ACT Onco® + Report

PATIENT		
Identifier: 洪睿承		Patient ID: 45543042
Date of Birth: Feb 21, 2007		Gender: Male
Diagnosis: Osteosarcoma		
ORDERING PHYSICIAN		
Name: 顏秀如醫師		Tel: 886-228712121
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SPECIMEN		
Specimen ID: S11226789B	Collection site: Lung	Type: FFPE tissue
Date received: Jun 26, 2023	Lab ID: AA-23-04122	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
CCNE1 Amplification	-	Palbociclib, Trastuzumab
KDR Amplification	Pazopanib, Sunitinib	-
KIT Amplification	-	Imatinib, Nilotinib, Sunitinib
PDGFRA Amplification	Imatinib, Pazopanib, Sorafenib, Sunitinib	-

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
Not detected		

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr17	*TP53*	Homozygous deletion	0
Chr13	*BRCA2*	Heterozygous deletion	1
Chr16	*PALB2*	Heterozygous deletion	1
Chr17	*NF1*	Heterozygous deletion	1
Chr19	*STK11*	Heterozygous deletion	1
Chr3	*ATR*	Heterozygous deletion	1
Chr5	*RAD50*	Heterozygous deletion	1
Chr4	*KDR, KIT*	Amplification	7
Chr19	*CCNE1*	Amplification	11
Chr4	*PDGFRA*	Amplification	16

- 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)	2.6 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 53% 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 3A		
KIT Amplification	Imatinib, Nilotinib, Sunitinib	**resistant**
Level 4		
KDR Amplification	Pazopanib, Sunitinib	**sensitive**
PDGFRA Amplification	Imatinib, Pazopanib, Sorafenib, Sunitinib	**sensitive**
CCNE1 Amplification	Palbociclib, 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
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

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

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.

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VARIANT INTERPRETATION

ATR Heterozygous deletion

Biological Impact

Ataxia Telangiectasia and Rad3-related protein (ATR) gene encodes a serine/threonine kinase that is involved in the DNA damage response. ATR plays as a central coordinator of the DNA damage response (DDR) by responding to single-stranded regions of the DNA[1][2]and the maintenance of genome stability[3]. ATR has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[4][5]. Germline mutation of ATR is associated with cancer predisposition and Seckel syndrome, a condition associated with CNS disorders[6][7]. Somatic mutations of ATR are associated with microsatellite instability and are found in colorectal cancer[8], urothelial cancer[9], gastric cancer[10], endometrial cancer[11]and myelomas[12].

Therapeutic and prognostic relevance

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

In a clinical study, a metastatic castration-resistant prostate cancer patient harboring deleterious mutation in the ATR gene (K2106fs) had a PSA remission of 62% and PSA-PFS of 13 months by olaparib treatment[13].

ATR has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in ovarian cancer[14]and advanced solid tumors (NCT03297606; CAPTUR trial), rucaparib efficacy in ovarian cancer[15], niraparib efficacy in pancreatic cancer (NCT03553004), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative solid tumors (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[16]. 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[17]. 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[18]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[19].

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.

CCNE1 Amplification

Biological Impact

The CCNE1 gene encodes the cyclin E1 protein, a regulator of the cell cycle that activates the cyclin-dependent protein kinase 2 (CDK2) and plays a role in regulating cells' transition from G1 to S phase and the maintenance of genomic stability[20]. Increasing in cyclin E1 level, either by gene amplification or overexpression, is found in a diverse range of cancers and can be indicative of poor prognosis[21].

Therapeutic and prognostic relevance

There are no FDA-approved therapies targeting cyclin E1 currently available[22]. Dinaciclib, a CDK1/2 specific inhibitor, is currently under clinical evaluation[23]. A combination of dinaciclib, a small molecule CDK2 inhibitor, and AKT inhibitors that may selectively target patients with CCNE1-amplified high-grade serous ovarian cancer (HGSC) in preclinical setting[24]. A preclinical study in breast cancer cell lines showed that amplification of CCNE1 is associated with acquired resistance to CDK4/6 inhibition by palbociclib[25]. A study of HER2-amplified breast cancer patients indicated that amplification of CCNE1 was associated with trastuzumab resistance and shorter progression-free survival[26].

There are retrospective study and meta-analysis demonstrated that amplification and overexpression of CCNE1 are associated with poor survival in cancer patients[27][28]. From the result of PALOMA-3 phase III trial, pre-treated hormone receptor-positive/HER2-negative metastatic breast cancer patients were resistant to palbociclib treatment when CCNE1 was highly expressed (median PFS: CCNE1 high, 7.6 months; CCNE1 low, 14.1 months)[29]. CCNE1 amplification has been selected as an inclusion criteria for the trial examining palbociclib in malignant solid tumor (NCT02896335, NCT03155620, NCT01037790, NCT03526250).

KDR Amplification

Biological Impact

KDR (kinase domain receptor), also known as VEGFR2 or Flk-1, is a tyrosine kinase receptor for the vascular endothelial growth factor (VEGF) and involves in angiogenesis pathway[30]. Binding of VEGF to KDR results in activation of phospholipase C (PLC-gamma) and downstream signaling via protein kinase C (PKC) and RAF/MEK/ERK[31]. Mutations of KDR are rare in tumors, and alterations of KDR activity typically occur via KDR amplification and subsequent overexpression[32][33].

Therapeutic and prognostic relevance

To date, there are four VEGF inhibitors (sorafenib, sunitinib, pazopanib, bevacizumab) and one VEGFR2 inhibitor cabozantinib that are FDA-approved for the treatment of cancers[34][35][36]. Notably, a case report showed that an angiosarcoma patient with concurrent KDR and FLT4 amplification developed a progressive disease when treated with sorafenib, but experienced a potent antitumor response and achieved clinically stable disease for 6 months after receiving pazopanib therapy[37]. Besides, an angiosarcoma patient with upregulated VEGFR2 responded to sunitinib treatment[38]. VEGFR2 inhibitors like apatinib and vandetanib are in early clinical phase trial[39][40][41].

KDR amplification and/or mutation has been selected as an inclusion criteria for the trial examining cabozantinib in metastatic castrate resistant prostate cancer (mCRPC) (NCT04631744) and sunitinib in malignant solid tumors (NCT03297606). The increased copy number of KIT or KDR significantly correlated with a worse 5-year breast cancer-specific survival (BCSS) in triple-negative breast cancer (TNBC) patients[42].

KIT Amplification

Biological Impact

KIT is a proto-oncogene that encodes a type 3 transmembrane receptor tyrosine kinase. Activation of KIT through dimerization and autophosphorylation upon binding by its ligand results in increased intracellular PI3K/AKT/mTOR, MAPK/ERK and JAK/STAT signaling pathways to promote cell proliferation and survival[43]. KIT activating mutations are frequently found in 80 - 90% of gastrointestinal stromal tumors (GISTs) which distributed over multiple exons with different frequencies (exons 11 (66.1%), exon 9 (13%), exon 13 (1.2%), and exon 17 (0.6%))[44][45].

Therapeutic and prognostic relevance

NCCN guidelines recommend using KIT inhibitors (imatinib, sunitinib, nilotinib) for cutaneous melanoma patients with specific KIT hotspot mutations in exon 11 and exon 13, but not for those with KIT exon 17 mutations or amplification. Dasatinib and ripretinib are recommended for metastatic or unresectable cutaneous melanoma patients with KIT activating mutations. Also, imatinib is a preferred regimen for neoadjuvant therapy of resectable GIST with significant morbidity patient harboring KIT mutation, and ponatinib is recommended for advanced GIST patients with KIT exon 11 mutations.

KIT mutation has been determined as an inclusion criterion for the trials evaluating dasatinib, avapritinib, sunitinib, ponatinib, regorafenib, ripretinib, imatinib, and cabozantinib efficacies in various types of solid tumors (NCT03297606, NCT03353753, NCT03465722, NCT02272998, NCT02501551, NCT03353753, NCT02461849, NCT02712112, NCT04631744, NCT04116541).

The efficacy of U.S. FDA-approved KIT TKIs such as imatinib, sunitinib, regorafenib, and ripretinib for GIST strongly depends on the location of the activating KIT mutations[46][47][48][49][50][51]. Patients with GIST harboring KIT exon 9 mutations have intermediate sensitivity to imatinib and better survival than those with KIT exon 11 mutations[47]. Newly developing agents, including avapritinib, show potential to be better inhibitors for clinically relevant KIT/PDGFRA mutations in GIST[52]. Ponatinib and dasatinib show promise in GIST patients with KIT exon 11 mutations, with a disease control rate of 67% and partial control rate of 32%(DOI:10.1200/jco.2011.29.15_suppl.10006)[53]. Meanwhile, a Phase II trial involving melanoma showed a 38.5% response rate to nilotinib in patients with KIT exon 11 mutations[54].

Both KIT and PDGFRA overexpression were associated with high tumor grade, high proliferation index, and poor outcome in patients with the serous type of ovarian carcinoma[55].

A phase II trial of imatinib in melanoma showed that patients with KIT amplification had lower disease control rate compared with patients carrying KIT mutations (18% amplified vs. 77% mutated)[56].

NF1 Heterozygous deletion

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[57][58][59][60]. 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[61][62]. 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[63][64][65][66][67]. 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[68][69][70]. Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types[71], including myelodysplastic syndromes, melanomas, colon cancer[72], glioblastomas[73], lung cancer[74], ovarian cancer, and breast cancer[68].

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)[75].

NF1 depletion is associated with drug resistance to various inhibitors, such as RAF, EGFR, tamoxifen, and retinoic acid[71][76]. Loss of NF1 in lung adenocarcinomas, colorectal cancer, and BRAF-mutated melanomas is associated with resistance to anti-EGFR and BRAF inhibitors[77][78][79][80][81][82]. 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[83]. Trametinib is effective in treating neurofibromatosis type I-associated glioblastoma[84]. Patients with mutations in the mTOR pathway, including NF1, have responded to everolimus[85]. 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[86].

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[77], and MEK and mTOR inhibitors showed promise in NF1-deficient tumors[87][88]. Knockdown of NF1 also led to resistance to crizotinib and cabozantinib treatment in ROS1 fusion-positive cells[86].

PALB2 Heterozygous deletion

Biological Impact

The partner and localizer of BRCA2 (PALB2) gene encodes a protein that plays a critical role in homologous recombination repair (HRR) through its ability to interact with BRCA2 in nuclear foci, promoting its localization and stability in key nuclear structures[89]. The Fanconi anemia complementation group (FANC) which 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)[90][91][92]. PALB2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function[93]. Biallelic germline loss-of-function mutations in PALB2 cause Fanconi anemia, whereas monoallelic loss-of-function mutations are associated with an increased risk of breast cancer and pancreatic cancer[94]. 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[95][96].

Therapeutic and prognostic relevance

Olaparib and talazoparib are FDA-approved for treating mCRPC patients harboring mutations in homologous recombination repair (HRR) genes, including PALB2.

The NCCN guidelines recommend rucaparib as maintenance therapy for pancreatic adenocarcinoma patients with PALB2 mutations after platinum-based therapy. For breast cancer patients with stage IV disease and germline PALB2 alterations, olaparib treatment is recommended by the NCCN guidelines regardless of subtype.

PALB2 mutation has been determined as an inclusion criterion for the trials evaluating rucaparib, niraparib, and talazoparib efficacies in various types of solid tumors (NCT02401347, NCT03553004, NCT02952534)[15][97].

A case report demonstrated an exceptional response to mitomycin C and cisplatin treatment in a gemcitabine-resistant pancreatic cancer patient with biallelic inactivation of PALB2[98].

PDGFRA Amplification

Biological Impact

The PDGFRA gene encodes for the protein platelet-derived growth factor alpha (PDGFRA). The Ligand binding to the extracellular domain of PDGFRA induces receptor dimerization, enabling autophosphorylation of specific tyrosine residues and subsequently results in the activation of downstream pathways such as RAS-MAPK, PI3K and PLC-γ that are involved in developmental and cellular responses[99][100]. Mutations, insertions, deletions, fusions and genomic amplification of PDGFRA lead to its activation in several tumor types: ~7% of gastrointestinal stromal tumors (GISTs) have PDGFRA activating mutations and these mutations are mutually exclusive from KIT mutations[101]; activating mutations in PDGFRA have been observed in ~5% of Chinese melanoma patients[102]; amplification of PDGFRA is the second most frequent receptor tyrosine kinase amplification in glioblastoma (GBM)[103][104][105][73][106], intimal sarcomas[107], malignant peripheral nerve sheath tumors[108], non-small cell lung adenocarcinomas and non-small cell lung squamous cell carcinomas[109].

Therapeutic and prognostic relevance

A retrospective study showed that either KIT, PDGFRA, or EGFR amplification in glioma at the time of the first diagnosis was associated with an unfavorable overall survival[110].

In a preclinical study, a PDGFRA-amplified cell line was sensitive to imatinib, sunitinib and sorafenib treatment, demonstrated by disruption of downstream signaling and reduced cell viability in vitro[111]. Another study also showed that pazopanib could inhibit tumor growth in the PDGFRA-amplified pleomorphic liposarcoma xenograft mouse model[112].

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[113][114]. Mutations in the components of the MRN complex could increase susceptibility to familial breast cancer[115][116], gastric cancer[117], colorectal cancer[118], and urothelial cancer[119]. 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[120]. 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[121].

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[121]. 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).

STK11 Heterozygous deletion

Biological Impact

The serine/threonine kinase 11 (STK11, also known as LKB1) gene encodes the multifunctional serine/threonine kinase, a tumor suppressor that functions as an inhibitor for the mTOR signaling pathway[122][123]. STK11 is a haploinsufficient

gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[124][125]. In the mouse model, loss of STK11 promotes aggressive endometrial and squamous cell carcinomas[126][127]. Mutations in STK11 have been found in lung, breast, cervical, testicular, and liver cancers, as well as malignant melanoma, pancreatic and biliary carcinoma[128]. Germline mutations in STK11 are found in 30-70% of Peutz-Jeghers syndrome[129].

Therapeutic and prognostic relevance

A clinical study in a pancreatic cancer patient with Peutz-Jeghers syndrome whose tumor harboring an STK11 D194E mutation coupled with the loss of heterozygosity of the other STK11 allele displayed partial response to the everolimus treatment[130]. In another clinical case study, an adrenocorticotropic pituitary carcinoma patient whose tumor bearing an STK11 inactivating mutation responded to a combination of everolimus and radiotherapy[131].

Preclinical data suggested that lung cancer cell lines with STK11 inactivating mutations may confer increased sensitivity to the MEK-1 and MEK-2 inhibitor, trametinib[132].

Inactivating mutations of STK11 was shown to be associated with resistance to immune checkpoint blockade in KRAS-mutant lung adenocarcinoma (LUAC) and NSCLC (DOI: 10.1200/JCO.2017.35.15_suppl.9016)[133][134][135]. It was proposed that loss of STK11 negatively impacts the number and function of tumor-infiltrating T cells (TILs) and PD-L1 expression on tumor cells and therefore results in an ineffective response to PD-1-targeting antibodies[136].

TP53 Homozygous deletion

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[137]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[138].

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)[139].

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[140]. 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[141].

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[142][143][144]. 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)[145]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[146][147]. 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[148].

US FDA-APPROVED DRUG(S)

Binimetinib (MEKTOVI)

Binimetinib is an oral kinase inhibitor that targets MEK. Binimetinib is developed and marketed by Array BioPharma under the trade name MEKTOVI.

- FDA Approval Summary of Binimetinib (MEKTOVI)

MEKTOVI[149] NCT01909453	**Melanoma** (Approved on 2018/06/27)
	BRAF V600E/K
	Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3]

Cobimetinib (COTELLIC)

Cobimetinib is a reversible inhibitor which targets MEK1 and MEK2. Cobimetinib is developed by Exelixis and Genentech, and marketed by Genentech under the trade name COTELLIC.

- FDA Approval Summary of Cobimetinib (COTELLIC)

coBRIM[150] NCT01689519	**Melanoma** (Approved on 2015/11/10)
	BRAF V600E/K
	Cobimetinib + vemurafenib vs. Placebo + vemurafenib [PFS(M): 12.3 vs. 7.2]

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[151] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[152] 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[153] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[154] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]

RECORD-1[155] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

Imatinib (GLEEVEC)

Imatinib is an oral, small molecule inhibitor of tyrosine kinase enzymes, namely, the Abelson proto-oncogene (ABL), c-KIT, and platelet-derived growth factor receptor (PDGFR). Imatinib is developed and marketed by Novartis under the trade name GLEEVEC.

- FDA Approval Summary of Imatinib (GLEEVEC)

[156] NCT00022737	**Acute lymphocytic leukemia** (Approved on 2013/01/25)
	-
	Imatinib [EFS(%): 70]
	Gastrointestinal stromal tumor (Approved on 2012/01/31)
	KIT positive
	Imatinib [RFS(%): 42 (imatinib for 12)| 25 (imatinib for 36)]
	Gastrointestinal stromal tumor (Approved on 2009/02/10)
	KIT+
	Imatinib vs. Placebo [RFS(%): 21 vs. 28]
	Myelodysplastic myeloproliferative cancer (Approved on 2006/10/19)
	-
	Imatinib [MCyR(%): 39, CHR(%): 45]
[157]	**Acute lymphocytic leukemia** (Approved on 2006/10/19)
	Ph+
	Imatinib [MCyR(%): 35, CHR(%): 19]
	Dermatofibrosarcoma protuberans (Approved on 2006/10/19)
	-
	Imatinib [ORR(%): 83.0]
	Systemic mastocytosis (Approved on 2006/10/19)
	-
	Imatinib [CHR(%): 29]
	Chronic eosinophilic leukemia (Approved on 2006/10/19)
	-
	Imatinib [CHR(%): 61]
[158] NCT00471497	**Chronic myeloid leukemia** (Approved on 2003/05/20)
	Ph+
	Imatinib vs. Nilotinib [MMR(%): 22 vs. 44]
[159] NCT00333840	**Chronic myeloid leukemia** (Approved on 2003/04/18)
	-
	Imatinib vs. Interferon-α+ cytarabine [PFS(%): 81.2 vs. 60.6]
[160] NCT00009906	**Gastrointestinal stromal tumor** (Approved on 2002/02/01)
	-
	Imatinib [PFS(M): 18.9 (imatinib 400 mg)| 23.2 (imatinib 800 mg)]

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[161] 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[162] 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[163] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[164] 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[165] 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[166] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[167] 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[168] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

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[169] NCT00753688	**Sarcoma** (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]
VEG105192[170] NCT00334282	**Renal cell carcinoma** (Approved on 2009/10/19)
	-
	Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]

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[15] 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]

Sorafenib (NEXAVAR)

Sorafenib is a small molecule multi-kinase inhibitor that targets multiple kinase families including VEGFR, PDGFRB, and the RAF family kinases. Sorafenib is co-developed and co-marketed by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals under the trade name NEXAVAR.

- FDA Approval Summary of Sorafenib (NEXAVAR)

DECISION[171] NCT00984282	**Differentiated thyroid carcinoma** (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
SHARP[172] NCT00105443	**Hepatocellular carcinoma** (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]
TARGET[173] NCT00073307	**Renal cell carcinoma** (Approved on 2005/12/20)
	-
	Sorafenib vs. Placebo [PFS(D): 167 vs. 84]

Sunitinib (SUTENT)

Sunitinib is an oral, small molecule, multi-kinase inhibitor that targets receptor tyrosine kinase including platelet-derived growth factor receptor-α, -β (PDGFR-α, -β), vascular endothelial growth factor receptors-1, -2, -3 (VEGFR-1, -2, -3), c-kit, Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET), thereby inhibiting angiogenesis. Sunitinib is developed and marketed by Pfizer under the trade name SUTENT.

- FDA Approval Summary of Sunitinib (SUTENT)

[174][175][176] NCT00428597	**Pancreatic cancer** (Approved on 2011/05/20)
	-
	Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]
[177][178] NCT00083889	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib vs. Ifn-α [PFS(W): 47.3 vs. 22]
[179][180][178] NCT00077974	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 34.0]
[180][178] NCT00054886	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 36.5]
[181] NCT00075218	**Gastrointestinal stromal tumor** (Approved on 2006/01/26)
	-
	Sunitinib vs. Placebo [TTP(W): 27.3 vs. 6.4]

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[182] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

Temsirolimus (TORISEL)

Temsirolimus is a soluble ester of sirolimus (rapamycin, brand-name drug Rapamune) and functions as an inhibitor of mammalian target of rapamycin complex (mTORC). The inhibitory molecular mechanism is similar to Everolimus. Temsirolimus is developed by Wyeth Pharmaceuticals and marketed by Pfizer under the trade name TORISEL.

- FDA Approval Summary of Temsirolimus (TORISEL)

[183] NCT00065468	**Renal cell carcinoma** (Approved on 2007/05/30)
	-
	Temsirolimus vs. Ifn-α [OS(M): 10.9 vs. 7.3]

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[184] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[185] 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]

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COMBI-d[186] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[187] 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

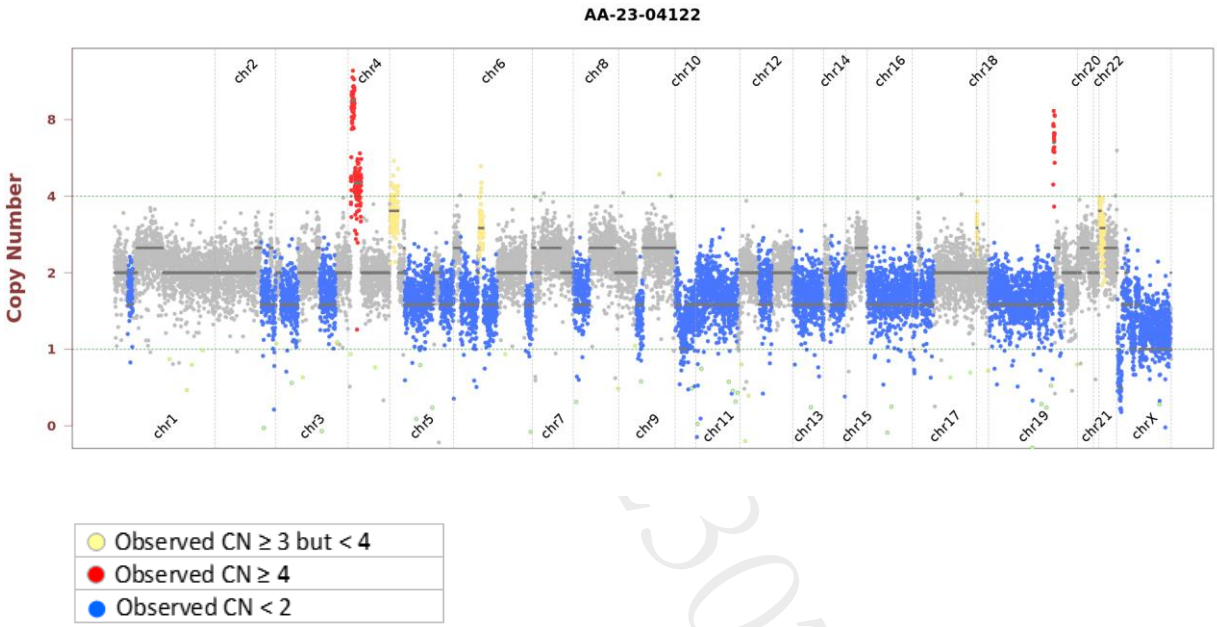
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
Not Detected							

- 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
ASXL1	G587C	13	c.1759G>T	NM_015338	-	14.3%	1224
ATM	E1353K	27	c.4057G>A	NM_000051	-	43.6%	518
AXL	R4W	1	c.10C>T	NM_021913	-	98.2%	283
BRD4	T221M	5	c.662C>T	NM_058243	-	28.0%	858
EPHA2	Splice region	-	c.1738+8G>A	NM_004431	-	42.7%	881
KMT2A	Q2337R	27	c.7010A>G	NM_001197104	-	51.2%	823
MAP3K1	G616W	10	c.1846G>T	NM_005921	-	28.1%	1415
MSH2	I632V	12	c.1894A>G	NM_000251	-	41.5%	518
PALB2	T1012I	10	c.3035C>T	NM_024675	-	69.4%	607
PALB2	V425M	4	c.1273G>A	NM_024675	COSM1286951	67.3%	928
POLD1	D644E	16	c.1932C>G	NM_001256849	-	50.3%	922
PRKN	R396G	11	c.1186A>G	NM_004562	-	34.3%	1339
PTCH1	Splice region	-	c.2560+7C>T	NM_000264	-	46.8%	2490
RXRA	E243G	5	c.728A>G	NM_002957	-	16.1%	801
TSC2	I195V	6	c.583A>G	NM_000548	-	71.6%	559

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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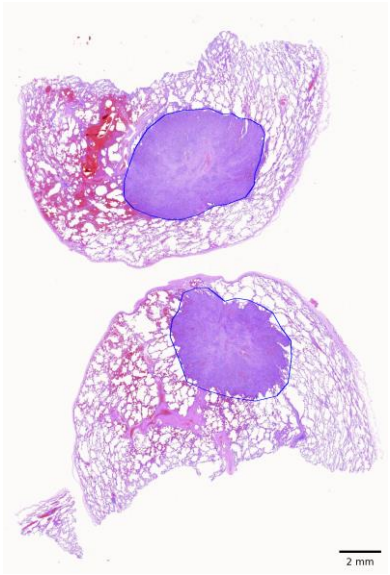
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Jun 08, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11226789B
- Collection site: Lung
- Examined by: Dr. Yun-An Chen
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 45%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 85%
  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: 1072x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 132

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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:
醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

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

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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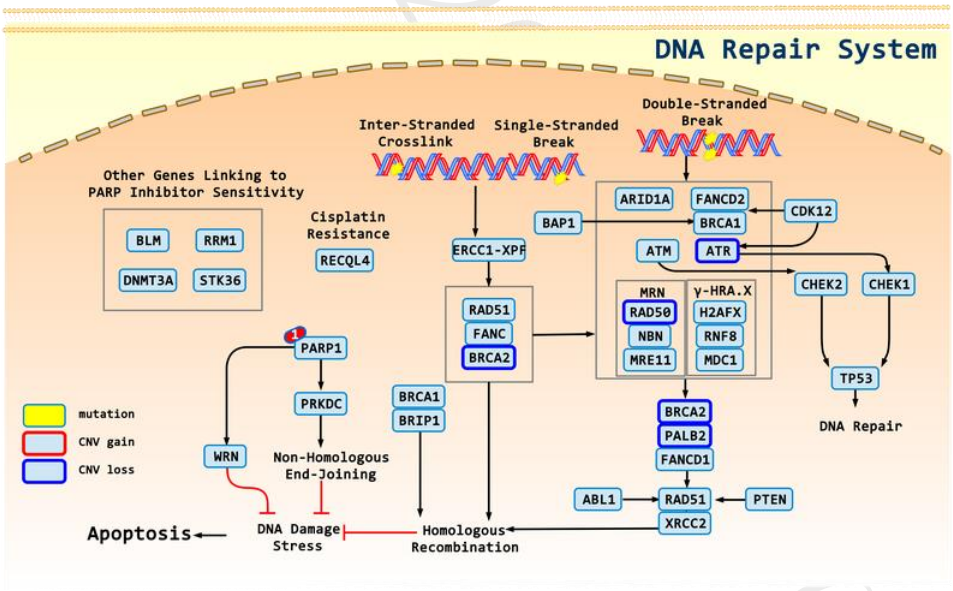
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
NF1	Binimetinib, Cobimetinib, Trametinib, Selumetinib, Everolimus, Temsirolimus	**sensitive**
STK11	Binimetinib, Cobimetinib, Trametinib, Everolimus, Temsirolimus	**sensitive**
ATR	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
PALB2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RAD50	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
NF1	Afatinib, Cabozantinib, Crizotinib, Erlotinib, Gefitinib, Lapatinib, Cetuximab, Trastuzumab, Vemurafenib	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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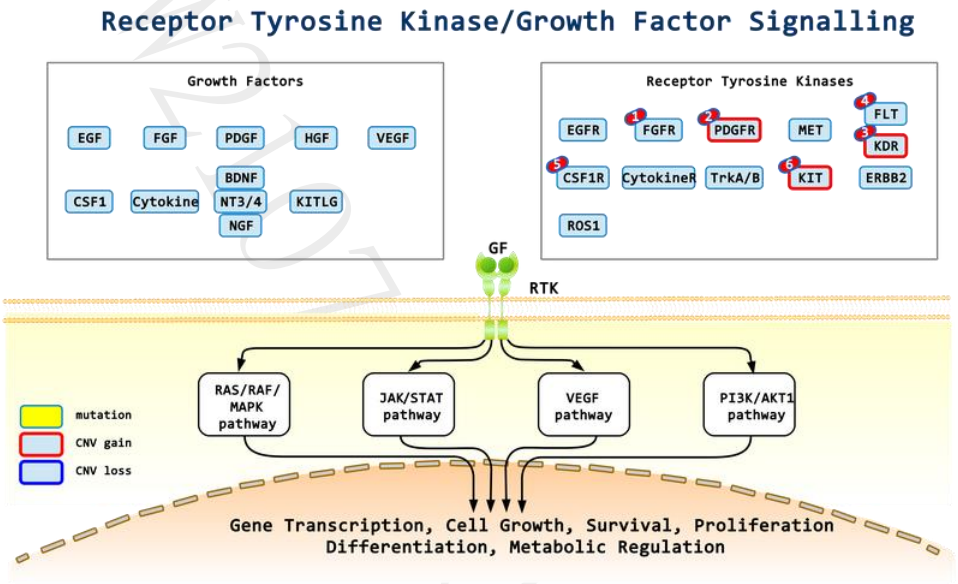
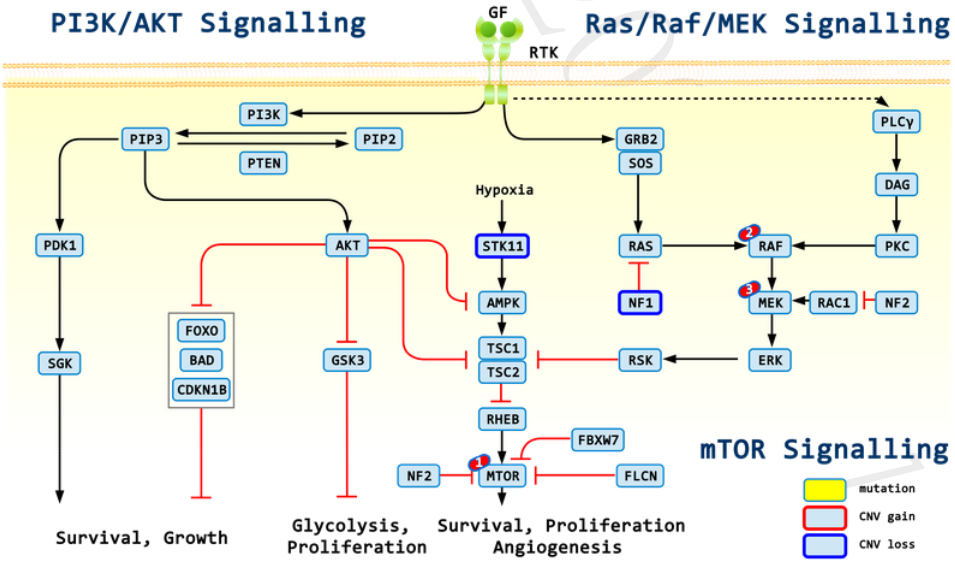


1: Pazopanib; 2: Imatinib, Sunitinib, Pazopanib; 3: Sunitinib, Pazopanib; 4: Sunitinib, Pazopanib; 5: Sunitinib; 6: Imatinib, Sunitinib, Pazopanib, Sorafenib



1: Everolimus, Temsirolimus; 2: Sorafenib; 3: Trametinib, Selumetinib, Binimetinib, Cobimetinib

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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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