ACT Onco® + Report

PATIENT		
Identifier: 李美蓉		Patient ID: 41926618
Date of Birth: Sep 26, 1968		Gender: Female
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
Name: 趙恒勝醫師		Tel: 886-228712121
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SPECIMEN		
Specimen ID: S11216072D	Collection site: Lung	Type: FFPE tissue
Date received: Jun 19, 2023	Lab ID: AA-23-04026	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	
EGFR L858R	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-	-
FANCA H330fs	-	-	Talazoparib

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
FANCA H330fs	Olaparib, Rucaparib	-
NF1 R416*	Everolimus, Selumetinib, Trametinib	Cabozantinib, Crizotinib, Erlotinib, Gefitinib, Afatinib, Lapatinib, Vemurafenib, Cetuximab, Trastuzumab
EGFR Amplification	Afatinib, Erlotinib, Gefitinib, Osimertinib, Cetuximab, Necitumumab, Panitumumab	-
FLT4 Amplification	Pazopanib	-

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
EGFR	L858R	86.2%
FANCA	H330fs	47.8%
NF1	R416*	18.4%
TP53	P152L	23.8%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr13	*BRCA2*	Heterozygous deletion	1
Chr5	*RAD50*	Heterozygous deletion	1
Chr5	*FLT4*	Amplification	7
Chr7	*EGFR*	Amplification	36

- 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)	1.9 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:
- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 31% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- 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 1		
EGFR L858R	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	**sensitive**
Level 3A		
FANCA H330fs	Talazoparib	**sensitive**
Level 3B		
FANCA H330fs	Olaparib, Rucaparib	**sensitive**
NF1 R416*	Selumetinib	**sensitive**
EGFR Amplification	Afatinib, Erlotinib, Gefitinib, Osimertinib, Cetuximab, Necitumumab, Panitumumab	**sensitive**
Level 4		
NF1 R416*	Everolimus, Trametinib	**sensitive**
FLT4 Amplification	Pazopanib	**sensitive**
NF1 R416*	Cabozantinib, Crizotinib, Erlotinib, Gefitinib, Afatinib, Lapatinib, Vemurafenib, Cetuximab, Trastuzumab	**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
EGFR aberration	Likely associated with WORSE response to ICIs

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 R416*	Tamoxifen	**Less sensitive**	Clinical	Breast cancer

OTHERS

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AG	Irinotecan-based regimens	Level 1B
Clinical Interpretation: Patients with the AG genotype and cancer who are treated with irinotecan-based regimens may have an increased risk of diarrhea and neutropenia as compared to patients with the GG genotype, or a decreased risk of diarrhea and neutropenia compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk of diarrhea and neutropenia.				

* Level of evidence was defined by PharmGKB (https://www.pharmgkb.org/page/clinAnnLevels)

Level 1A: Clinical annotations describe variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation.
Level 1B: Clinical annotations describe variant-drug combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label.
Level 2A: Variants in Level 2A clinical annotations are found in PharmGKB's Tier 1 Very Important Pharmacogenes (VIPs). These variants are in known pharmacogenes, implying causation of drug phenotype is more likely.

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.

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VARIANT INTERPRETATION

EGFR L858R, Amplification

Biological Impact

The EGFR gene encodes for the Epidermal Growth Factor Receptor, a receptor tyrosine kinase which binds to its ligands, including Epidermal Growth Factor (EGF) and Transforming Growth Factor-alpha (TGF-alpha), activates downstream signaling pathways, including the canonical oncogenic MAPK and PI3K/AKT/mTOR signaling cascades[1]. Increased EGFR activity by mutations and/or amplification of the EGFR gene has been described in a wide range of cancers, such as lung, brain, colorectal and head and neck cancer[2]. Mutations in the kinase domain of EGFR are commonly observed in non-small cell lung cancer (NSCLC), resulting in a constitutively activated form of the receptor[3]. On the other hand, in the brain and colorectal cancers, the most prevalent EGFR alteration is copy number amplification that results in receptor overexpression[4].

EGFR L858R is a missense mutation at position 858, located in exon 21, which encodes part of the kinase domain, from a leucine to an arginine residue[5]. The two most common EGFR alterations, L858R mutation and exon 19 deletions can result in constitutive activation of signal transduction pathways, leading to cell proliferation or anti-apoptosis without ligand binding[6].

Therapeutic and prognostic relevance

There is accumulated clinical evidence suggested that patients with MDM2/MDM4 amplification 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) inhibitors therapies[7](Annals of Oncology (2017) 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376).

EGFR mutation has been determined as an inclusion criteria for the trials examining afatinib efficacy in malignant glioma and pediatric tumors (NCT02423525, NCT02372006).The first- and second-generation EGFR-TKIs, including dacomitinib, erlotinib, gefitinib, and afatinib, have been approved by the U.S. FDA as first-line treatments for non-small cell lung cancer patients with EGFR exon 19 deletion or L858R mutation. Osimertinib, a third-generation EGFR-TKI, has also been approved by the U.S. FDA. It is indicated for adjuvant treatment or first-line treatment of metastatic NSCLC patients with EGFR exon 19 deletion or L858R mutation.

A phase III trial (NCT01774721) show that dacomitinib significantly improved PFS over gefitinib in first-line treatment of patients with EGFR-mutation-positive NSCLC[8]. Another phase III trial (NCT00949650) demonstrated that median PFS among lung cancer patients with exon 19 deletion or L858R EGFR mutation (n=308) was 13.6 months for afatinib and 6.9 months for chemotherapy[9]. Results from a double-blind, phase 3 trial further showed that osimertinib significantly demonstrated longer PFS than standard EGFR-TKIs (18.9 months vs. 10.2 months) in previously untreated EGFR mutation–positive (exon 19 deletion or L858R) advanced NSCLC[10].

Increased EGFR copy number is associated with tumor response to panitumumab, an EGFR-targeted antibody, in colorectal cancer patients, based on data from a phase III study[11]. A recent Phase II trial of cetuximab (another approved anti-EGFR antibody) oxaliplatin/leucovorin/5-fluorouracil therapy in first-line setting also demonstrated an association between higher EGFR copy number and better overall survival in gastric cancer patients[12]. The addition of cetuximab to chemotherapy reduced the risk of death by 44% for advanced squamous non–small cell lung cancer (NSCLC) patients with EGFR-amplified tumor, according to clinical trial findings presented at the 2015 World Conference on Lung Cancer. Preclinical data of gastric cancer (GC)-derived xenograft also showed that EGFR amplification or overexpression is associated with response to cetuximab[13]. Besides, a phase III study of necitumumab showed squamous cell lung cancer patients with EGFR amplification had improved overall survival (14.8 versus 7.6 months, p = 0.033) (NCT00981058)[14].

Increased EGFR copy number has been shown to be associated with better response and survival in gefitinib or erlotinib treatment for NSCLC[15][16][17][18][19][20], esophageal cancer[21], and mucinous urethral adenocarcinoma[22]. Concurrent amplification of EGFR and ERBB2 is associated with response to afatinib in patients with trastuzumab-refractory esophagogastric cancer[23]. However, dacomitinib has been reported with a limited single-agent activity in recurrent glioblastoma with EGFR amplification in a phase II trial[24]. EGFR amplification has been determined as an inclusion criterion for the trials evaluating erlotinib, afatinib, and osimertinib efficacy in PDAC with co-expressing EGFR and c-Met (NCT03213626), glioblastoma (NCT03732352), urothelial tract carcinoma (NCT02780687), and brain cancer (NCT02423525).

FANCA H330fs

Biological Impact

The Fanconi anemia, complementation group A (FANCA) gene encodes for a protein that is a member of the Fanconi anemia complementation group (FANC), which currently includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (also called BRIP1), FANCL, FANCM and FANCN (also called PALB2) are involved in the repair of DNA double-strand breaks (DSBs) by homologous recombination (HR)[25][26]. Fanconi Anemia is an autosomal recessive disease characterized by hematological abnormalities, bone marrow failure, limb deformities, skin hyperpigmentation, and susceptibility to hematologic and solid malignancies, such as acute myeloid leukemia and head and neck carcinoma[27][28].

H330fs mutation results in a change in the amino acid sequence beginning at 330, likely to cause premature truncation of the functional FANCA protein (UniProtKB). This mutation is predicted to lead to a loss of FANCA protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

Talazoparib is FDA-approved for treating mCRPC patients harboring mutations in homologous recombination repair (HRR) genes, including FANCA.

FANCA has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in advanced solid tumors (NCT03297606; CAPTUR trial) and ovarian cancer[29], rucaparib efficacy in ovarian cancer[30]or prostate cancer[31](NCT03533946), niraparib efficacy in metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma (NCT03840967), pancreatic cancer (NCT03553004), and prostate cancer (NCT02854436), and talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

In a phase II (TOPARP-B) trial, a castration-resistant prostate cancer patients harboring FANCA deleterious mutations had a PSA50 response after olaparib treatment[32]. In another phase II trial, 1 of 4 patients with deleterious FANCA alterations also had a PSA response and complete radiographic response after rucaparib treatment[31].

NF1 R416*

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[33][34][35][36]. 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[37][38]. 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[39][40][41][42][43]. 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[44][45][46].

Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types[47], including myelodysplastic syndromes, melanomas, colon cancer[48], glioblastomas[49], lung cancer[50], ovarian cancer, and breast cancer[44].

R416* mutation results in a premature truncation of the NF1 protein at amino acid 416 (UniProtKB). This mutation is predicted to lead to a loss of NF1 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

Selumetinib is FDA-approved for treating pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

In the NCCN guidelines for CNS cancers, selumetinib is recommended as a treatment option for recurrent or progressive NF-1 mutated glioma patient.

NF1 mutation/ loss has been determined as an inclusion criterion for the trials evaluating selumetinib efficacy in solid tumors (NCT02664935, NCT03155620)[51].

NF1 depletion is associated with drug resistance to various inhibitors, such as RAF, EGFR, tamoxifen, and retinoic acid[47][52]. Loss of NF1 in lung adenocarcinomas, colorectal cancer, and BRAF-mutated melanomas is associated with resistance to anti-EGFR and BRAF inhibitors[53][54][55][56][57][58]. NF1 loss contributes to trastuzumab resistance in HER2-positive metastatic gastric cancer, but a combination of HER2 and MEK/ERK inhibitors may overcome this resistance[59]. Trametinib is effective in treating neurofibromatosis type I-associated glioblastoma[60]. Patients with mutations in the mTOR pathway, including NF1, have responded to everolimus[61]. However, a patient with metastatic lung cancer harboring CCDC6-ROS1 and NF1 truncating mutation treated with crizotinib had a short overall survival of one month[62].

NF1 depletion has been linked to drug resistance to several inhibitors in vitro, including RAF, EGFR, and trastuzumab. However, adding MEK inhibitors could restore sensitivity to erlotinib[53], and MEK and mTOR inhibitors showed promise in NF1-deficient tumors[63][64]. Knockdown of NF1 also led to resistance to crizotinib and cabozantinib treatment in ROS1 fusion-positive cells[62].

TP53 P152L

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[65]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[66].

TP53 P152L lies within the DNA-binding domain of the p53 protein (UniProtKB). This mutation results in decreased p53 transactivation activity and inability to suppress colony formation in vitro[67].

Therapeutic and prognostic relevance

Despite having a high mutation rate in cancers, there are currently no approved targeted therapies for TP53 mutations. A phase II trial demonstrated that Wee1 inhibitor (AZD1775) in combination with carboplatin was well tolerated and showed promising anti-tumor activity in TP53-mutated ovarian cancer refractory or resistant (< 3 months) to standard first-line therapy (NCT01164995)[68].

In a retrospective study (n=19), advanced sarcoma patients with TP53 loss-of-function mutations displayed improved progression-free survival (208 days versus 136 days) relative to patients with wild-type TP53 when treated with pazopanib[69]. Results from another Phase I trial of advanced solid tumors (n=78) demonstrated that TP53 hotspot mutations are associated with better clinical response to the combination of pazopanib and vorinostat[70].

Advanced solid tumor and colorectal cancer patients harboring a TP53 mutation have been shown to be more sensitive to bevacizumab when compared with patients harboring wild-type TP53[71][72][73]. In a pilot trial (n=21), TP53-negative breast cancer patients demonstrated increased survival following treatment with bevacizumab in combination with chemotherapy agents, Adriamycin (doxorubicin) and Taxotere (docetaxel)[74]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[75][76]. In a retrospective study of non-small cell lung cancer (NSCLC), TP53 mutations were associated with high expression of VEGF-A, the primary target of bevacizumab, offering a mechanistic explanation for why patients exhibit improved outcomes after bevacizumab treatment when their tumors harbor mutant TP53 versus wild-type TP53[77].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[78]. BRCA2 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[79]. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia[80]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[81].

Therapeutic and prognostic relevance

Multiple PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have been approved by the U.S. FDA for the treatment of cancer. Olaparib is approved for multiple settings in advanced ovarian cancer, metastatic breast cancer with BRCA mutations, metastatic pancreatic cancer, and mCRPC with BRCA mutation or HRR gene mutations, including BRCA. Rucaparib is approved for maintenance treatment of recurrent ovarian cancer with BRCA mutations and mCRPC with BRCA mutations. Niraparib is approved for maintenance treatment of advanced ovarian cancer and recurrent ovarian cancer with BRCA mutations. Talazoparib is approved for locally advanced or metastatic breast cancer with BRCA mutations and mCRPC with HRR gene mutations, including BRCA.

According to the NCCN guidelines, rucaparib is recommended as recurrence therapy for patients with BRCA-mutated ovarian cancer who have been treated with multiple lines of chemotherapy. It is also recommended as maintenance therapy for patients with metastatic pancreatic cancer who have undergone prior platinum-based therapy and harbor germline or somatic BRCA mutations. Additionally, niraparib is recommended as maintenance therapy for ovarian cancer patients with BRCA mutations.

FLT4 Amplification

Biological Impact

The FLT4 (FMS-like tyrosine kinase 4) gene encodes for a vascular endothelial growth factor receptor 3 (VEGFR3), which involves in lymphangiogenesis and the maintenance of lymphatic endothelium[82]. VEGFR3 has been shown to mediate cell proliferation, survival, and chemoresistance in leukemia[83], and to promote invasion and metastasis of human lung adenocarcinoma cells[84]. Mutations in FLT4 cause hereditary Nonne-Milroy disease, an autosomal dominant form of primary lymphedema type IA[85]. In addition to lymphatic endothelial cells, FLT4 is also expressed in lung adenocarcinoma[86], colorectal adenocarcinoma[87], head and neck carcinoma[88], prostate carcinoma[89], leukemia[83], and Kaposi's sarcoma[90]. FLT4 expression levels were also shown to correlate with different stages of cervical carcinogenesis[91].

Therapeutic and prognostic relevance

In a phase II trial of sorafenib in radiation-associated breast angiosarcomas, patients with co-amplification of MYC and FLT4 achieved complete or partial response (DOI: 10.1200/jco.2012.30.15_suppl.10019). In clinical studies, a subset of patients with secondary angiosarcoma, mostly related to radiation-induced breast cancer and postlymphedema, co-harbored MYC and FLT4 amplification. The MYC and FLT4 amplification was associated to poor prognosis[92][93].

A case report showed that an angiosarcoma patient with concurrent KDR and FLT4 amplification developed progressive disease by sorafenib treatment, and then the patient experienced a potent antitumor response and achieved clinically stable disease for 6 months after switching to pazopanib therapy[94].

RAD50 Heterozygous deletion

Biological Impact

The RAD50 gene encodes a highly-conserved DNA double-strand break (DSB) repair factor. It forms MRN complex with NBS1 and MRE11 protein and is involved in sensing and early processing of DSB, cell cycle checkpoints, DNA recombination and maintenance of telomeres[95][96]. Mutations in the components of the MRN complex could increase susceptibility to familial breast cancer[97][98], gastric cancer[99], colorectal cancer[100], and urothelial cancer[101]. RAD50 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[102]. Besides, RAD50 deletion was also suggested as a marker of BRCAness, a phenotype shared between non-BRCA1/2-mutated ovarian cancers and BRCA1/2-mutated ovarian cancers[103].

Therapeutic and prognostic relevance

Preclinical data showed that knockdown of the RAD50 gene in ovarian cancer cell lines was significantly associated with better responses to two PARP inhibitors, olaparib and rucaparib[103]. RAD50 has been selected as an inclusion criterion for the trials examining talazoparib efficacy in HER2-negative breast cancer, olaparib efficacy in breast cancer, rucaparib efficacy in metastatic prostate cancer and niraparib efficacy in any malignancy (except prostate) (NCT02401347, NCT03207347, NCT03344965, NCT03413995).

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US FDA-APPROVED DRUG(S)

Afatinib (GILOTRIF)

Afatinib acts as an irreversible covalent inhibitor of the ErbB family of receptor tyrosine kinases, including epidermal growth factor receptor (EGFR) and erbB-2 (HER2). Afatinib is developed and marketed by Boehringer Ingelheim under the trade name GILOTRIF (United States) and GIOTRIF (Europe).

- FDA Approval Summary of Afatinib (GILOTRIF)

LUX-Lung 8[104] NCT01523587	**Non-small cell lung carcinoma** (Approved on 2016/04/15)
	EGFR ex19del or L858R
	Afatinib vs. Erlotinib [PFS(M): 2.4 vs. 1.9]
LUX-Lung 3[105] NCT00949650	**Non-small cell lung carcinoma** (Approved on 2013/07/13)
	EGFR ex19del or L858R
	Afatinib vs. Pemetrexed + cisplatin [PFS(M): 11.1 vs. 6.9]

Cetuximab (ERBITUX)

Cetuximab is a recombinant, chimeric (human/mouse) monoclonal antibody that binds to the extracellular domain and inhibits epidermal growth factor receptor (EGFR). Cetuximab is developed by ImClone and marketed by Eli Lilly under the trade name ERBITUX.

- FDA Approval Summary of Cetuximab (ERBITUX)

BEACON CRC[106] NCT02928224	**Colorectal cancer** (Approved on 2020/04/08)
	BRAF V600E
	Encorafenib in combination with cetuximab vs. Irinotecan or folfiri with cetuximab [OS(M): 8.4 vs. 5.4]
CRYSTAL[107] NCT00154102	**Colorectal cancer** (Approved on 2012/07/06)
	KRAS Wild-type/EGFR-expressing
	Cetuximab + 5-fluorouracil + folinic acid + irinotecan vs. 5-fluorouracil + folinic acid + irinotecan [PFS(M): 8.9 vs. 8.1]
EXTREME[108] NCT00122460	**Head and neck cancer** (Approved on 2011/11/07)
	-
	Cetuximab + cisplatin/carboplatin + 5-fu vs. Cisplatin/carboplatin + 5-fu [OS(M): 10.1 vs. 7.4]
[109] NCT00004227	**Head and neck cancer** (Approved on 2006/03/01)
	-
	Cetuximab + radiation vs. Radiation [OS(M): 49 vs. 29.3]
[110] NCT00063141	**Colorectal cancer** (Approved on 2004/02/12)
	KRAS Wild-type/EGFR-expressing
	Cetuximab + irinotecan vs. Irinotecan [DOR(M): 5.7 vs. 4.2]

Dacomitinib (VIZIMPRO)

Dacomitinib is an oral kinase inhibitor that targets EGFR. Dacomitinib is developed and marketed by Pfizer under the trade name VIZIMPRO.

- FDA Approval Summary of Dacomitinib (VIZIMPRO)

ARCHER 1050[8] NCT01774721	**Non-small cell lung carcinoma** (Approved on 2018/09/27)
	EGFR ex19del or L858R
	Dacomitinib vs. Gefitinib [PFS(M): 14.7 vs. 9.2]

Erlotinib (TARCEVA)

Erlotinib is a small molecule, reversible inhibitor of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase. Erlotinib is developed by OSI Pharmaceuticals, Genentech and Roche, and marketed by Astellas Pharm Global Development under the trade name TARCEVA.

- FDA Approval Summary of Erlotinib (TARCEVA)

RELAY NCT02411448	**Non-small cell lung carcinoma** (Approved on 2020/05/29)
	EGFR ex19del or L858R
	Erlotinib + ramucirumab vs. Erlotinib + placebo [PFS(M): 19.4 vs. 12.4]
EURTAC[111] NCT00446225	**Non-small cell lung carcinoma** (Approved on 2013/05/14)
	EGFR ex19del or L858R
	Erlotinib vs. Cisplatin + gemcitabine or cisplatin + docetaxel or carboplatin + gemcitabine or carboplatin + docetaxel [PFS(M): 10.4 vs. 5.2]
PA.3[112] NCT00026338	**Pancreatic cancer** (Approved on 2005/11/02)
	-
	Gemcitabine vs. Placebo [OS(M): 6.4 vs. 6]

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[113] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[114] 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[115] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[116] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[117] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

Gefitinib (IRESSA)

Gefitinib is a small molecule inhibitor of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase. Gefitinib is developed and marketed by AstraZeneca under the trade name IRESSA.

- FDA Approval Summary of Gefitinib (IRESSA)

IFUM[118] NCT01203917	**Non-small cell lung carcinoma** (Approved on 2015/07/13)
	EGFR ex19del or L858R
	Gefitinib [ORR(%): 50.0]

Necitumumab (PORTRAZZA)

Necitumumab is a recombinant human IgG1 monoclonal antibody against the human epidermal growth factor receptor (EGFR) and blocks the binding of EGFR to its ligands. Necitumumab is developed and marketed by Eli Lilly under the trade name PORTRAZZA.

- FDA Approval Summary of Necitumumab (PORTRAZZA)

SQUIRE[119] NCT00981058	**Lung squamous cell carcinoma** (Approved on 2015/11/14)
	-
	Gemcitabine + cisplatin vs. Placebo [OS(M): 11.5 vs. 9.9]

Niraparib (ZEJULA)

Niraparib is an oral, small molecule inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1 and -2 (PARP-1, -2). Niraparib is developed and marketed by Tesaro under the trade name ZEJULA.

- FDA Approval Summary of Niraparib (ZEJULA)

PRIMA NCT02655016	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2020/04/29)
	-
	Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
NOVA[120] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27)
	-
	Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

Olaparib (LYNPARZA)

Olaparib is an oral, small molecule inhibitor of poly (ADP-ribose) polymerase-1, -2, and -3 (PARP-1, -2, -3). Olaparib is developed by KuDOS Pharmaceuticals and marketed by AstraZeneca under the trade name LYNPARZA.

- FDA Approval Summary of Olaparib (LYNPARZA)

PROpel NCT03732820	**Prostate cancer** (Approved on 2023/05/31)
	BRCA mutation
	Olaparib + abiraterone + prednisone vs. Placebo + abiraterone + prednisone [rPFS(M): not reached vs. 8]
OlympiA NCT02032823	**Her2-negative high-risk early breast cancer** (Approved on 2022/03/11)
	HER2-/gBRCA mutation
	Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound[121] NCT02987543	**Prostate cancer** (Approved on 2020/05/19)
	HRR genes mutation
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1[122] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[123] NCT02184195	**Pancreatic adenocarcinoma** (Approved on 2019/12/27)
	gBRCA mutation
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1[124] NCT01844986	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19)
	gBRCA mutation or sBRCA mutation
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD[125] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[126] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA mutation
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19[127] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

Osimertinib (TAGRISSO)

Osimertinib is a third-generation tyrosine kinase inhibitor (TKI) for patients with tumors harboring EGFR T790M mutation. Osimertinib is developed and marketed by AstraZeneca under the trade name TAGRISSO.

- FDA Approval Summary of Osimertinib (TAGRISSO)

ADAURA NCT02511106	**Non-small cell lung carcinoma** (Approved on 2020/12/18)
	EGFR ex19del or L858R
	Osimertinib vs. Placebo + adjuvant chemotherapy [DFS(M): NR vs. 19.6]
FLAURA[10] NCT02296125	**Non-small cell lung carcinoma** (Approved on 2018/04/18)
	EGFR ex19del or L858R
	Osimertinib vs. Gefitinib or erlotinib [PFS(M): 18.9 vs. 10.2]

AURA3[128] NCT02151981	**Non-small cell lung carcinoma** (Approved on 2017/03/30)
	EGFR T790M
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA[129] NCT01802632	**Non-small cell lung carcinoma** (Approved on 2015/11/13)
	EGFR T790M
	Osimertinib [ORR(%): 59.0]

Panitumumab (VECTIBIX)

Panitumumab is a fully human monoclonal antibody against the human epidermal growth factor receptor (EGFR) and binds to the extracellular domain to prevent its activation. Panitumumab is developed by Abgenix and Amgen, and marketed by the latter under the trade name VECTIBIX.

- FDA Approval Summary of Panitumumab (VECTIBIX)

Study 20050203[130] NCT01412957	**Colorectal cancer** (Approved on 2017/06/29)
	KRAS Wild-type
	Panitumumab + bsc vs. Bsc [OS(M): 10 vs. 6.9]
PRIME[131] NCT00364013	**Colorectal cancer** (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab + folfox vs. Folfox [PFS(M): 9.6 vs. 8]
ASPECCT[132] NCT01001377	**Colorectal cancer** (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab vs. Cetuximab [OS(M): 10.4 vs. 10]
Study 20080763[133] NCT00113763	**Colorectal cancer** (Approved on 2006/09/27)
	KRAS Wild-type
	Panitumumab + bsc vs. Bsc [PFS(M): 3.2 vs. 2]

Pazopanib (VOTRIENT)

Pazopanib is an oral, small molecule, multi-kinase inhibitor that targets receptor tyrosine kinase including vascular endothelial growth factor receptor-1, -2, -3 (VEGFR-1, -2, -3), platelet-derived growth factor receptor-α, -β (PDGFR-α, -β), c-kit, fibroblast growth factor-1 and -3 (FGFR-1, -3), thereby inhibiting angiogenesis. Pazopanib is developed and marketed by GlaxoSmithKline under the trade name VOTRIENT.

- FDA Approval Summary of Pazopanib (VOTRIENT)

PALETTE[134] NCT00753688	**Sarcoma** (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]
VEG105192[135] NCT00334282	**Renal cell carcinoma** (Approved on 2009/10/19)
	-
	Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]

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Rucaparib (RUBRACA)

Rucaparib is an inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1, -2 and -3 (PARP-1, -2, -3). Rucaparib is developed and marketed by Clovis Oncology under the trade name RUBRACA.

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[30] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	-
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]

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)
	-
	Selumetinib [ORR(%): 66.0]

Talazoparib (TALZENNA)

Talazoparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2. Talazoparib is developed and marketed by Pfizer under the trade name TALZENNA.

- FDA Approval Summary of Talazoparib (TALZENNA)

TALAPRO-2 NCT03395197	**Prostate cancer** (Approved on 2023/06/20)
	HRR genes mutation
	Talazoparib + enzalutamide vs. Placebo + enzalutamide [rPFS(M): Not reached vs. 13.8]
EMBRACA[136] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

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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)

CDRB436G2201 NCT02684058	**Low-grade glioma** (Approved on 2023/03/09)
	BRAF V600E
	Dabrafenib + trametinib vs. Carboplatin + vincristine [ORR(%): 46.6 vs. 10.8]
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]
BRF117019[137] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[138] 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[139] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[140] 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

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

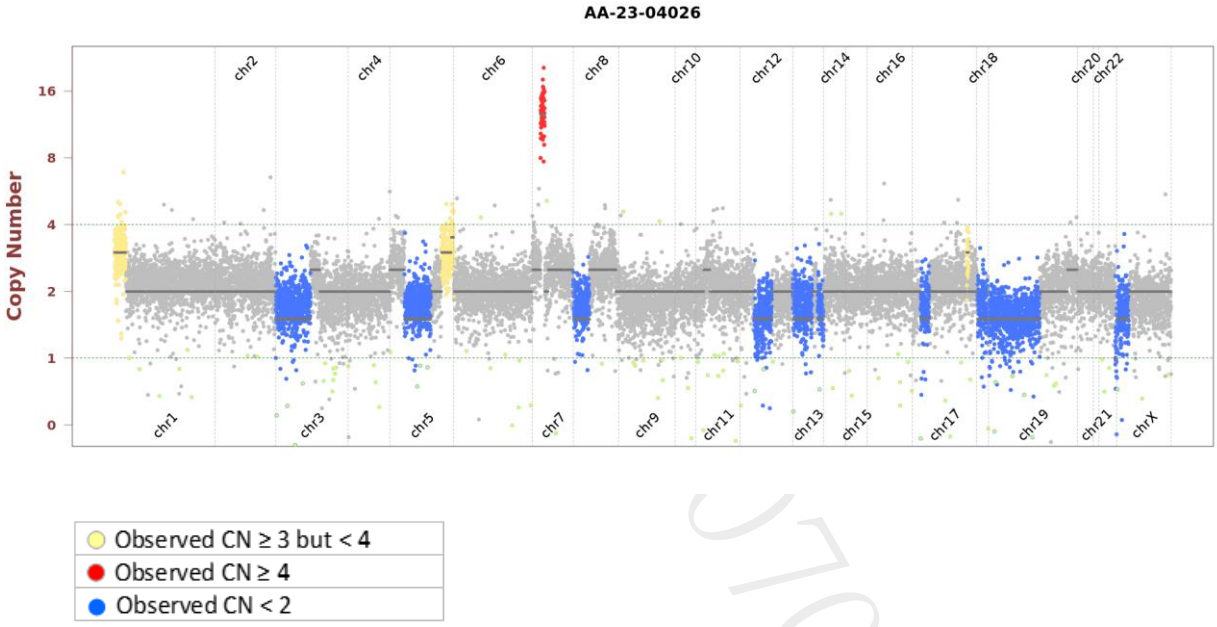
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
EGFR	L858R	21	c.2573T>G	NM_005228	COSM6224	86.2%	3966
FANCA	H330fs	11	c.987_990del	NM_000135	-	47.8%	1257
NF1	R416*	11	c.1246C>T	NM_001042492	COSM27353	18.4%	473
TP53	P152L	5	c.455C>T	NM_000546	COSM10790	23.8%	730

- 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
ADAMTS16	S657R	13	c.1971C>G	NM_139056	COSM3994342	53.6%	1372
AR	M887V	8	c.2659A>G	NM_000044	COSM7340389	38.1%	680
ARID1B	Splice region	17	c.4854C>T	NM_017519	-	52.3%	570
BRD4	V228I	5	c.682G>A	NM_058243	-	63.5%	836
BRIP1	L340F	8	c.1018C>T	NM_032043	-	67.0%	1121
CCNB1	R308K	6	c.923G>A	NM_031966	-	23.8%	286
DNMT3A	T44M	3	c.131C>T	NM_175629	-	53.2%	703
FGFR3	A429T	10	c.1285G>A	NM_000142	-	51.5%	1640
INSR	T858A	13	c.2572A>G	NM_000208	-	57.1%	553
KMT2C	R380L	8	c.1139G>T	NM_170606	COSM225885	7.5%	3994
MUC16	T4052S	3	c.12154A>T	NM_024690	COSM2700871	54.6%	707
NBN	Splice region	-	c.2235-8C>T	NM_002485	-	11.3%	213
PIK3R3	R255Q	6	c.764G>A	NM_003629	COSM5418556	48.4%	1089
PRKCA	Splice region	-	c.1855-8C>T	NM_002737	-	51.0%	1385
SMARCB1	Splice region	8	c.1116G>A	NM_003073	COSM1003	44.8%	996
SYNE1	S8409G	139	c.25225A>G	NM_182961	-	53.3%	781
VHL	P2H	1	c.5C>A	NM_000551	-	63.7%	411

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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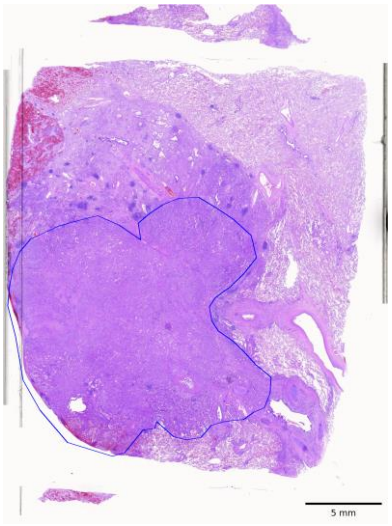
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Apr 13, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11216072D
- Collection site: Lung
- Examined by: Dr. Yun-An Chen
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 20%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 40%
    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: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 907x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 145

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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).

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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.

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:
醫檢師黃靖婷 博士
Ching-Ting Huang Ph.D.
檢字第 016511 號

CT Huang

Sign Off
解剖病理專科醫師王業翰
Yeh-Han Wang M.D.
病解字第 000545 號

Yehn

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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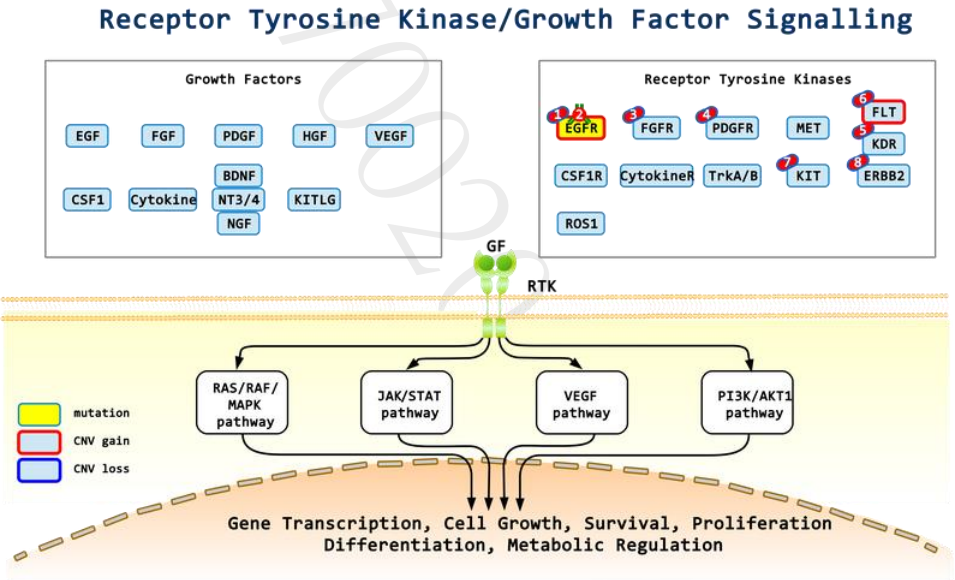
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RAD50	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Gefitinib, Afatinib, Erlotinib, Osimertinib, Dacomitinib; 2: Cetuximab, Panitumumab, Necitumumab; 3: Pazopanib; 4: Pazopanib; 5: Pazopanib; 6: Pazopanib; 7: Pazopanib; 8: Afatinib

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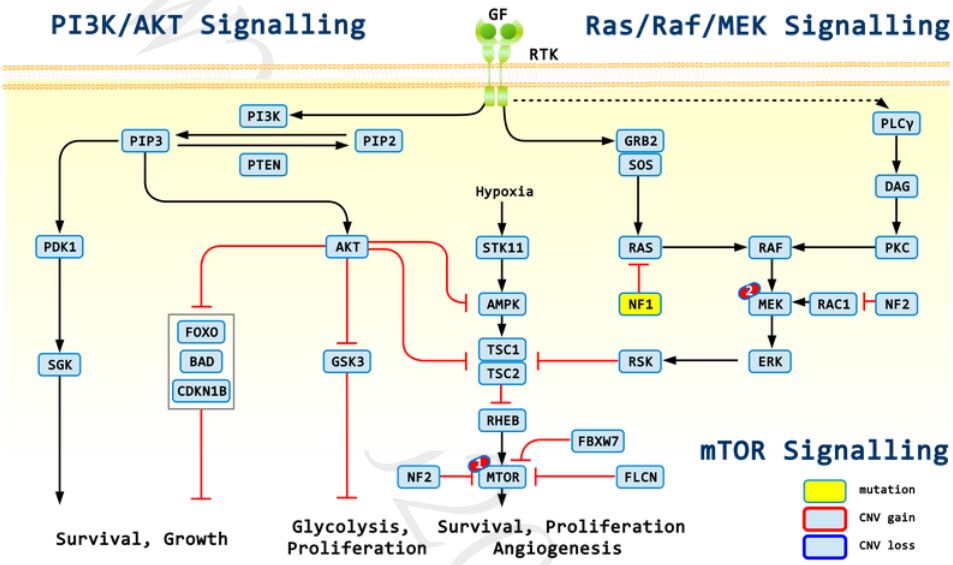
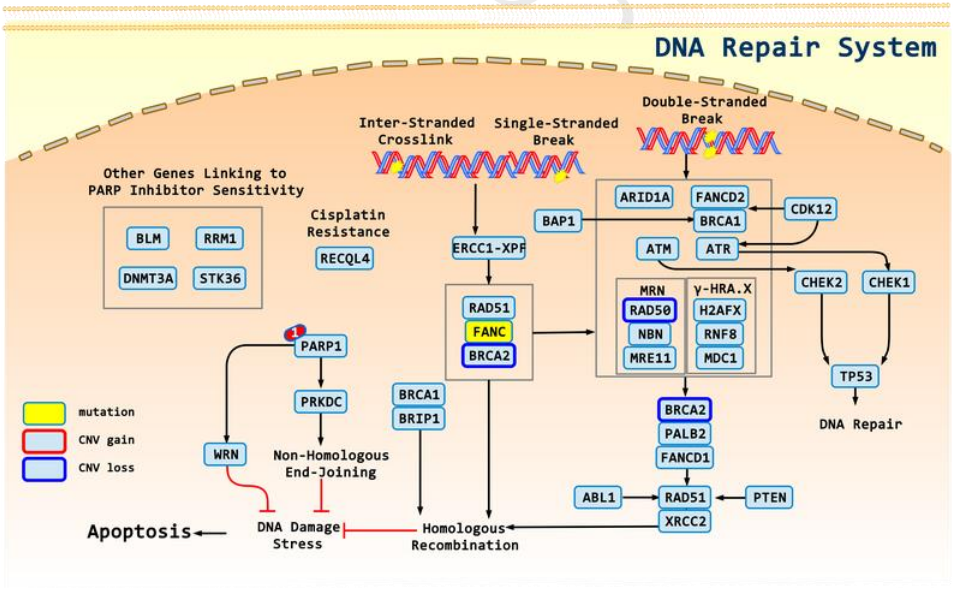


1: Everolimus; 2: Trametinib, Selumetinib



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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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: 18045542; 2007, Cell;131(5):1018
SnapShot: EGFR signaling pathway.

2. PMID: 10880430; 2000, EMBO J;19(13):3159-67
The ErbB signaling network: receptor heterodimerization in development and cancer.

3. PMID: 15329413; 2004, Proc Natl Acad Sci U S A;101(36):13306-11
EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib.

4. PMID: 11426640; 2000, Oncogene;19(56):6550-65
The EGF receptor family as targets for cancer therapy.

5. PMID: 17318210; 2007, Nat Rev Cancer;7(3):169-81
Epidermal growth factor receptor mutations in lung cancer.

6. PMID: 22263017; 2010, J Thorac Dis;2(1):48-51
Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update.

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

8. PMID: 28958502; 2017, Lancet Oncol;18(11):1454-1466
Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial.

9. PMID: 29653820; 2018, Clin Lung Cancer;19(4):e465-e479
Afatinib as First-line Treatment of Older Patients With EGFR Mutation-Positive Non-Small-Cell Lung Cancer: Subgroup Analyses of the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 Trials.

10. PMID: 29151359; 2018, N Engl J Med;378(2):113-125
Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer.

11. PMID: 17664472; 2007, J Clin Oncol;25(22):3238-45
Epidermal growth factor receptor gene copy number and clinical outcome of metastatic colorectal cancer treated with panitumumab.

12. PMID: 22152101; 2011, BMC Cancer;11():509
Biomarker analysis of cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric and oesophago-gastric junction cancer: results from a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO).

13. PMID: 24141978; 2013, Sci Rep;3():2992
A subset of gastric cancers with EGFR amplification and overexpression respond to cetuximab therapy.

14. PMID: 29158193; 2018, J Thorac Oncol;13(2):228-236
EGFR Gene Copy Number by FISH May Predict Outcome of Necitumumab in Squamous Lung Carcinomas: Analysis from the SQUIRE Study.

15. PMID: 19102716; 2009, Pharmacogenomics;10(1):59-68
EGFR-targeted therapies in lung cancer: predictors of response and toxicity.

16. PMID: 15870435; 2005, J Natl Cancer Inst;97(9):643-55
Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer.

17. PMID: 15998906; 2005, J Clin Oncol;23(28):6838-45
Increased epidermal growth factor receptor gene copy number detected by fluorescence in situ hybridization associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: a Southwest Oncology Group Study.

18. PMID: 16204011; 2005, J Clin Oncol;23(31):8081-92

Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials.

19. PMID: 23557218; 2013, J Transl Med;11():90
High EGFR copy number predicts benefits from tyrosine kinase inhibitor treatment for non-small cell lung cancer patients with wild-type EGFR.

20. PMID: 26141217; 2015, Lung Cancer;89(3):337-42
Concurrence of EGFR amplification and sensitizing mutations indicate a better survival benefit from EGFR-TKI therapy in lung adenocarcinoma patients.

21. PMID: 28537764; 2017, J Clin Oncol;35(20):2279-2287
Gefitinib and EGFR Gene Copy Number Aberrations in Esophageal Cancer.

22. PMID: 28057415; 2017, Clin Genitourin Cancer;15(4):e727-e734
Comprehensive Genomic Analysis of Metastatic Mucinous Urethral Adenocarcinoma Guides Precision Oncology Treatment: Targetable EGFR Amplification Leading to Successful Treatment With Erlotinib.

23. PMID: 30463996; 2019, Cancer Discov;9(2):199-209
EGFR and MET Amplifications Determine Response to HER2 Inhibition in ERBB2-Amplified Esophagogastric Cancer.

24. PMID: 28575464; 2017, Neuro Oncol;19(11):1522-1531
Phase II trial of dacomitinib, a pan-human EGFR tyrosine kinase inhibitor, in recurrent glioblastoma patients with EGFR amplification.

25. PMID: 23325218; 2013, Nature;493(7432):356-63
Fanconi anaemia and the repair of Watson and Crick DNA crosslinks.

26. PMID: 15905196; 2005, Carcinogenesis;26(10):1731-40
The Fanconi anemia group A protein modulates homologous repair of DNA double-strand breaks in mammalian cells.

27. PMID: 25754594; 2015, Hum Mutat;36(5):562-8
Loss-of-Function FANCL Mutations Associate with Severe Fanconi Anemia Overlapping the VACTERL Association.

28. PMID: 28678401; 2017, Cancer;123(20):3943-3954
Assessing the spectrum of germline variation in Fanconi anemia genes among patients with head and neck carcinoma before age 50.

29. PMID: 30353044; 2018, Br J Cancer;119(11):1401-1409
Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes.

30. PMID: 28916367; 2017, Lancet;390(10106):1949-1961
Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial.

31. PMID: 32086346; 2020, Clin Cancer Res;26(11):2487-2496
Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: Analysis From the Phase II TRITON2 Study.

32. PMID: 31806540; 2020, Lancet Oncol;21(1):162-174
Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial.

33. 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.

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

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

36. PMID: 2121370; 1990, Cell;63(4):843-9

The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21.

37. 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.

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

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

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

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

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

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

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

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

46. 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.

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

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

49. 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.

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

51. PMID: 32669708; 2020, Nature;583(7818):807-812
The National Lung Matrix Trial of personalized therapy in lung cancer.

52. 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.

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

54. 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.

55. 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.

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

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

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

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

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

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

62. PMID: 32122926; 2020, Clin Cancer Res;26(12):2932-2945
MAPK Pathway Alterations Correlate with Poor Survival and Drive Resistance to Therapy in Patients with Lung Cancers Driven by ROS1 Fusions.

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

64. 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.

65. PMID: 24739573; 2014, Nat Rev Cancer;14(5):359-70
Unravelling mechanisms of p53-mediated tumour suppression.

66. PMID: 21125671; 2011, J Pathol;223(2):137-46
Haplo-insufficiency: a driving force in cancer.

67. PMID: 25584008; 2015, J Clin Oncol;33(6):602-9
Prevalence and functional consequence of TP53 mutations in pediatric adrenocortical carcinoma: a children's oncology group study.

68. PMID: 27998224; 2016, J Clin Oncol;34(36):4354-4361
Phase II Study of WEE1 Inhibitor AZD1775 Plus Carboplatin in Patients With TP53-Mutated Ovarian Cancer Refractory or Resistant to First-Line Therapy Within 3 Months.

69. PMID: 26646755; 2016, Ann Oncol;27(3):539-43
TP53 mutational status is predictive of pazopanib response in advanced sarcomas.

70. PMID: 25669829; 2015, Ann Oncol;26(5):1012-1018
Phase I study of pazopanib and vorinostat: a therapeutic approach for inhibiting mutant p53-mediated angiogenesis and facilitating mutant p53 degradation.

71. PMID: 27466356; 2016, Mol Cancer Ther;15(10):2475-2485
TP53 Alterations Correlate with Response to VEGF/VEGFR Inhibitors: Implications for Targeted Therapeutics.

72. PMID: 23670029; 2013, Oncotarget;4(5):705-14
P53 mutations in advanced cancers: clinical characteristics, outcomes, and correlation between progression-free survival and bevacizumab-containing therapy.

73. PMID: 17145525; 2006, Semin Oncol;33(5 Suppl 10):S8-14
Bevacizumab in combination with chemotherapy: first-line treatment of patients with metastatic colorectal cancer.

74. PMID: 21399868; 2011, Int J Oncol;38(5):1445-52
p53, HER2 and tumor cell apoptosis correlate with clinical outcome after neoadjuvant bevacizumab plus chemotherapy in breast cancer.

75. PMID: 20549698; 2011, Int J Cancer;128(8):1813-21
p53 status influences response to tamoxifen but not to fulvestrant in breast cancer cell lines.

76. PMID: 10786679; 2000, Cancer Res;60(8):2155-62
Complete sequencing of TP53 predicts poor response to systemic therapy of advanced breast cancer.

77. PMID: 25672981; 2015, Cancer Res;75(7):1187-90
VEGF-A Expression Correlates with TP53 Mutations in Non-Small Cell Lung Cancer: Implications for Antiangiogenesis Therapy.

78. PMID: 11239455; 2001, Mol Cell;7(2):263-72
BRCA2 is required for homology-directed repair of chromosomal breaks.

79. PMID: 17597348; 2007, Ann Surg Oncol;14(9):2510-8
Heterogenic loss of the wild-type BRCA allele in human breast tumorigenesis.

80. PMID: 22193408; 2011, Nat Rev Cancer;12(1):68-78
BRCA1 and BRCA2: different roles in a common pathway of genome protection.

81. PMID: 27283171; 2016, J Natl Compr Canc Netw;14(6):795-806
The Relevance of Hereditary Cancer Risks to Precision Oncology: What Should Providers Consider When Conducting Tumor Genomic Profiling?

82. PMID: 10762646; 2000, Int J Mol Med;5(5):447-56
Signaling pathways induced by vascular endothelial growth factor (review).

83. PMID: 11877295; 2002, Blood;99(6):2179-84
Vascular endothelial growth factor (VEGF)-C signaling through FLT-4 (VEGFR-3) mediates leukemic cell proliferation, survival, and resistance to chemotherapy.

84. PMID: 16530705; 2006, Cancer Cell;9(3):209-23
The VEGF-C/Flt-4 axis promotes invasion and metastasis of cancer cells.

85. PMID: 11292664; 2001, FASEB J;15(6):1028-36
VEGFR3 gene structure, regulatory region, and sequence polymorphisms.

86. PMID: 12875690; 2003, Chin Med J (Engl);116(5):727-30
Clinical significance of co-expression of VEGF-C and VEGFR-3 in non-small cell lung cancer.

87. PMID: 12168824; 2002, Anticancer Res;22(3):1463-6
Expression of the vascular endothelial growth factor receptor-3 (VEGFR-3) and its ligand VEGF-C in human colorectal adenocarcinoma.

88. PMID: 12784238; 2003, Head Neck;25(6):464-74
Vascular endothelial growth factor C and vascular endothelial growth factor receptor 3 expression in squamous cell carcinomas of the head and neck.

89. PMID: 15701844; 2005, Clin Cancer Res;11(2 Pt 1):584-93
Stage-specific characterization of the vascular endothelial growth factor axis in prostate cancer: expression of lymphangiogenic markers is associated with advanced-stage disease.

90. PMID: 10068212; 1999, Lab Invest;79(2):243-51
Expression of vascular endothelial growth factor receptor-3 and podoplanin suggests a lymphatic endothelial cell origin of Kaposi's sarcoma tumor cells.

91. PMID: 14648657; 2003, J Pathol;201(4):544-54
Expression of vascular endothelial growth factor (VEGF)-C and VEGF-D, and their receptor VEGFR-3, during different stages of cervical carcinogenesis.

92. PMID: 20949568; 2011, Genes Chromosomes Cancer;50(1):25-33
Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions.

93. PMID: 26735859; 2016, Am J Surg Pathol;40(5):645-55
Recurrent CIC Gene Abnormalities in Angiosarcomas: A Molecular Study of 120 Cases With Concurrent Investigation of PLCG1, KDR, MYC, and FLT4 Gene Alterations.

94. PMID: 27160228; 2016, J Natl Compr Canc Netw;14(5):499-502
Antitumor Response of VEGFR2- and VEGFR3-Amplified Angiosarcoma to Pazopanib.

95. PMID: 9315668; 1997, Mol Cell Biol;17(10):6087-96
hMre11 and hRad50 nuclear foci are induced during the normal cellular response to DNA double-strand breaks.

96. PMID: 16467875; 2006, Cell Res;16(1):45-54
The role of NBS1 in DNA double strand break repair, telomere stability, and cell cycle checkpoint control.

97. PMID: 16385572; 2006, Int J Cancer;118(11):2911-6
Evaluation of RAD50 in familial breast cancer predisposition.

98. PMID: 24894818; 2014, Breast Cancer Res;16(3):R58
Rare key functional domain missense substitutions in MRE11A, RAD50, and NBN contribute to breast cancer susceptibility: results from a Breast Cancer Family Registry case-control mutation-screening study.

99. PMID: 18440592; 2008, Hum Pathol;39(6):925-32
Gastric cancer with high-level microsatellite instability: target gene mutations, clinicopathologic features, and long-term survival.

100. PMID: 11196187; 2001, Cancer Res;61(1):36-8
Frameshift mutations at coding mononucleotide repeats of the hRAD50 gene in gastrointestinal carcinomas with microsatellite instability.

101. PMID: 24934408; 2014, Cancer Discov;4(9):1014-21
Synthetic lethality in ATM-deficient RAD50-mutant tumors underlies outlier response to cancer therapy.

102. PMID: 16474176; 2006, Carcinogenesis;27(8):1593-9
RAD50 and NBS1 are breast cancer susceptibility genes associated with genomic instability.

103. PMID: 27016230; 2016, Gynecol Oncol;141(1):57-64
Copy number deletion of RAD50 as predictive marker of BRCAness and PARP inhibitor response in BRCA wild type ovarian cancer.

104. PMID: 26156651; 2015, Lancet Oncol;16(8):897-907
Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial.

105. PMID: 23816960; 2013, J Clin Oncol;31(27):3327-34
Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.

106. PMID: 33503393; 2021, J Clin Oncol;39(4):273-284
Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated BRAF V600E-Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study.

107. PMID: 19339720; 2009, N Engl J Med;360(14):1408-17
Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer.

108. PMID: 18784101; 2008, N Engl J Med;359(11):1116-27
Platinum-based chemotherapy plus cetuximab in head and neck cancer.

109. PMID: 16467544; 2006, N Engl J Med;354(6):567-78
Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.

110. PMID: 15269313; 2004, N Engl J Med;351(4):337-45
Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.

111. PMID: 22285168; 2012, Lancet Oncol;13(3):239-46
Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial.

112. PMID: 17452677; 2007, J Clin Oncol;25(15):1960-6
Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group.

113. 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.

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

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

116. 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.

117. 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.

118. PMID: 24263064; 2014, Br J Cancer;110(1):55-62
First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study.

119. PMID: 26045340; 2015, Lancet Oncol;16(7):763-74
Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial.

120. PMID: 27717299; 2016, N Engl J Med;375(22):2154-2164
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer.

121. PMID: 32343890; 2020, N Engl J Med;382(22):2091-2102
Olaparib for Metastatic Castration-Resistant Prostate Cancer.

122. PMID: 31851799; 2019, N Engl J Med;381(25):2416-2428
Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer.

123. PMID: 31157963; 2019, N Engl J Med;381(4):317-327
Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer.

124. PMID: 30345884; 2018, N Engl J Med;379(26):2495-2505
Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.

125. PMID: 28578601; 2017, N Engl J Med;377(6):523-533
Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation.

126. PMID: 28754483; 2017, Lancet Oncol;18(9):1274-1284
Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial.

127. PMID: 27617661; 2016, Lancet Oncol;17(11):1579-1589
Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial.

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128. PMID: 27959700; 2017, N Engl J Med;376(7):629-640
Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer.

129. PMID: 25923549; 2015, N Engl J Med;372(18):1689-99
AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer.

130. PMID: 27736842; 2016, Br J Cancer;115(10):1206-1214
A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer.

131. PMID: 24024839; 2013, N Engl J Med;369(11):1023-34
Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer.

132. PMID: 24739896; 2014, Lancet Oncol;15(6):569-79
Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study.

133. PMID: 17470858; 2007, J Clin Oncol;25(13):1658-64
Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer.

134. PMID: 22595799; 2012, Lancet;379(9829):1879-86
Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial.

135. PMID: 20100962; 2010, J Clin Oncol;28(6):1061-8
Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial.

136. PMID: 30110579; 2018, N Engl J Med;379(8):753-763
Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation.

137. 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.

138. 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.

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

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