ACT Onco® + Report

PATIENT		
Name: 游鳳凰		Patient ID: 30972760
Date of Birth: Sep 20, 1957		Gender: Female
Diagnosis: Melanoma		
ORDERING PHYSICIAN		
Name: 劉峻宇醫師		Tel: 886-228712121
Facility: 臺北榮總		
Address: 臺北市北投區石牌路二段 201 號		
SPECIMEN		
Specimen ID: S11128446A	Collection site: Soft tissue, left foot	Type: FFPE tissue
Date received: Aug 04, 2022	Lab ID: AA-22-04550	D/ID: NA

ABOUT ACTOnco®+

The test is a next-generation sequencing (NGS)-based assay developed for efficient and comprehensive genomic profiling of cancers. This test interrogates coding regions of 440 genes associated with cancer treatment, prognosis and diagnosis. Genetic mutations detected by this test include small-scale mutations like single nucleotide variants (SNVs), small insertions and deletions (InDels) (≤ 15 nucleotides) and large-scale genomic alterations like copy number alterations (CNAs). The test also includes an RNA test, detecting fusion transcripts of 13 genes.

SUMMARY FOR ACTIONABLE VARIANTS

VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Probable Effects in Patient's Cancer Type		Probable Sensitive in Other Cancer Types
	Sensitive	Resistant	
Not detected			

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
NF1 Splice donor	Everolimus, Selumetinib, Trametinib	Afatinib, Erlotinib, Gefitinib, Cetuximab, Lapatinib, Trastuzumab, Vemurafenib
CDK4 Amplification	Abemaciclib, Palbociclib, Ribociclib	-

Note:

- The above summary tables present genomic variants and biomarkers based on the three-tiered approach proposed by US FDA for reporting tumor profiling NGS testing. "Variants/biomarkers with evidence of clinical significance" refers to mutations that are widely recognized as standard-of-care biomarkers (FDA level 2/AMP tier 1). "Variants/biomarkers with potential clinical significance" refers to mutations that are not included in the standard of care but are informational for clinicians, which are commonly biomarkers used as inclusion criterial for clinical trials (FDA level 3/AMP tier 2).
- The therapeutic agents and possible effects to a given drug are based on mapping the variants/biomarkers with ACT Genomics clinical knowledge database. The mapping results only provide information for reference, but not medical recommendation.
- Please refer to corresponding sections for more detailed information about genomic alteration and clinical relevance listed above.

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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
NF1	Splice donor	37.1%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr12	*MDM2*	Amplification	6¥
Chr12	*ERBB3*	Amplification	10
Chr5	*TERT*	Amplification	23
Chr12	*CDK4*	Amplification	33

¥ Increased gene copy number was observed.

- Fusions

Fusion Gene & Exon	Transcript ID
No fusion gene detected in this sample	

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	< 1 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 80% tumor purity.
- TMB was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is < 30%.

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3B		
CDK4 Amplification	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
NF1 Splice donor	Selumetinib	**sensitive**
Level 4		
NF1 Splice donor	Everolimus, Trametinib	**sensitive**
NF1 Splice donor	Afatinib, Erlotinib, Gefitinib, Cetuximab, Lapatinib, Trastuzumab, Vemurafenib	**resistant**

Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence in professional guidelines or peer-reviewed journals.

Level	Description
1	FDA-recognized biomarkers predictive of response or resistance to FDA approved drugs in this indication
2	Standard care biomarkers (recommended by the NCCN guideline) predictive of response or resistance to FDA approved drugs in this indication
3A	Biomarkers predictive of response or resistance to therapies approved by the FDA or NCCN guideline in a different cancer type
3B	Biomarkers that serve as inclusion criteria for clinical trials (minimal supportive data required)
4	Biomarkers that show plausible therapeutic significance based on small studies, few case reports, or preclinical studies

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

No genomic alterations detected to confer sensitivity or lack of benefit to immune checkpoint therapies.

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
Not detected	

Note: Tumor non-genomic factors, such as patient germline genetics, PDL1 expression, tumor microenvironment, epigenetic alterations or other factors not provided by this test may affect ICI response.

CHEMOTHERAPIES

No genomic alterations detected in this tumor predicted to confer sensitivity or lack of benefit to chemotherapies.

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
NF1 Splice donor	Tamoxifen	**Less sensitive**	Clinical	Breast cancer

OTHERS

No genomic alterations detected in this tumor predicted to confer sensitivity or lack of benefit to other therapies.

Note:
Therapeutic implications provided in the test are based solely on the panel of 440 genes sequenced. Therefore, alterations in genes not covered in this panel, epigenetic and post-transcriptional and post-translational factors may also determine a patient's response to therapies. In addition, several other patient-associated clinical factors, including but not limited to, prior lines of therapies received, dosage and combinations with other therapeutic agents, patient's cancer types, sub-types, and/or stages, may also determine the patient's clinical response to therapies.

VARIANT INTERPRETATION

NF1 Splice donor

Biological Impact

The neurofibromin 1 (NF1) gene encodes a GTPase activating protein (GAP) which is an important negative regulator of the Ras cellular proliferation pathways[1][2][3][4]. Besides, NF1 also physically interacts with the N-terminal domain of focal adhesion kinase (FAK) and involves in the regulation of cell adhesion, growth, and other pathways[5][6]. NF1 is considered a classical haploinsufficient tumor suppressor gene with loss of one allele through inherited or acquired mutation may lead to reduced protein expression and is insufficient to execute normal cellular functions contributing to tumor development[7][8][9][10][11]. NF1 syndrome is a germline condition resulting in a predisposition to several types of cancer such as neurofibromas, melanoma, lung cancer, ovarian cancer, breast cancer, colorectal cancer, hematological malignancies[12][13][14]. Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types[15], including myelodysplastic syndromes, melanomas, colon cancer[16], glioblastomas[17], lung cancer[18], ovarian cancer, and breast cancer[12].

NF1 c.4577+1G>A is a variant located at the splice donor region, which may result in the exon skipping.

Therapeutic and prognostic relevance

In April 2020, the U.S. FDA has approved selumetinib for pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN). A phase II trial (NCT02664935, NLMT) demonstrated that selumetinib in combination with docetaxel resulted in a confirmed ORR of 28.5% (4/14), durable clinical benefit (DCB) rate of 50% (7/14), and mPFS of 5.3 months in lung adenocarcinoma patients harboring NF1 loss[19]. NF1 loss has been determined as an inclusion criterion for the trials evaluating selumetinib efficacies in lung cancer (NCT02664935) and NF1-associated tumors (NCT03326388).

NF1 depletion has been associated with drug resistance to RAF and EGFR inhibitors, tamoxifen, and retinoic acid[15][20]. For example, loss of NF1 was identified in patients with lung adenocarcinomas or colorectal cancer who presented resistance to anti-EGFR treatment, including erlotinib, gefitinib, afatinib, and cetuximab, respectively[21][22][23]. Loss of NF1 in patients with BRAF-mutated melanomas was also suggested conferring resistance to BRAF inhibitors[24][25][26][27].

Notably, preclinical studies further revealed that the addition of a MEK inhibitor could restore the sensitivity to erlotinib[21]. Also, in a liquid biopsy-based ctDNA profiling study of HER2-positive metastatic gastric cancer, NF1 loss (either induced by mutation or deletion) was suggested as a novel mechanism contributes to trastuzumab resistance. The cell-based study also showed that the trastuzumab and lapatinib resistance could be overcome with a combination of HER2 and MEK/ERK inhibitors[28].A case study had reported that MEK inhibitor, trametinib, was effective in a treatment-refractory neurofibromatosis type I-associated glioblastoma[29]. Various preclinical data had also supported the activity of MEK and mTOR inhibitors in NF1-deficient tumors[30][31][32][33][34][35]. In an NGS-based study, patients harboring mutations in the mTOR pathway, including mTOR, TSC1, TSC2, NF1, PIK3CA, and PIK3CG responded to everolimus[36].

CDK4 Amplification

Biological Impact

The cyclin-dependent kinase 4 (CDK4) gene encodes a serine/threonine kinase that functions in the regulation of CDK kinases in the cell cycle. CDK4 forms a complex with cyclin-dependent kinase 6 (CDK6) and cyclin D, leading to G1-S cell-cycle transition by inhibiting the retinoblastoma (RB) protein[37]. Dysregulation of CDK4/6 activity by gene amplification, activating mutations or loss of CDKN2A has been reported in breast cancer, melanoma, glioblastoma and sarcomas[38][39][40][41][42].

Therapeutic and prognostic relevance

Results from clinical studies of liposarcoma and endocrine-resistant, hormone receptor-positive breast cancer showed that CDK4 amplification is predictive of sensitivity to CDK4/6 inhibitor palbociclib in RB-expressing tumors[43][44][45].

Abemaciclib, another CDK4/6 inhibitor, showed acceptable toxicity profile and preliminary efficacy in a Phase I trial of multiple tumor types, including breast cancer, non-small cell lung cancer (NSCLC) and other solid tumors[46].

Of note, CDK4 amplification has been selected as an inclusion criterion for the trial examining CDK4/6 inhibitors in different types of malignant solid tumors (NCT03310879, NCT02187783, NCT02154490).

ERBB3 Amplification

Biological Impact

The ERBB3 (also known as HER3) gene encodes a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases[47]. HER3 lacks or has little intrinsic tyrosine kinase activity. Upon binding of its ligand, neu differentiation factor (NDF), HER3 forms a heterodimer with ErbB2[48]and subsequently activates various mitogenic signaling cascades, including the PI3K/AKT/mTOR, STAT and RAS/RAF/MAPK[49][50][51]. Aberrant expression or alterations of the ErbB family play crucial roles in the development and progression of cancer[52]. Enhanced expression of HER2 has been observed in a broad spectrum of human cancers, including gastric, bladder, uterine, colorectal, and breast cancers[53]. HER3 is the preferred heterodimeric partner for EGFR in melanoma and pancreatic carcinoma[54][55], while in breast cancer, HER3 preferably heterodimerizes with HER2 and plays a critical role in HER2-mediated tumorigenesis.

Therapeutic and prognostic relevance

Currently, there are no FDA-approved anti-HER3 therapies for patients with solid tumors. A variety of strategies targeting HER3 including pan HER approach, abrogating its dimerization partners' kinase activity using small molecule inhibitors (e.g. lapatinib, erlotinib, gefitinib, afatinib, and neratinib) or direct targeting of its extracellular domain (e.g. including AV-203 (Abstract nr 2509, AACR 2012)) are under investigation[56][57].

Preclinical data indicated that HER3 expression level is a predictive biomarker of pertuzumab (an anti-HER2 antibody) efficacy in HER2 low-expressing pancreatic cancer[58].

ERBB3 mutation has been selected as an inclusion criteria for the trial examining afatinib in urothelial tract carcinoma, non-small cell lung carcinoma (NSCLC) and malignant solid tumor (NCT02780687, NCT01523587, NCT03810872)[59][60].

Accumulating evidence indicates that overexpression of HER3 associates with worse survival in cancer patients with solid tumors[61], besides, HER3 signaling plays a major role causing treatment failure in cancer therapy[62][63][56]. For example, elevated HER3 expression of HER3 in HER2-overexpressing breast cancer cells results in resistance to hormone therapy (tamoxifen)[64], HER2-targeted therapy (trastuzumab and lapatinib)[65], and chemotherapy (paclitaxel). Besides, the high expression of ERBB3 has associated with gefitinib resistance in head and neck squamous cell carcinoma (HNSCC) cell lines[66].

The amplification of ERBB3 was associated with poor response to chemotherapy, higher distant metastasis rate, poor PFS and OS of primary osteosarcoma patients[67].

In a prospective study, a gallbladder cancer patient harboring ERBB3 amplification demonstrated a partial response for 1.8 months by lapatinib and capecitabine treatment[68].

MDM2 Amplification

Biological Impact

The Mouse double minute 2 proto-oncogene (MDM2) gene encodes a E3-ubiquitin ligase that negatively regulates the protein level of p53[69][70][71]. Overexpression or amplification of MDM2 has been shown to disrupt the MDM2/p53 balance, leading to the malignant transformation in a wide range of cancers[72].

Therapeutic and prognostic relevance

Small molecules inhibiting the MDM2-p53 protein-protein interaction to reactivate p53 function are currently under preclinical studies and in early clinical trials[73]. Nutlin-3, a MDM2 inhibitor, when synergized with cisplatin, has been shown to disrupt the interaction between MDM2 and TP53, and induce apoptosis in TP53 wild-type ovarian cancer cells[74], non-small cell lung cancer (NSCLC) cells[75], and nasopharyngeal carcinoma cells[76]. Clinical and preclinical studies showed that overexpression of MDM2 can confer resistance to cisplatin[77][78].

The retrospective studies demonstrated that EGFR-mutated NSCLC patients harboring MDM2 amplification were associated with resistance to EGFR-TKIs and showed poor prognosis after treatment[79][80][81][82].

MDM2 amplification was shown to be a potential mechanism of primary or acquired resistance to cabozantinib and MDM2 inhibitors in clinical development can be targeted therapeutics (Journal of Clinical Oncology, 34, 9068-9068).

Importantly, results from a study suggested that patients with amplification of the MDM2 family members, including MDM2 and MDM4, or EGFR aberrations exhibited poor clinical outcome and demonstrated a significantly increased rate of tumor growth (hyper-progression) after receiving immune checkpoint (PD-1/PD-L1) therapy[83].

TERT Amplification

Biological Impact

The TERT gene encodes the catalytic subunit of telomerase, an enzyme that maintains telomere length and genomic integrity[84]. Upregulation of TERT promotes cancer development and progression via modulation of Wnt-catenin and nuclear factor kappa B signaling[85][86], and mitochondrial RNA processing[87]. Activating mutations in the TERT promoter have been identified in a number of cancer types including melanoma, hepatocellular carcinoma, urothelial carcinoma, medulloblastoma, and glioma whereas TERT gene amplification is implicated in lung cancer, cervical cancer, breast cancer, Merkel cell carcinoma, neuroblastoma and adrenocortical carcinoma[88][89][90][91][92].

Therapeutic and prognostic relevance

Imetelstat (GRN163L), a telomere inhibitor which has been shown to inhibit cell proliferation in various cancer cell lines and tumor xenografts is currently in clinical trials[84].

TERT gene amplification is an independent poor prognostic marker for disease-free survival in non-small cell lung cancer (NSCLC) and breast cancer[93][94][95].

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US FDA-APPROVED DRUG(S)

Abemaciclib (VERZENIO)

Abemaciclib is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. Abemaciclib is developed and marketed by Eli Lilly under the trade name VERZENIO.

- FDA Approval Summary of Abemaciclib (VERZENIO)

monarchE NCT03155997	**Breast cancer** (Approved on 2021/10/12)
	HR-positive, HER2-negative
	Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3[96] NCT02246621	**Breast cancer** (Approved on 2018/02/26)
	HR-positive, HER2-negative
	Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 2[97] NCT02107703	**Breast cancer** (Approved on 2017/09/28)
	HR-positive, HER2-negative
	Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1[98] NCT02102490	**Breast cancer** (Approved on 2017/09/28)
	HR-positive, HER2-negative
	Abemaciclib [ORR(%): 19.7 vs. 17.4]

Everolimus (AFINITOR)

Everolimus, a derivative of sirolimus, works as an inhibitor of mammalian target of rapamycin complex 1 (mTORC1) and blocks mTORC1-mediated downstream signals for cell growth, proliferation, and survival. Everolimus is developed and marketed by Novartis under the trade name AFINITOR.

- FDA Approval Summary of Everolimus (AFINITOR)

RADIANT-4[99] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[100] NCT00863655	**Breast cancer** (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
EXIST-2 NCT00790400	**Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma** (Approved on 2012/04/26)
	-
	Everolimus vs. Placebo [ORR(%): 41.8 vs. 0]
RADIANT-3[101] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[102] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[103] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

Palbociclib (IBRANCE)

Palbociclib is an oral, cyclin-dependent kinase (CDK) inhibitor specifically targeting CDK4 and CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Palbociclib is developed and marketed by Pfizer under the trade name IBRANCE.

- FDA Approval Summary of Palbociclib (IBRANCE)

PALOMA-2[104] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+, HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[105] NCT01942135	**Breast cancer** (Approved on 2016/02/19)
	ER+, HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

Ribociclib (KISQALI)

Ribociclib is a cyclin-dependent kinase (CDK) inhibitor specifically targeting cyclin D1/CDK4 and cyclin D3/CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Ribociclib is developed by Novartis and Astex Pharmaceuticals and marketed by Novartis under the trade name KISQALI.

- FDA Approval Summary of Ribociclib (KISQALI)

MONALEESA-2[106] NCT01958021	**Breast cancer** (Approved on 2017/03/13)
	HR+, HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

Selumetinib (KOSELUGO)

Selumetinib is a kinase inhibitor. Selumetinib is developed and marketed by AstraZeneca under the trade name KOSELUGO.

- FDA Approval Summary of Selumetinib (KOSELUGO)

SPRINT NCT01362803	**Plexiform neurofibromas** (Approved on 2020/04/10)
	Neurofibromatosis type 1
	Selumetinib [ORR(%): 66.0]

Trametinib (MEKINIST)

Trametinib is an anti-cancer inhibitor which targets MEK1 and MEK2. Trametinib is developed and marketed by GlaxoSmithKline (GSK) under the trade name MEKINIST.

- FDA Approval Summary of Trametinib (MEKINIST)

BRF117019, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060, NCT02124772	**Cancer** (Approved on 2022/06/22)
	BRAF V600E
	Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0]

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BRF117019[107] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[108] NCT01336634	**Non-small cell lung cancer** (Approved on 2017/06/22)
	BRAF V600E
	Trametinib + dabrafenib vs. Dabrafenib [ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9]
COMBI-d[109] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[110] NCT01245062	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

Trials were searched by applying filters: study status, patient's diagnosis, intervention, location and/or biomarker(s). Please visit https://clinicaltrials.gov to search and view for a complete list of open available and updated matched trials.

No trial has been found.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

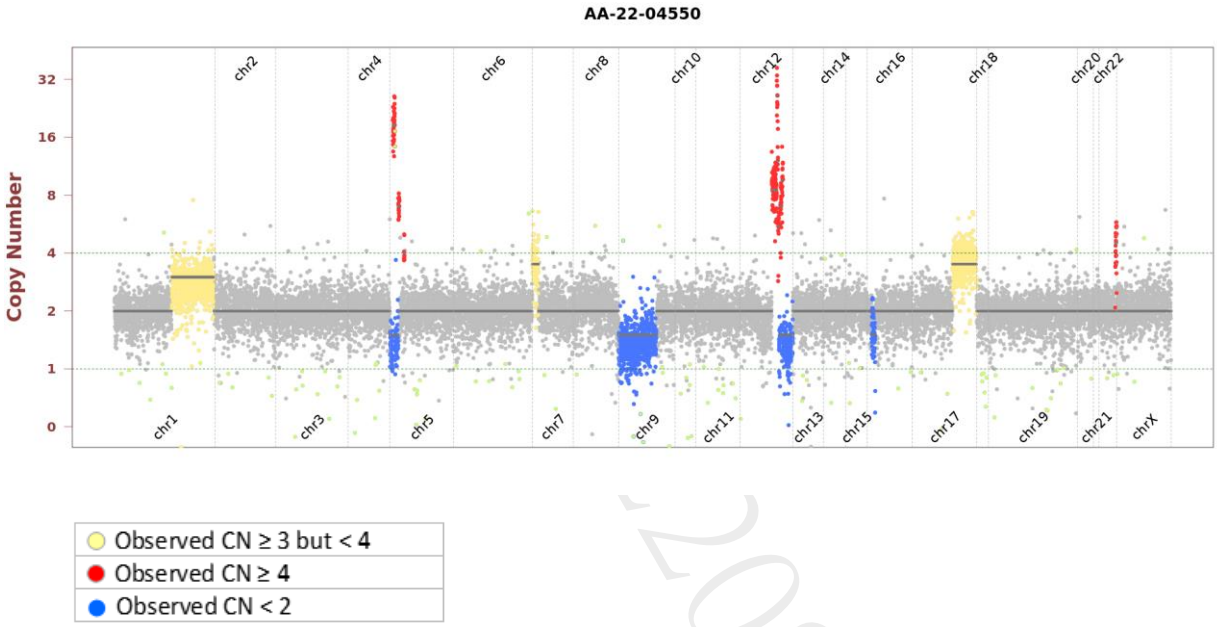
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
NF1	Splice donor	-	c.4577+1G>A	NM_001042492	-	37.1%	804

- Copy Number Alterations

Observed copy number (CN) for each evaluated position is shown on the y-axis. Regions referred to as amplification or deletion are shown in color. Regions without significant changes are represented in gray.



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OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ADGRA2	Splice region	-	c.1833+7G>A	NM_032777	-	59.9%	247
ADGRA2	L474W	10	c.1421T>G	NM_032777	-	57.9%	392
BCL9	P1158L	10	c.3473C>T	NM_004326	-	38.4%	1535
FLT1	Splice region	-	c.1661-3T>C	NM_002019	-	53.0%	542
NF1	M968R	22	c.2903T>G	NM_001042492	-	35.2%	744
NOTCH2	R1260H	23	c.3779G>A	NM_024408	COSM6947255	50.2%	1508
PIK3CA	K733R	15	c.2198A>G	NM_006218	COSM6148	50.2%	877
PRKCI	Splice region	-	c.223+3G>A	NM_002740	-	51.2%	625
RPTOR	Splice region	-	c.2243-7C>T	NM_020761	-	67.1%	1642
SYNE1	R7412H	122	c.22235G>A	NM_182961	-	47.7%	1049

Note:

- This table enlists variants detected by the panel other than those with clinical relevance (reported in Testing Result section). The clinical impact of a genetic variant is determined according to ACT Genomics in-house clinical knowledge database. A negative result does not necessarily indicate absence of biological effect on the tumor. Some variants listed here may possibly have preclinical data or may show potential clinical relevance in the future.

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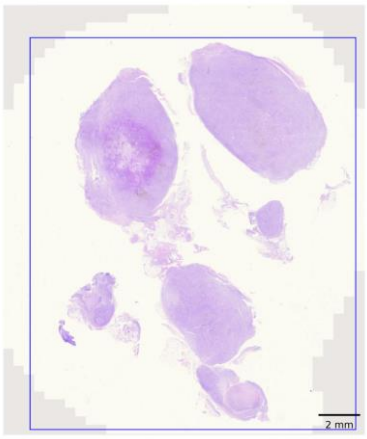
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Jul 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11128446A
- Collection site: Soft tissue, left foot
- Examined by: Dr. Yeh-Han Wang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 80%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 80%
    3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
    4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
    5. Additional comment: NA
- Manual macrodissection: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 858x
- Target Base Coverage at 100x: 93%

RNA test

- Average unique RNA Start Sites per control GSP2: 202

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LIMITATIONS

1. This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject to validation by Sanger or other technologies.
2. The possibility cannot be excluded that certain pathogenic variants detected by other sequencing tools may not be reported in the test because of technical limitation of bioinformatics algorithm or the NGS sequencing platform, e.g. low coverage.
3. This test has been designed to detect fusions in 13 genes sequenced. Therefore, fusion in genes not covered by this test would not be reported. For novel fusions detected in this test, Sanger sequencing confirmation is recommended if residue specimen is available.

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

Extracted genomic DNA was amplified using primers targeting coding exons of analyzed genes and subjected to library construction. Barcoded libraries were subsequently conjugated with sequencing beads by emulsion PCR and enriched using Ion Chef system. Sequencing was performed according to Ion Proton or Ion S5 sequencer protocol (Thermo Fisher Scientific).

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite. Coverage depth was calculated using Torrent Coverage Analysis plug-in. Single nucleotide variants (SNVs) and short insertions/deletions (InDels) were identified using the Torrent Variant Caller plug-in. VEP (Variant Effect Predictor) was used to annotate every variant using databases from Clinvar, COSMIC and Genome Aggregation database. Variants with coverage ≥ 20, allele frequency ≥ 5% and actionable variants with allele frequency ≥ 2% were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at 100x ≥ 85% with a mean coverage ≥ 500x.

Variants reported in Genome Aggregation database with > 1% minor allele frequency (MAF) were considered as polymorphisms. ACT Genomics in-house database was used to determine technical errors. Clinically actionable and biologically significant variants were determined based on the published medical literature.

The copy number alterations (CNAs) were predicted as described below:
Amplicons with read counts in the lowest 5th percentile of all detectable amplicons and amplicons with a coefficient of variation ≥ 0.3 were removed. The remaining amplicons were normalized to correct the pool design bias. ONCOCNV (an established method for calculating copy number aberrations in amplicon sequencing data by Boeva et al., 2014) was applied for the normalization of total amplicon number, amplicon GC content, amplicon length, and technology-related biases, followed by segmenting the sample with a gene-aware model. The method was used as well for establishing the baseline of copy number variations.

Tumor mutational burden (TMB) was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The TMB calculation predicted somatic variants and applied a machine learning model with a cancer hotspot correction. TMB may be reported as “TMB-High”, “TMB-Low” or “Cannot Be Determined”. TMB-High corresponds to ≥ 7.5 mutations per megabase (Muts/Mb); TMB-Low corresponds to < 7.5 Muts/Mb. TMB is reported as “Cannot Be Determined” if the tumor purity of the sample is < 30%.

Classification of microsatellite instability (MSI) status is determined by a machine learning prediction algorithm. The change of a number of repeats of different lengths from a pooled microsatellite stable (MSS) baseline in > 400 genomic loci are used as the features for the algorithm. The final output of the results is either microsatellite Stable (MSS) or microsatellite instability high (MSI-H).

RNA test

Extracted RNA was reverse-transcribed and subjected to library construction. Sequencing was performed according to Ion Proton or Ion S5 sequencer protocol (Thermo Fisher Scientific). To ensure sequencing quality for fusion variant analysis, the average unique RNA Start Sites (SS) per control Gene Specific Primer 2 (GSP 2) should be ≥ 10.

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The fusion analysis pipeline aligned sequenced reads to the human reference genome, identified regions that map to noncontiguous regions of the genome, applied filters to exclude probable false-positive events and, annotated previously characterized fusion events according to Quiver Gene Fusion Database, a curated database owned and maintained by ArcherDX. In general, samples with detectable fusions need to meet the following criteria: (1) Number of unique start sites (SS) for the GSP2 ≥ 3; (2) Number of supporting reads spanning the fusion junction ≥ 5; (3) Percentage of supporting reads spanning the fusion junction ≥ 10%; (4) Fusions annotated in Quiver Gene Fusion Database.

DATABASE USED

- Reference genome: Human genome sequence hg19
- COSMIC v.92
- Genome Aggregation database r2.1.1
- ClinVar (version 20210404)
- ACT Genomics in-house database
- Quiver Gene Fusion Database version 5.1.18

Variant Analysis:
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GENE LIST

SNV & CNV

ABCB1*	ABCC2*	ABCG2*	ABL1	ABL2	ADAMTS1	ADAMTS13	ADAMTS15	ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9
ADAMTSL1	ADGRA2	ADH1C*	AKT1	AKT2	AKT3	ALDH1A1*	ALK	AMER1	APC	AR	ARAF
ARID1A	ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2	AXL
B2M	BAP1	BARD1	BCL10	BCL2*	BCL2L1	BCL2L2*	BCL6	BCL9	BCOR	BIRC2	BIRC3
BLM	BMPR1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2*	BTK	BUB1B	CALR
CANX	CARD11	CASP8	CBFB	CBL	CCNA1	CCNA	CCNB1	CCNB2	CCNB3	CCND1	CCND2
CCND3	CCNE1	CCNE2	CCNH	CD19	CD274	CD58	CD70*	CD79A	CD79B	CDC73	CDH1
CDK1	CDK12	CDK2	CDK4	CDK5	CDK6	CDK7	CDK8	CDK9	CDKN1A	CDKN1B	CDKN2A
CDKN2B	CDKN2C	CEBPA*	CHEK1	CHEK2	CIC	CREBBP	CRKL	CRLF2	CSF1R	CTCF	CTLA4
CTNNA1	CTNNB1	CUL3	CYLD	CYP1A1*	CYP2B6*	CYP2C19*	CYP2C8*	CYP2D6	CYP2E1*	CYP3A4*	CYP3A5*
DAXX	DCUN1D1	DDR2	DICER1	DNMT3A	DOT1L	DPYD	DTX1	E2F3	EGFR	EP300	EPCAM
EPHA2	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2	ERBB3	ERBB4	ERCC1	ERCC2	ERCC3	ERCC4
ERCC5	ERG	ESR1	ESR2	ETV1	ETV4	EZH2	FAM46C	FANCA	FANCC	FANCD2	FANCE
FANCF	FANCG	FANCL	FAS	FAT1	FBXW7	FCGR2B	FGF1*	FGF10	FGF14	FGF19*	FGF23
FGF3	FGF4*	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLT1	FLT3	FLT4
FOXL2*	FOXP1	FRG1	FUBP1	GATA1	GATA2	GATA3	GNA11	GNA13	GNAQ	GNAS	GREM1
GRIN2A	GSK3B	GSTP1*	GSTT1*	HGF	HIF1A	HIST1H1C*	HIST1H1E*	HNF1A	HR	HRAS*	HSP90AA1
HSP90AB1	HSPA4	HSPA5	IDH1	IDH2	IFNL3*	IGF1	IGF1R	IGF2	IKBKB	IKBKE	IKZF1
IL6	IL7R	INPP4B	INSR	IRF4	IRS1	IRS2*	JAK1	JAK2	JAK3	JUN*	KAT6A
KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT	KMT2A	KMT2C	KMT2D	KRAS	LCK	LIG1
LIG3	LMO1	LRP1B	LYN	MALT1	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAP3K7	MAPK1	MAPK3
MAX	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MPL	MRE11
MSH2	MSH6	MTHFR*	MTOR	MUC16	MUC4	MUC6	MUTYH	MYC	MYCL	MYCN	MYD88
NAT2*	NBN	NEFH	NF1	NF2	NFE2L2	NFKB1	NFKBIA	NKX2-1*	NOTCH1	NOTCH2	NOTCH3
NOTCH4	NPM1	NQO1*	NRAS	NSD1	NTRK1	NTRK2	NTRK3	PAK3	PALB2	PARP1	PAX5
PAX8	PBRM1	PDCD1	PDCD1LG2	PDGFRA	PDGFRB	PDIA3	PGF	PHOX2B*	PIK3C2B	PIK3C2G	PIK3C3
PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1	PIK3R2	PIK3R3	PIM1	PMS1	PMS2	POLB	POLD1
POLE	PPARG	PPP2R1A	PRDM1	PRKAR1A	PRKCA	PRKCB	PRKCG	PRKCI	PRKCQ	PRKDC	PRKN
PSMB8	PSMB9	PSME1	PSME2	PSME3	PTCH1	PTEN	PTGS2	PTPN11	PTPRD	PTPRT	RAC1
RAD50	RAD51	RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10	RECQL4
REL	RET	RHOA	RICTOR	RNF43	ROS1	RPPH1	RPTOR	RUNX1	RUNX1T1	RXRA	SDHA
SDHB	SDHC	SDHD	SERPINB3	SERPINB4	SETD2	SF3B1	SGK1	SH2D1A*	SLC19A1*	SLC22A2*	SLCO1B1*
SLCO1B3*	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1*	SOX2*	SOX9	SPEN	SPOP
SRC	STAG2	STAT3	STK11	SUFU	SYK	SYNE1	TAF1	TAP1	TAP2	TAPBP	TBX3
TEK	TERT	TET1	TET2	TGFBR2	TMSB4X*	TNF	TNFAIP3	TNFRSF14	TNFSF11	TOP1	TP53
TPMT*	TSC1	TSC2	TSHR	TYMS	U2AF1	UBE2A*	UBE2K	UBR5	UGT1A1*	USH2A	VDR*
VEGFA	VEGFB	VHL	WT1	XIAP	XPO1	XRCC2	ZNF217				

*Analysis of copy number alterations NOT available.

FUSION

ALK	BRAF	EGFR	FGFR1	FGFR2	FGFR3	MET	NRG1	NTRK1	NTRK2	NTRK3	RET	ROS1

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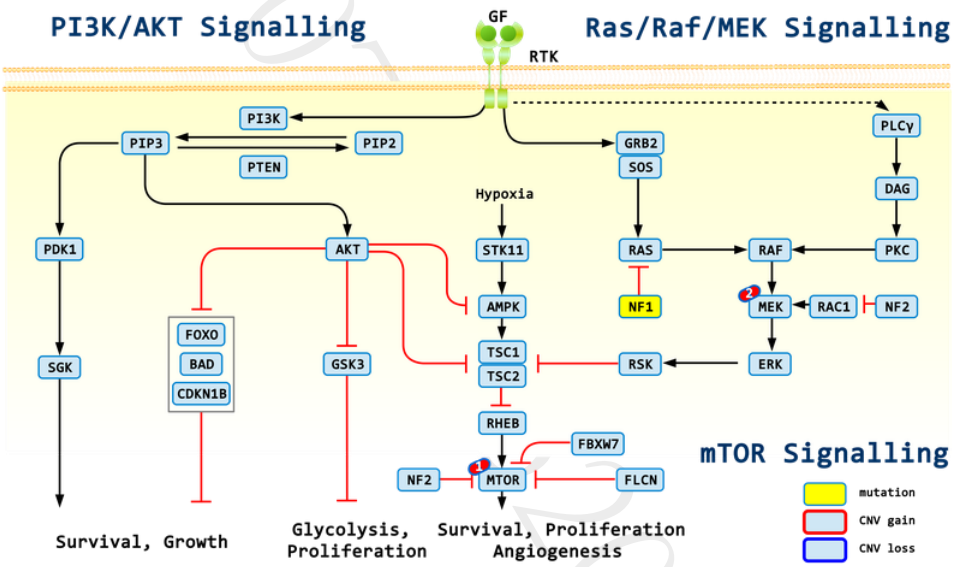
APPENDIX

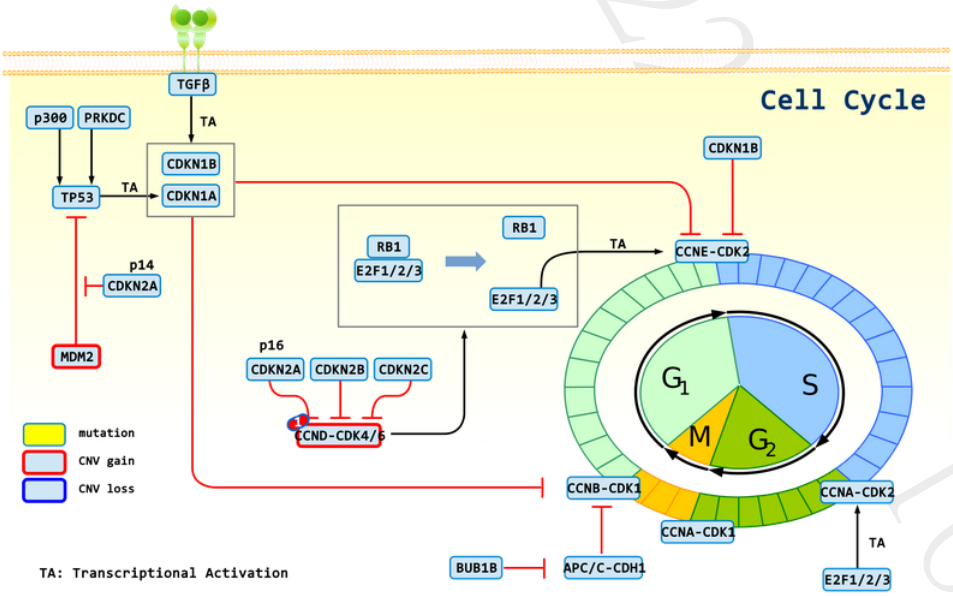
POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Not Applicable.

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Everolimus; 2: Trametinib, Selumetinib



1: Abemaciclib, Palbociclib, Ribociclib

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DISCLAIMER

法律聲明

本檢驗報告僅提供專業醫療參考，結果需經專業醫師解釋及判讀。基因突變資訊非必具備藥物或治療有效性指標，反之亦然。本檢驗報告提供之用藥指引不聲明或保證其臨床有效性，反之亦然。本基因檢測方法係由本公司研究開發，已經過有效性測試。
本檢驗報告非經本公司許可，不得私自變造、塗改，或以任何方式作為廣告及其他宣傳之用途。
本公司於提供檢驗報告後，即已完成本次契約義務，後續之報告解釋、判讀及用藥、治療，應自行尋求相關專業醫師協助，若需將報告移件其他醫師，本人應取得該醫師同意並填寫移件申請書，主動告知行動基因，行動基因僅能配合該醫師意願與時間提供醫師解說。

醫療決策需由醫師決定

任何治療與用藥需經由醫師在考慮病患所有健康狀況相關資訊包含健檢、其他檢測報告和病患意願後，依照該地區醫療照護標準由醫師獨立判斷。醫師不應僅依據單一報告結果(例如本檢測或本報告書內容)做決策。

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

藥物潛在臨床效益(或缺乏潛在臨床效益)的實證證據是依據至少一篇臨床療效個案報告或臨床前試驗做為評估。本公司盡力提供適時及準確之資料，但由於醫學科技之發展日新月異，本公司不就本報告提供的資料是否為準確、適宜或最新作保證。

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REFERENCE

1. PMID: 8563751; 1996, Nat Genet;12(2):144-8
Loss of NF1 results in activation of the Ras signaling pathway and leads to aberrant growth in haematopoietic cells.

2. PMID: 1946382; 1991, Proc Natl Acad Sci U S A;88(21):9658-62
Identification of the neurofibromatosis type 1 gene product.

3. PMID: 2116237; 1990, Cell;62(3):599-608
The neurofibromatosis type 1 gene encodes a protein related to GAP.

4. PMID: 2121370; 1990, Cell;63(4):843-9
The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21.

5. PMID: 14502561; 2003, J Cell Physiol;197(2):214-24
NF1 modulates the effects of Ras oncogenes: evidence of other NF1 function besides its GAP activity.

6. PMID: 19479903; 2009, Mol Carcinog;48(11):1005-17
Neurofibromin physically interacts with the N-terminal domain of focal adhesion kinase.

7. PMID: 28680740; 2017, Adv Med Biol;118():83-122
Haploinsufficient tumor suppressor genes.

8. PMID: 10442636; 1999, Oncogene;18(31):4450-9
Haploinsufficiency for the neurofibromatosis 1 (NF1) tumor suppressor results in increased astrocyte proliferation.

9. PMID: 16288202; 2006, Oncogene;25(16):2297-303
Nf1 haploinsufficiency augments angiogenesis.

10. PMID: 18089636; 2008, Hum Mol Genet;17(7):936-48
Rac1 mediates the osteoclast gains-in-function induced by haploinsufficiency of Nf1.

11. PMID: 7920653; 1994, Nat Genet;7(3):353-61
Tumour predisposition in mice heterozygous for a targeted mutation in Nf1.

12. PMID: 25026295; 2014, Oncotarget;5(15):5873-92
The NF1 gene revisited - from bench to bedside.

13. PMID: 29892687; 2018, Gynecol Oncol Rep;23():41-44
Clonal lineage of high grade serous ovarian cancer in a patient with neurofibromatosis type 1.

14. PMID: 29926297; 2018, Breast Cancer Res Treat;171(3):719-735
Breast cancer in women with neurofibromatosis type 1 (NF1): a comprehensive case series with molecular insights into its aggressive phenotype.

15. PMID: 28637487; 2017, Hum Genomics;11(1):13
The NF1 somatic mutational landscape in sporadic human cancers.

16. PMID: 15840687; 2005, Gut;54(8):1129-35
NF1 gene loss of heterozygosity and expression analysis in sporadic colon cancer.

17. PMID: 20129251; 2010, Cancer Cell;17(1):98-110
Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1.

18. PMID: 27158780; 2016, Nat Genet;48(6):607-16
Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas.

19. PMID: 32669708; 2020, Nature;583(7818):807-812

The National Lung Matrix Trial of personalized therapy in lung cancer.

20. PMID: 21482774; 2012, Proc Natl Acad Sci U S A;109(8):2730-5
Genome-wide functional screen identifies a compendium of genes affecting sensitivity to tamoxifen.

21. PMID: 24535670; 2014, Cancer Discov;4(5):606-19
Reduced NF1 expression confers resistance to EGFR inhibition in lung cancer.

22. PMID: 29703253; 2018, BMC Cancer;18(1):479
SMAD4 and NF1 mutations as potential biomarkers for poor prognosis to cetuximab-based therapy in Chinese metastatic colorectal cancer patients.

23. PMID: 30858928; 2019, Oncotarget;10(14):1440-1457
CRISPR-induced RASGAP deficiencies in colorectal cancer organoids reveal that only loss of NF1 promotes resistance to EGFR inhibition.

24. PMID: 24576830; 2014, Cancer Res;74(8):2340-50
Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence.

25. PMID: 23171796; 2013, Cancer Discov;3(3):338-49
Elucidating distinct roles for NF1 in melanomagenesis.

26. PMID: 23288408; 2013, Cancer Discov;3(3):350-62
A genome-scale RNA interference screen implicates NF1 loss in resistance to RAF inhibition.

27. PMID: 24265153; 2014, Cancer Discov;4(1):94-109
The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma.

28. PMID: 30269082; 2019, Gut;68(7):1152-1161
Liquid biopsies to track trastuzumab resistance in metastatic HER2-positive gastric cancer.

29. PMID: 26936308; 2016, J Clin Pharm Ther;41(3):357-359
Prolonged disease control with MEK inhibitor in neurofibromatosis type I-associated glioblastoma.

30. PMID: 22573716; 2012, Cancer Res;72(13):3350-9
Sensitivity of glioblastomas to clinically available MEK inhibitors is defined by neurofibromin 1 deficiency.

31. PMID: 19727076; 2009, Nature;461(7262):411-4
Response and resistance to MEK inhibition in leukaemias initiated by hyperactive Ras.

32. PMID: 23858101; 2013, Mol Cancer Ther;12(9):1906-17
NF1 deletion generates multiple subtypes of soft-tissue sarcoma that respond to MEK inhibition.

33. PMID: 23221341; 2013, J Clin Invest;123(1):340-7
MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors.

34. PMID: 18483311; 2008, Mol Cancer Ther;7(5):1237-45
Effective in vivo targeting of the mammalian target of rapamycin pathway in malignant peripheral nerve sheath tumors.

35. PMID: 23209032; 2013, Clin Cancer Res;19(2):450-61
Prognostic significance of AKT/mTOR and MAPK pathways and antitumor effect of mTOR inhibitor in NF1-related and sporadic malignant peripheral nerve sheath tumors.

36. PMID: 26859683; 2016, Oncotarget;7(9):10547-56
Next-generation sequencing reveals somatic mutations that confer exceptional response to everolimus.

37. PMID: 12432268; 2002, Cancer Biol Ther;1(3):226-31
Cycling to cancer with cyclin D1.

38. PMID: 8101826; 1993, Genes Dev;7(8):1572-83
Subunit rearrangement of the cyclin-dependent kinases is associated with cellular transformation.

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39. PMID: 8221695; 1993, Cancer Res;53(22):5535-41
Coamplification of the CDK4 gene with MDM2 and GLI in human sarcomas.

40. PMID: 8586464; 1995, Glia;15(3):289-96
Gene amplification in human gliomas.

41. PMID: 9916925; 1999, Am J Pathol;154(1):113-8
Gene amplification and overexpression of CDK4 in sporadic breast carcinomas is associated with high tumor cell proliferation.

42. PMID: 24089445; 2013, Clin Cancer Res;19(19):5320-8
The cell-cycle regulator CDK4: an emerging therapeutic target in melanoma.

43. PMID: 23569312; 2013, J Clin Oncol;31(16):2024-8
Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma.

44. PMID: 27124835; 2016, JAMA Oncol;2(7):937-40
Progression-Free Survival Among Patients With Well-Differentiated or Dedifferentiated Liposarcoma Treated With CDK4 Inhibitor Palbociclib: A Phase 2 Clinical Trial.

45. PMID: 25501126; 2015, Clin Cancer Res;21(5):995-1001
CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment.

46. PMID: 27217383; 2016, Cancer Discov;6(7):740-53
Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non-Small Cell Lung Cancer, and Other Solid Tumors.

47. PMID: 19536107; 2009, Nat Rev Cancer;9(7):463-75
Novel anticancer targets: revisiting ERBB2 and discovering ERBB3.

48. PMID: 9130710; 1997, EMBO J;16(7):1647-55
ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling.

49. PMID: 22785351; 2012, Nat Rev Cancer;12(8):553-63
The ERBB network: at last, cancer therapy meets systems biology.

50. PMID: 7515147; 1994, Mol Cell Biol;14(6):3550-8
ErbB3 is involved in activation of phosphatidylinositol 3-kinase by epidermal growth factor.

51. PMID: 12853564; 2003, Proc Natl Acad Sci U S A;100(15):8933-8
The ErbB2/ErbB3 heterodimer functions as an oncogenic unit: ErbB2 requires ErbB3 to drive breast tumor cell proliferation.

52. PMID: 19208461; 2009, Curr Opin Cell Biol;21(2):177-84
ErbB receptors and signaling pathways in cancer.

53. PMID: 23680147; 2013, Cancer Cell;23(5):603-17
Oncogenic ERBB3 mutations in human cancers.

54. PMID: 18698037; 2008, Clin Cancer Res;14(16):5188-97
HER3 is a determinant for poor prognosis in melanoma.

55. PMID: 20647770; 2010, Cancer Biol Ther;10(6):555-63
ErbB3 expression promotes tumorigenesis in pancreatic adenocarcinoma.

56. PMID: 30057690; 2018, Oncol Rev;12(1):355
HER3 signaling and targeted therapy in cancer.

57. PMID: 30109175; 2018, Acta Pharm Sin B;8(4):503-510
Understanding the biology of HER3 receptor as a therapeutic target in human cancer.

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58. PMID: 25216528; 2014, Oncotarget;5(16):7138-48
HER3 as biomarker and therapeutic target in pancreatic cancer: new insights in pertuzumab therapy in preclinical models.

59. PMID: 27044931; 2016, J Clin Oncol;34(18):2165-71
Afatinib Activity in Platinum-Refractory Metastatic Urothelial Carcinoma in Patients With ERBB Alterations.

60. PMID: 29902295; 2018, JAMA Oncol;4(9):1189-1197
Association of ERBB Mutations With Clinical Outcomes of Afatinib- or Erlotinib-Treated Patients With Lung Squamous Cell Carcinoma: Secondary Analysis of the LUX-Lung 8 Randomized Clinical Trial.

61. PMID: 20485140; 2010, Ann Surg;251(6):1107-16
HER-3 overexpression is prognostic of reduced breast cancer survival: a study of 4046 patients.

62. PMID: 20816829; 2010, Semin Cell Dev Biol;21(9):944-50
The role of HER3, the unpretentious member of the HER family, in cancer biology and cancer therapeutics.

63. PMID: 24886126; 2014, Mol Cancer;13():105
Targeting of erbB3 receptor to overcome resistance in cancer treatment.

64. PMID: 16000581; 2005, Clin Cancer Res;11(13):4835-42
Can molecular markers predict when to implement treatment with aromatase inhibitors in invasive breast cancer?

65. PMID: 20064507; 2010, Exp Cell Res;316(7):1083-100
Mechanisms of resistance to HER family targeting antibodies.

66. PMID: 16818711; 2006, Clin Cancer Res;12(13):4103-11
Signaling via ErbB2 and ErbB3 associates with resistance and epidermal growth factor receptor (EGFR) amplification with sensitivity to EGFR inhibitor gefitinib in head and neck squamous cell carcinoma cells.

67. PMID: 31663373; 2019, Scand J Clin Lab Invest;79(8):601-612
Clinicopathological and prognostic values of ErbB receptor family amplification in primary osteosarcoma.

68. PMID: 33354548; 2020, South Asian J Cancer;9(2):74-79
Genomic Landscape and Targeted Treatment of Gallbladder Cancer: Results of a First Ongoing Prospective Study.

69. PMID: 25550088; 2015, Immunol Res;61(3):250-9
The roles of IL-2 and IL-10 enhance anti-CD45RBmAb immune inhibition in allograft skin.

70. PMID: 8875929; 1996, Science;274(5289):948-53
Structure of the MDM2 oncoprotein bound to the p53 tumor suppressor transactivation domain.

71. PMID: 1535557; 1992, Cell;69(7):1237-45
The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivation.

72. PMID: 9671804; 1998, Nucleic Acids Res;26(15):3453-9
The MDM2 gene amplification database.

73. PMID: 18834305; 2009, Annu Rev Pharmacol Toxicol;49():223-41
Small-molecule inhibitors of the MDM2-p53 protein-protein interaction to reactivate p53 function: a novel approach for cancer therapy.

74. PMID: 24136147; 2013, Br J Cancer;109(10):2685-95
Nutlin-3 preferentially sensitises wild-type p53-expressing cancer cells to DR5-selective TRAIL over rhTRAIL.

75. PMID: 26125230; 2015, Oncotarget;6(26):22666-79
The MDM2-inhibitor Nutlin-3 synergizes with cisplatin to induce p53 dependent tumor cell apoptosis in non-small cell lung cancer.

76. PMID: 26252575; 2015, Oncol Rep;34(4):1692-700
Nutlin-3 sensitizes nasopharyngeal carcinoma cells to cisplatin-induced cytotoxicity.

77. PMID: 16815295; 2006, Biochem Biophys Res Commun;347(1):60-6

p73 and MDM2 confer the resistance of epidermoid carcinoma to cisplatin by blocking p53.

78. PMID: 27646943; 2016, J Clin Oncol;34(33):4000-4007
Genetic Determinants of Cisplatin Resistance in Patients With Advanced Germ Cell Tumors.

79. PMID: 32391110; 2020, Oncol Lett;19(6):4169-4176
Genetic alterations in epidermal growth factor receptor-tyrosine kinase inhibitor-naïve non-small cell lung carcinoma.

80. PMID: 30391576; 2019, J Thorac Oncol;14(2):193-202
Concurrent Genetic Alterations Predict the Progression to Target Therapy in EGFR-Mutated Advanced NSCLC.

81. PMID: 32611363; 2020, Mol Med;26(1):66
Primary resistance to first-generation EGFR-TKIs induced by MDM2 amplification in NSCLC.

82. PMID: 15165086; 2004, Lung Cancer;43(3):285-95
MDM2 gene amplification: a new independent factor of adverse prognosis in non-small cell lung cancer (NSCLC).

83. PMID: 28351930; 2017, Clin Cancer Res;23(15):4242-4250
Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate.

84. PMID: 21332640; 2011, J Cell Mol Med;15(7):1433-42
Targeting telomerase-expressing cancer cells.

85. PMID: 19571879; 2009, Nature;460(7251):66-72
Telomerase modulates Wnt signalling by association with target gene chromatin.

86. PMID: 23159929; 2012, Nat Cell Biol;14(12):1270-81
Telomerase directly regulates NF-κB-dependent transcription.

87. PMID: 19701182; 2009, Nature;461(7261):230-5
An RNA-dependent RNA polymerase formed by TERT and the RMRP RNA.

88. PMID: 23348506; 2013, Science;339(6122):957-9
Highly recurrent TERT promoter mutations in human melanoma.

89. PMID: 23530248; 2013, Proc Natl Acad Sci U S A;110(15):6021-6
TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal.

90. PMID: 11103775; 2000, Cancer Res;60(22):6230-5
Frequent amplification of the telomerase reverse transcriptase gene in human tumors.

91. PMID: 12007187; 2002, Genes Chromosomes Cancer;34(3):269-75
Amplification of the telomerase reverse transcriptase (hTERT) gene in cervical carcinomas.

92. PMID: 25301727; 2014, Oncotarget;5(20):10048-57
TERT promoter mutations and gene amplification: promoting TERT expression in Merkel cell carcinoma.

93. PMID: 16641908; 2006, Br J Cancer;94(10):1452-9
Amplification of telomerase (hTERT) gene is a poor prognostic marker in non-small-cell lung cancer.

94. PMID: 27982019; 2017, Cancer Gene Ther;24(1):20-27
The associations of TERT-CLPTM1L variants and TERT mRNA expression with the prognosis of early stage non-small cell lung cancer.

95. PMID: 29100407; 2017, Oncotarget;8(44):77540-77551
TERT promoter status and gene copy number gains: effect on TERT expression and association with prognosis in breast cancer.

96. PMID: 28968163; 2017, J Clin Oncol;35(32):3638-3646
MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer.

97. PMID: 28580882; 2017, J Clin Oncol;35(25):2875-2884

ACT Onco® + Report

MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy.

98. PMID: 28533223; 2017, Clin Cancer Res;23(17):5218-5224
MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer.

99. PMID: 26703889; 2016, Lancet;387(10022):968-977
Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study.

100. PMID: 22149876; 2012, N Engl J Med;366(6):520-9
Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.

101. PMID: 21306238; 2011, N Engl J Med;364(6):514-23
Everolimus for advanced pancreatic neuroendocrine tumors.

102. PMID: 23158522; 2013, Lancet;381(9861):125-32
Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial.

103. PMID: 18653228; 2008, Lancet;372(9637):449-56
Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial.

104. PMID: 27959613; 2016, N Engl J Med;375(20):1925-1936
Palbociclib and Letrozole in Advanced Breast Cancer.

105. PMID: 26030518; 2015, N Engl J Med;373(3):209-19
Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer.

106. PMID: 27717303; 2016, N Engl J Med;375(18):1738-1748
Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer.

107. PMID: 29072975; 2018, J Clin Oncol;36(1):7-13
Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer.

108. PMID: 27080216; 2016, Lancet Oncol;17(5):642-50
Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial.

109. PMID: 25265492; 2014, N Engl J Med;371(20):1877-88
Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma.

110. PMID: 22663011; 2012, N Engl J Med;367(2):107-14
Improved survival with MEK inhibition in BRAF-mutated melanoma.