

ACT Onco[®] + Report

PATIENT		
Identifier: 陳冠宇		Patient ID: 21429265
Date of Birth: Nov 21, 1990		Gender: Male
Diagnosis: Metastatic sarcoma		
ORDERING PHYSICIAN		
Name: 顏秀如醫師		Tel: 886-228712121
Facility: 臺北榮總		
Address: 臺北市北投區石牌路二段 201 號		
SPECIMEN		
Specimen ID: S11153274B	Collection site: Lung	Type: FFPE tissue
Date received: Feb 04, 2023	Lab ID: AA-23-00707	D/ID: NA

ABOUT ACT Onco[®]+

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	
MET Amplification	-	-	Capmatinib, Crizotinib, Tepotinib

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
CDKN2A Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	-
ALK Amplification	Lorlatinib	-
KDR Amplification	Cabozantinib, Pazopanib, Sunitinib	-
PDGFRA Amplification	Imatinib, Pazopanib, Sorafenib, Sunitinib	-
CRKL Amplification	-	Gefitinib
MAPK1 Amplification	-	Erlotinib
MET Amplification	Cabozantinib	Afatinib, Cetuximab, Dacomitinib, Erlotinib, Gefitinib, Osimertinib, Panitumumab

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 criteria 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
TP53	E285K	55.6%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr9	CDKN2A	Homozygous deletion	0
Chr7	KMT2C	Heterozygous deletion	1
Chr22	CRKL, MAPK1	Amplification	6
Chr4	KDR, PDGFRA	Amplification	6
Chr7	MET	Amplification	6
Chr2	ALK	Amplification	7

- Fusions

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

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

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

Note:

- 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 51% 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		
MET Amplification	Capmatinib, Crizotinib, Tepotinib	sensitive
MET Amplification	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	resistant
Level 3B		
CDKN2A Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	sensitive
KDR Amplification	Cabozantinib	sensitive
MET Amplification	Cabozantinib	sensitive
Level 4		
ALK Amplification	Lorlatinib	sensitive
KDR Amplification	Pazopanib, Sunitinib	sensitive
PDGFRA Amplification	Imatinib, Pazopanib, Sorafenib, Sunitinib	sensitive
CRKL Amplification	Gefitinib	resistant
MAPK1 Amplification	Erlotinib	resistant
MET Amplification	Cetuximab, Panitumumab	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

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AA	Irinotecan-based regimens	Level 1B

Clinical Interpretation:

Patients with the AA 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 AG or GG 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

TP53 E285K

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[1]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[2].

E285K mutation is located in the DNA-binding domain (DBD) of the p53 protein^[3]. This mutation resulted in a temperature-dependent decrease in transcriptional activation by p53 in vitro^[4].

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)^[5].

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^[6]. 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^[7].

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^{[8][9][10]}. 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)^[11]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[12][13]}. 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^[14].

ALK Amplification

Biological Impact

Anaplastic lymphoma kinase (ALK) gene encodes a receptor tyrosine kinase that belongs to the insulin receptor superfamily which was first described as a fusion partner in the t(2;5) chromosomal translocation in anaplastic large cell lymphoma in 1994^[15]. ALK activating mutations and gene fusions with a variety of translocation partners are commonly found in cancers, leading to the enhanced mitogenic and anti-apoptotic signaling pathways, including STAT3, MAPK, and PI3K pathways^{[16][17][18]}. Cancer types with ALK alterations include non-small cell lung cancer (NSCLC), anaplastic large cell lymphoma, inflammatory myofibroblastic tumor (IMT), neuroblastoma, and rhabdomyosarcoma^[19].

Therapeutic and prognostic relevance

Crizotinib, a tyrosine kinase inhibitor (TKI), is the first-generation ALK inhibitor, which was approved by the U.S. FDA for the first-line treatment of patients with ALK-positive advanced NSCLC in 2011^[20]. Later, second-generation ALK inhibitors such as ceritinib, alectinib, and brigatinib were granted approval by the U.S. FDA for the treatment of patients with ALK-positive metastatic NSCLC who has progressed on or are intolerant to crizotinib^{[21][22][23]}. Of note, both ceritinib and alectinib showed better treatment effect in ALK-positive metastatic NSCLC with brain metastasis^{[24][21]}. Furthermore, lorlatinib, the third-generation ALK inhibitor, was approved by the U.S. FDA in 2018 for the treatment of patients with refractory ALK-positive, and previously treated with one or more ALK inhibitors^{[25][26]}. In NCCN guidelines for NSCLC, alectinib, brigatinib, and lorlatinib are the preferred therapies for both first -line and complete planned systemic therapy.

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NSCLC cell lines harboring ALK high copy number exhibited increased sensitivity to ALK inhibitor (crizotinib) (J Clin Oncol, 30, no. 15_suppl 7533, 2012). Crizotinib also demonstrated antitumor activity in neuroblastoma and inflammatory breast cancer (IBC) tumor cells carrying amplified wild-type ALK^{[27][28]}. In another preclinical study, crizotinib and lorlatinib effectively inhibited cell viability of ALK-amplified neuroblastoma cell line^[29].

However, ALK amplification has been observed in five patients with ALK-positive NSCLC who have progressed on crizotinib treatment, suggesting that ALK amplification may be a potential mechanism of acquired resistance to crizotinib^{[30][31]}.

CDKN2A Homozygous deletion

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53^{[32][33][34]}. CDKN2A has been reported as a haploinsufficient tumor suppressor with one copy loss that may lead to weak protein expression and is insufficient to execute its original physiological functions^[35]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation^{[36][37]}.

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors^{[38][39]}. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments^{[40][41][42]}. However, there are clinical studies that demonstrated CDKN2A nuclear expression, CDKN2A/CDKN2B co-deletion, or CDKN2A inactivating mutation was not associated with clinical benefit from CDK4/6 inhibitors, such as palbociclib and ribociclib, in RB-positive patients^{[43][44][45]}. However, CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

The phase II TAPUR trial demonstrated clinical benefits to palbociclib monotherapy in advanced NSCLC or head and neck cancer harboring a CDKN2A mutation or copy number loss. However, pancreatic and biliary cancer patients harboring a CDKN2A mutation or copy number loss did not demonstrate an objective response or stable disease when treated with palbociclib monotherapy for 16 weeks (DOI: 10.1200/JCO.2021.39.15_suppl.6043)^{[46][47]}.

Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for the treatment of ER+ and HER2- breast cancer^{[39][48][49]}.

In a Phase I trial, a KRAS wild-type squamous non-small cell lung cancer (NSCLC) patient with CDKN2A loss had a partial response when treated with CDK4/6 inhibitor abemaciclib^[41]. Administration of combined palbociclib and MEK inhibitor PD-0325901 yield promising progression-free survival among patients with KRAS mutant non-small cell lung cancer (NSCLC) (AACR 2017, Abstract CT046). Moreover, MEK inhibitor in combination with CDK4/6 inhibitor demonstrates significant anti-KRAS-mutant NSCLC activity and radiosensitizing effect in preclinical models^[50].

A retrospective analysis demonstrated that concurrent deletion of CDKN2A with EGFR mutation in patients with non-small cell lung cancer (NSCLC), predicts worse overall survival after EGFR-TKI treatment^[51].

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CRKL Amplification

Biological Impact

The CRKL gene encodes an oncogenic protein that facilitates signal transduction from multiple different kinases to downstream targets, including the BCR-ABL translocation kinase that enhances transformation in chronic myelogenous leukemia (CML)^{[52][53]}. Amplification of CRKL has been implicated in lung and gastric cancer^{[54][55]}.

Therapeutic and prognostic relevance

Preclinical data suggest that amplification of the CRKL gene is associated with acquired resistance to EGFR tyrosine kinase inhibitor, gefitinib, in lung cancer^[54].

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^[56]. 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^[57]. Mutations of KDR are rare in tumors, and alterations of KDR activity typically occur via KDR amplification and subsequent overexpression^{[58][59]}.

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^{[60][61][62]}. 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^[63]. Besides, an angiosarcoma patient with upregulated VEGFR2 responded to sunitinib treatment^[64]. VEGFR2 inhibitors like apatinib and vandetanib are in early clinical phase trial^{[65][66][67]}.

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^[68].

KMT2C Heterozygous deletion

Biological Impact

Lysine methyltransferase 2C (KMT2C) gene encodes the histone methyltransferase MLL3, which methylates lysine residue four on the tail of histone H3 (H3K4)^[69] and regulates the gene expression during development and hematopoiesis^{[70][71][72]}. KMT2C is ubiquitously expressed, and its function is essential for normal embryonal development and cell proliferation^[73]. Genetic deletion of the region containing KMT2C is the most common chromosomal abnormality in acute myeloid leukemia^{[74][75]}, and KMT2C mutation has been reported in breast cancer, cutaneous squamous cell carcinoma, and leukemia^{[76][77][78][79][80]}. KMT2C was implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^[81]. Animal studies revealed that MLL3 haploinsufficiency enhances hematopoietic stem cells (HSCs) self-renewal capacity and induces extensive division of HSCs (AACR; Cancer Res 2018;78(13 Suppl): Abstract nr 4996).

Therapeutic and prognostic relevance

Preclinical studies of cell lines and xenograft models demonstrated that cells with reduced KMT2C expression and activity are deficient in homologous recombination-mediated double-strand break DNA repair and therefore, are more sensitive to olaparib, a PARP1/2 inhibitor^[82].

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A meta-analysis indicated that low levels of KMT2C expression was associated with better overall survival in pancreatic ductal adenocarcinoma (PDAC) patients^[83]. However, another study of ER-positive breast cancer patients (n = 401) demonstrated that low KMT2C expression was associated with worse overall survival^[84].

MAPK1 Amplification

Biological Impact

The MAPK1 gene (mitogen-activated protein kinase 1, also known as ERK2) encodes for a serine/threonine kinase, a member of the MAP kinase family (also known as extracellular signal-regulated kinases (ERKs)), involved in the RAS-RAF-MEK-ERK signal transduction pathway. Upon triggering by mitosis and differentiation factors as well as cytokines, MAPK1 is phosphorylated by its upstream kinases, resulting in its homodimerization and translocation to the nucleus where it phosphorylates its target proteins^{[85][86][87]}. MAPK1 and MAPK3 are two homologs that show functional redundancy for cell proliferation^{[88][89][87]}. Although MAPK1 mutations are rarely found in human tumors, the recurrent mutation, E322K, is found in cervical and head and neck cancers and amplification is observed in ovarian cancer^{[90][91][92]}.

Therapeutic and prognostic relevance

A few Inhibitors of MAPK1/3 (ERK2 and ERK1) are being explored as complementary and alternative options to RAF and MEK inhibition in cases of resistance or partial response^{[93][94][95]}. More recently, a characterization of the 'dual-mechanism' ERK inhibitor SCH772984 (Merck/Schering Plough) was reported^[96].

MAPK1 amplification has been reported in an erlotinib resistant EGFR mutant non-small cell lung cancer (NSCLC) patient and MAPK1-amplified cells demonstrated a decrease in sensitivity to cytotoxic chemotherapy and EGFR therapy^[97].

Patients with type II ovarian carcinoma harboring MAPK1 amplification had poorer progression-free survival than patients without MAPK1 amplification^[92].

MET Amplification

Biological Impact

The Mesenchymal-Epithelial Transition (MET) is an oncogene that encodes the MET receptor tyrosine kinase (c-MET, also called HGFR, hepatocyte growth factor receptor). Binding of HGF leads to autophosphorylation and activation of MET and downstream effectors through the PI3K/AKT and RAS/RAF/MEK pathways, which regulates cell growth, proliferation, migration, and angiogenesis^{[98][99]}. Gene amplification or overexpression of the MET occur in a wide range of cancers, including breast cancer^[100], non-small cell lung cancer (NSCLC)^[101], prostate cancer^[102], renal papillary carcinoma^{[103][104]}, glioblastoma^[105], hepatocellular carcinoma^[106], and gastric cancer^[107].

Therapeutic and prognostic relevance

MET amplification is known as an acquired mechanism conferring resistance to 1) EGFR-directed tyrosine kinase inhibitors including gefitinib, afatinib, erlotinib, and osimertinib, in patients with NSCLC^{[108][109][110][111]}; 2) anti-EGFR mAb therapies in colorectal cancer (CRC) and head and neck cancer^{[112][113][114][115][116]}; and 3) sunitinib, a multi-targeted tyrosine kinase inhibitor in renal cell carcinoma cells^{[117][118]}. Furthermore, MET amplification and overexpression has been implicated as a causative factor in acquired cetuximab resistance in head and neck squamous cell carcinoma.

In NCCN guidelines for NSCLC, high-level MET amplification has been suggested as an emerging biomarker for crizotinib, capmatinib and tepotinib in patients with metastatic NSCLC^[119](DOI: 10.1200/jco.2014.32.15_suppl.8001). In the phase 2 GEOMETRY mono-1 study (NCT02414139), patients with high-level MET-amplified advanced NSCLC showed responses to capmatinib in both treated and treatment naïve cohorts. The DOR, PFS, and OS were similar in both treated and treatment naïve patients (DOR: ~8 months; PFS: ~4 months. OS: ~10 months)^[120].

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The results of the phase II VISION trial (NCT02864992) indicated that tepotinib showed meaningful efficacy in advanced NSCLC patients with MET amplification. The overall response rate is 41.7% and the mPFS is 4.2 months (Journal of Clinical Oncology 39, no. 15_suppl 9021-9021). In addition, results from clinical studies of squamous cell carcinoma of lung (SCC), and esophagogastric adenocarcinoma also showed that patients with MET-amplified tumors responded to crizotinib^{[121][122]}.

Combinations of EGFR TKIs like gefitinib, erlotinib, osimertinib, and icotinib with c-MET inhibitor crizotinib were proposed to overcome the acquired resistance induced by EGFR-directed TKIs mediated MET amplification and were successfully evaluated in clinical settings^{[123][124][125][126][127][128]}. Besides, there is a case report showed that EGFR-mutated NSCLC patients with acquired MET amplification responded to combination therapy with bevacizumab and erlotinib^[129]. A phase Ib/II trial in NSCLC patients who failed EGFR inhibitor therapy showed that patients with mutated EGFR and MET amplification (copy number >6) responded to the combination treatment with capmatinib and gefitinib (Overall response rate: 47%, disease control rate: 75%)^[130].

Cabozantinib is a small molecule inhibitor of MET, VEGFR2, KIT and RET and was approved by the U.S. FDA for the treatment of progressive, metastatic medullary thyroid cancer^{[131][132]}. MET amplification has been selected as an inclusion criteria for the trial examining cabozantinib in NSCLC (NCT01639508) (NCT03911193).

MET amplification and exon 14 splice site mutations are associated with higher c-Met protein expression and poor prognosis in patients with NSCLC and esophageal squamous cell carcinoma^{[133][134]}. Besides, the plasma level of c-MET was associated with poor outcome in patients with hepatocellular carcinoma^[135].

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^{[136][137]}. 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^[138]; activating mutations in PDGFRA have been observed in ~5% of Chinese melanoma patients^[139]; amplification of PDGFRA is the second most frequent receptor tyrosine kinase amplification in glioblastoma (GBM)^{[105][140][141][142][143]}, intimal sarcomas^[144], malignant peripheral nerve sheath tumors^[145], non-small cell lung adenocarcinomas and non-small cell lung squamous cell carcinomas^[146].

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^[147].

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^[148]. Another study also showed that pazopanib could inhibit tumor growth in the PDGFRA-amplified pleomorphic liposarcoma xenograft mouse model^[149].

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US FDA-APPROVED DRUG(S)

Abemaciclib (VERZENIO)

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

- FDA Approval Summary of Abemaciclib (VERZENIO)

MONARCH E NCT03155997	Breast cancer (Approved on 2021/10/12)
	HR+/HER2- Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3^[150] NCT02246621	Breast cancer (Approved on 2018/02/26)
	HR+/HER2- Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 2^[49] NCT02107703	Breast cancer (Approved on 2017/09/28)
	HR+/HER2- Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1^[151] NCT02102490	Breast cancer (Approved on 2017/09/28)
	HR+/HER2- Abemaciclib [ORR(%): 19.7 vs. 17.4]

Cabozantinib (COMETRIQ)

Cabozantinib is a small molecule inhibitors of multiple tyrosine kinases, including RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, and TIE-2. Cabozantinib is developed and marketed by Exelixis under the trade names COMETRIQ (capsule) and CABOMETYX (tablet).

- FDA Approval Summary of Cabozantinib (COMETRIQ)

EXAM^[152] NCT00704730	Thyroid cancer (Approved on 2012/11/29)
	- Cabozantinib vs. Placebo [PFS(M): 11.2 vs. 4]

Cabozantinib (CABOMETYX)

Cabozantinib is a small molecule inhibitors of multiple tyrosine kinases, including RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, and TIE-2. Cabozantinib is developed and marketed by Exelixis under the trade names COMETRIQ (capsule) and CABOMETYX (tablet).

- FDA Approval Summary of Cabozantinib (CABOMETYX)

COSMIC-311 NCT03690388	Differentiated thyroid cancer (dct) (Approved on 2021/09/17)
	- Cabozantinib vs. Placebo [PFS(M): 11 vs. 1.9, ORR(%): 18.0 vs. 0]
CHECKMATE-9ER NCT03141177	Renal cell carcinoma (Approved on 2021/01/22)
	- Nivolumab + cabozantinib vs. Sunitinib [ORR(%): 55.7 vs. 27.1, PFS(M): 16.6 vs. 8.3, OS(M): NR vs. NR]

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CELESTIAL ^[62] NCT01908426	Hepatocellular carcinoma (Approved on 2019/01/14)
	-
	Cabozantinib vs. Placebo [OS(M): 10.2 vs. 8]
CABOSUN ^[153] NCT01835157	Renal cell carcinoma (Approved on 2017/12/09)
	-
	Cabozantinib vs. Sunitinib [PFS(M): 8.6 vs. 5.3]
METEOR ^[154] NCT01865747	Renal cell carcinoma (Approved on 2016/04/25)
	-
	Cabozantinib vs. Everolimus [PFS(M): 7.4 vs. 3.8]

Capmatinib (TABRECTA)

Capmatinib is an orally bioavailable inhibitor of the proto-oncogene c-Met (also known as hepatocyte growth factor receptor (HGFR)) with potential antineoplastic activity. Capmatinib is developed and marketed by Novartis under the trade name TABRECTA.

- FDA Approval Summary of Capmatinib (TABRECTA)

GEOMETRY mono-1 ^[120] NCT02414139	Non-small cell lung carcinoma (Approved on 2020/05/06)
	MET exon 14 skipping
	Capmatinib [ORR (Treatment naive) (%): 68, ORR (Previously treated)(%): 41]

Crizotinib (XALKORI)

Crizotinib is an inhibitor of the tyrosine kinases anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1), by competitively binding with the ATP-binding pocket. Crizotinib is developed and marketed by Pfizer under the trade name XALKORI.

- FDA Approval Summary of Crizotinib (XALKORI)

ADVL0912, A8081013 NCT00939770, NCT01121588	Inflammatory myofibroblastic tumor (Approved on 2022/08/05)
	ALK+
	Crizotinib [ORR(pediatric patients)(%): 86.0, ORR(adult patients)(%): 71.0]
ADVL0912 NCT00939770	Alk fusion-positive anaplastic large cell lymphoma (alcl) (Approved on 2021/01/14)
	ALK fusion
	Crizotinib [ORR(%): 88.0, DOR(M): 39 (maintained response for at least 6 months) vs. 22 (maintained response for at least 12 months)]
PROFILE 1001 ^[155] NCT00585195	Non-small cell lung carcinoma (Approved on 2016/03/11)
	ROS1+
	Crizotinib [ORR(%): 66.0]
PROFILE 1014 ^[156] NCT01154140	Non-small cell lung carcinoma (Approved on 2015/03/20)
	ALK+
	Crizotinib vs. Pemetrexed + cisplatin or pemetrexed + carboplatin [PFS(M): 10.9 vs. 7]
PROFILE 1007 ^[20] NCT00932893	Non-small cell lung carcinoma (Approved on 2013/11/20)
	ALK+
	Crizotinib vs. Pemetrexed or docetaxel [PFS(M): 7.7 vs. 3]

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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)

[157] 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]
[158]	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]
[159] NCT00471497	Chronic myeloid leukemia (Approved on 2003/05/20)
	Ph+
	Imatinib vs. Nilotinib [MMR(%): 22 vs. 44]
[160] NCT00333840	Chronic myeloid leukemia (Approved on 2003/04/18)
	-
	Imatinib vs. Interferon-α+ cytarabine [PFS(%): 81.2 vs. 60.6]
[161] NCT00009906	Gastrointestinal stromal tumor (Approved on 2002/02/01)
	-
	Imatinib [PFS(M): 18.9 (imatinib 400 mg) 23.2 (imatinib 800 mg)]

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Lorlatinib (LORBRENA)

Lorlatinib is a kinase inhibitor with in vitro activity against ALK and ROS1 as well as TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK. Lorlatinib demonstrated in vitro activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on crizotinib and other ALK inhibitors. Lorlatinib is developed and marketed by Pfizer under the trade name LORBRENA.

- FDA Approval Summary of Lorlatinib (LORBRENA)

Study B7461006 (CROWN) NCT03052608	Non-small cell lung carcinoma (Approved on 2021/03/03)
	ALK+
	Lorlatinib vs. Crizotinib [PFS(M): NR vs. 9.3]
Study B7461001 ^[25] NCT01970865	Non-small cell lung carcinoma (Approved on 2018/11/02)
	ALK+
	Lorlatinib [ORR(%): 48, ORR (intracranial)(%): 60]

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 ^[162] 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)

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 ^[163] 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 ^[164] NCT02477644	Ovarian cancer (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO ^[165] 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]

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SOLO-1 ^[166] 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 ^[167] NCT02000622	Breast cancer (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21 ^[168] 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 ^[169] NCT00753545	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

Palbociclib (IBRANCE)

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

- FDA Approval Summary of Palbociclib (IBRANCE)

PALOMA-2 ^[170] NCT01740427	Breast cancer (Approved on 2017/03/31)
	ER+/HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3 ^[171] NCT01942135	Breast cancer (Approved on 2016/02/19)
	ER+/HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

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 ^[172] NCT00753688	Sarcoma (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]
VEG105192 ^[173] NCT00334282	Renal cell carcinoma (Approved on 2009/10/19)
	-
	Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]

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Ribociclib (KISQALI)

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

- FDA Approval Summary of Ribociclib (KISQALI)

MONALEESA-2 ^[48] NCT01958021	Breast cancer (Approved on 2017/03/13)
	HR+/HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

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 ^[174] 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]

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 ^[175] NCT00984282	Differentiated thyroid carcinoma (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
SHARP ^[176] NCT00105443	Hepatocellular carcinoma (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]
TARGET ^[177] NCT00073307	Renal cell carcinoma (Approved on 2005/12/20)
	-
	Sorafenib vs. Placebo [PFS(D): 167 vs. 84]

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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)

[178][179][180] NCT00428597	Pancreatic cancer (Approved on 2011/05/20)
	- Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]
[181][182] NCT00083889	Renal cell carcinoma (Approved on 2007/02/02)
	- Sunitinib vs. Ifn- α [PFS(W): 47.3 vs. 22]
[183][184][182] NCT00077974	Renal cell carcinoma (Approved on 2007/02/02)
	- Sunitinib [ORR(%): 34.0]
[184][182] NCT00054886	Renal cell carcinoma (Approved on 2007/02/02)
	- Sunitinib [ORR(%): 36.5]
[185] 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)

EMBRACA ^[186] NCT01945775	Breast cancer (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

Tepotinib (TEPMETKO)

Tepotinib is a potent and selective c-Met inhibitor. Tepotinib is developed and marketed by EMD Serono, Inc. under the trade name TEPMETKO.

- FDA Approval Summary of Tepotinib (TEPMETKO)

VISION NCT02864992	Non-small cell lung carcinoma (Approved on 2021/02/03)
	MET exon 14 skipping
	Tepotinib [ORR (Treatment naive)(%): 43, ORR (Previously treated)(%): 43]

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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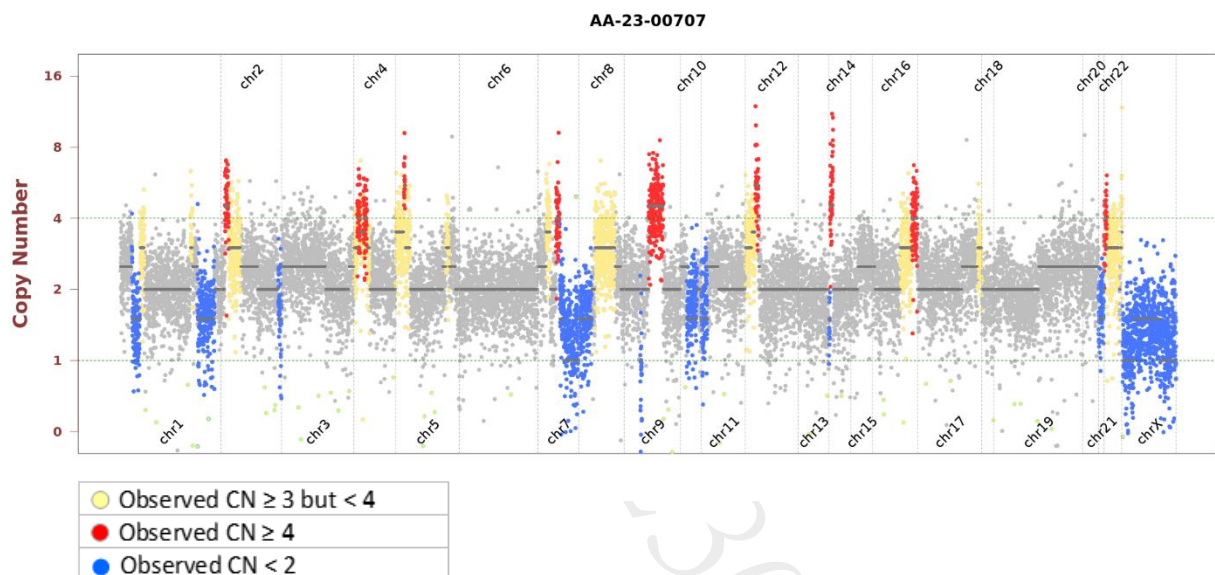
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
TP53	E285K	8	c.853G>A	NM_000546	COSM10722	55.6%	311

- 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
ADAMTS15	P438L	4	c.1313C>T	NM_139055	COSM6241419	67.7%	886
ADAMTS9	D658G	13	c.1973A>G	NM_182920	-	50.6%	656
ASXL1	Q780H	13	c.2340G>C	NM_015338	-	68.2%	453
BRCA2	H523R	10	c.1568A>G	NM_000059	COSM9110800	28.8%	593
MITF	E208G	4	c.623A>G	NM_198159	-	47.8%	1007
PSME2	L202I	10	c.604C>A	NM_002818	-	6.1%	3277
SYNE1	K4296N	78	c.12888A>T	NM_182961	-	9.9%	1458
ZNF217	P823L	3	c.2468C>T	NM_006526	-	37.8%	678

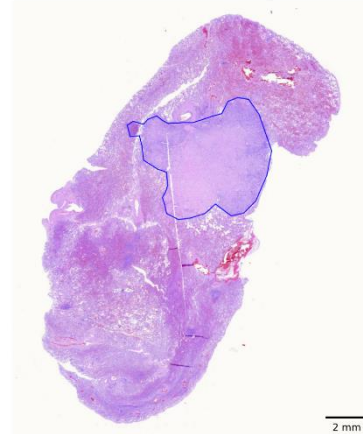
Note:

- 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: Jan 19, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11153274B
- Collection site: Lung
- Examined by: Dr. Yun-An Chen
 1. The percentage of viable tumor cells in total cells in the whole slide (%): 5%
 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: 718x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 191

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.

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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 $\geq 5\%$ and actionable variants with allele frequency $\geq 2\%$ were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at $100\times \geq 85\%$ with a mean coverage $\geq 500\times$.

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 .

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 $\geq 10\%$; (4) Fusions annotated in Quiver Gene Fusion Database.

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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

Yeh

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GENE LIST SNV & CNV

ABCB1*	ABCC2*	ABCG2*	ABL1	ABL2	ADAMTS1	ADAMTS13	ADAMTS15	ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9
ADAMTSL1	ADGRA2	ADH1C*	AKT1	AKT2	AKT3	ALDH1A1*	ALK	AMER1	APC	AR	ARAF
ARID1A	ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2	AXL
B2M	BAP1	BARD1	BCL10	BCL2*	BCL2L1	BCL2L2*	BCL6	BCL9	BCOR	BIRC2	BIRC3
BLM	BMP1R1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2*	BTB	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*	SLC01B1*
SLC01B3*	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOC1*	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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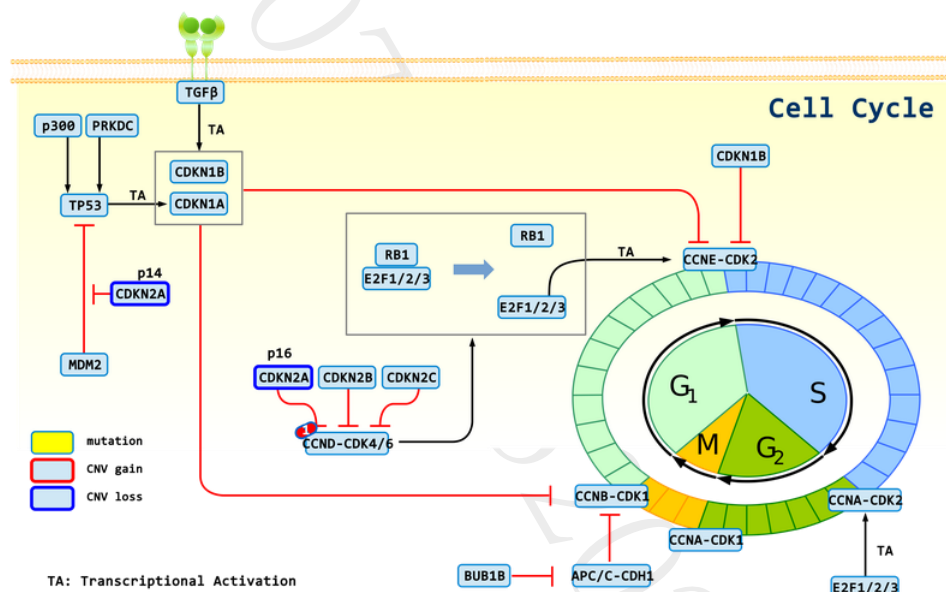
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
KMT2C	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive

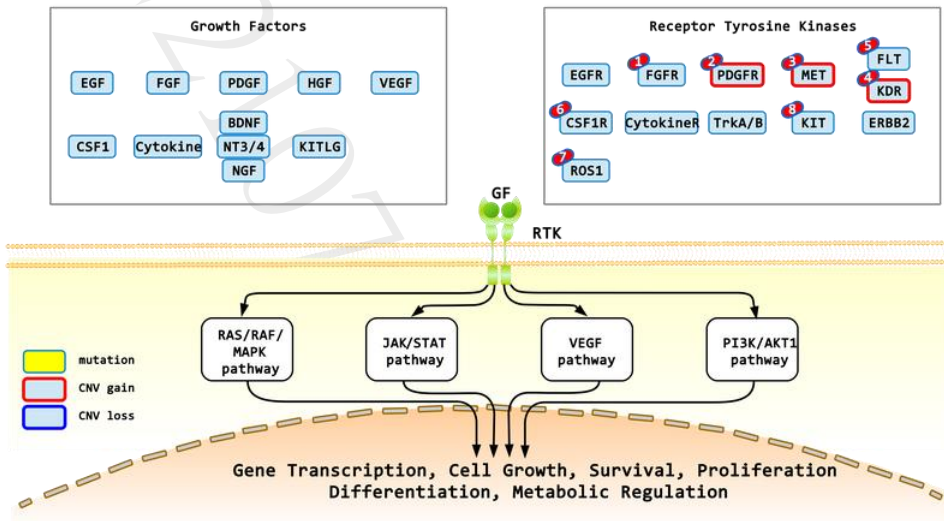
SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Abemaciclib, Palbociclib, Ribociclib

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Receptor Tyrosine Kinase/Growth Factor Signalling



1: Pazopanib; 2: Imatinib, Sunitinib, Pazopanib; 3: Cabozantinib, Crizotinib, Capmatinib, Tepotinib; 4: Sunitinib, Pazopanib, Cabozantinib; 5: Sunitinib, Pazopanib; 6: Sunitinib; 7: Lorlatinib, Crizotinib; 8: Imatinib, Sunitinib, Pazopanib, Sorafenib

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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。

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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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