 AACR 2023 – in revision Annals of Oncology



## Throwback to ESMO congress 2019 Barcelona

ResearchGate Home 18 Questions Jobs

Search for research, journals, people, etc.

Good job, Synnøve!

Your article reached 100 citations

Achieved on November 6, 2023

Article: Olaparib Monotherapy as Primary Treatment in Unselected Triple Negative Breast Cancer

## 08:30 - 10:00 Molecular targets and related treatments

CHAIRS : HIMISHA BELTRAN, DANIEL HEINRICH

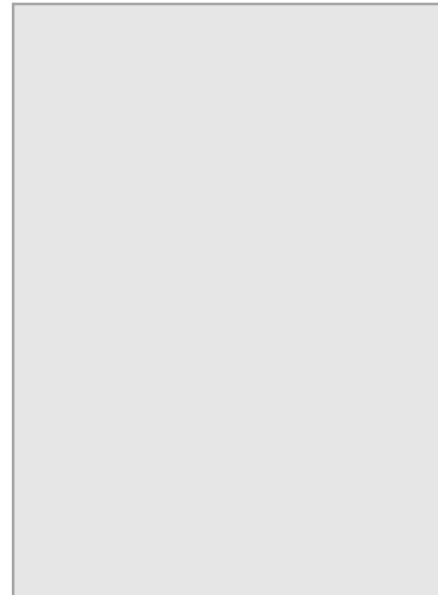
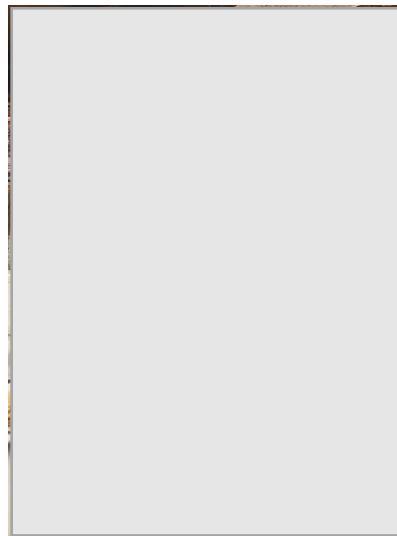
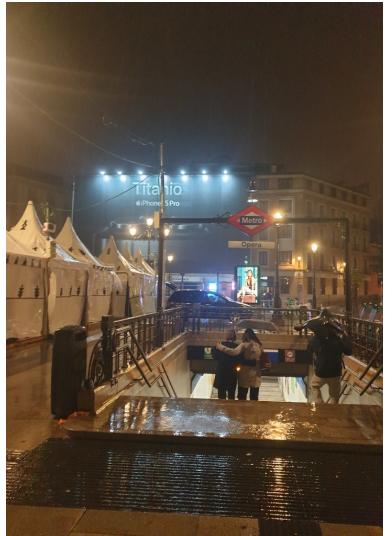


Hans Petter Eikesdal 1972 - 2023



**Daniel Heinrich**  
PSMA targeting

# 2023



## Key Takeaways from ESMO Early Breast Cancer 2023

- Exciting data in higher risk ER+ disease
  - CDK 4/6inhibitors are changing important outcomes for patients
  - select patients may benefit from ICIs
  - the key will be developing biomarkers to optimize benefits for patients
- Impact of neoadjuvant pembrolizumab on pCR and EFS in TNBC remains robust



**Ann H. Partridge**  
Breast cancer, early stage

Adjuvant CDK4/6i tx substantially improves EFS in eBC

All subgroups benefit including by Ki67, ER, PR

Goetz et al, ESMO 2023; Bardia et al, ESMO 2023

## Key Takeaways from ESMO Early Breast Cancer 2023

- Exciting data in higher risk ER+ disease
  - CDK 4/6inhibitors are changing important outcomes for patients
  - select patients may benefit from ICIs
  - the key will be developing biomarkers to optimize benefits for patients
- Impact of neoadjuvant pembrolizumab on pCR and EFS in TNBC remains robust
- Many selection strategies are being tested to “right size” breast cancer care
- The environment (both external and internal) affects breast cancer risk and outcomes; individual and societal change is possible and necessary



**Ann H. Partridge**  
Breast cancer, early stage