周仁春
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ACT Onco® + Report

PATIENT		
Identifier: 周仁春		Patient ID: 18886732
Date of Birth: Jun 03, 1960		Gender: Male
Diagnosis: Pancreatic cancer		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11204183A	Collection site: Liver	Type: FFPE tissue
Date received: Feb 09, 2023	Lab ID: AA-23-00832	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
KRAS G12V	-	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib, Panitumumab, Cetuximab
PIK3R1 S83*	Trametinib	-
SMAD4 V407fs	-	Cetuximab
AKT2 Amplification	-	Erlotinib
FGFR1 Amplification	Erdafitinib, Infigratinib, Lenvatinib, Pazopanib, Ponatinib, Regorafenib, Sunitinib	Palbociclib, Ribociclib
KRAS Amplification	Sorafenib	Cetuximab, Crizotinib, 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 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
KRAS	G12V	52.5%
PIK3R1	S83*	11.4%
SMAD4	V407fs	25.9%
TP53	Splice donor	30.7%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr15	*RAD51*	Heterozygous deletion	1
Chr8	*FGFR1*	Amplification	6
Chr12	*CDKN1B, KDM5A, KRAS*	Amplification	8
Chr19	*AKT2*	Amplification	8
Chr7	*CDK6*	Amplification	26

- 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)	3.2 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 35% 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		
KRAS G12V	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib, Panitumumab, Cetuximab	**resistant**
Level 3B		
FGFR1 Amplification	Erdafitinib, Infigratinib, Ponatinib, Regorafenib, Sunitinib	**sensitive**
Level 4		
PIK3R1 S83*	Trametinib	**sensitive**
FGFR1 Amplification	Lenvatinib, Pazopanib	**sensitive**
KRAS Amplification	Sorafenib	**sensitive**
SMAD4 V407fs	Cetuximab	**resistant**
AKT2 Amplification	Erlotinib	**resistant**
FGFR1 Amplification	Palbociclib, Ribociclib	**resistant**
KRAS Amplification	Cetuximab, Crizotinib, 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

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
SMAD4 V407fs	Fluorouracil	**Resistant**	Clinical	Colorectal cancer

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
FGFR1 Amplification	Letrozole	**Resistant**	Clinical	Estrogen-receptor positive breast cancer
	Tamoxifen	**Resistant**	Preclinical	Breast cancer

OTHERS

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

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

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VARIANT INTERPRETATION

KRAS G12V, Amplification

Biological Impact

The V-Ki-Ras2 Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (KRAS) gene encodes a small GTPase protein, a member of the RAS family of small GTPases, which catalyze the hydrolysis of GTP to GDP. RAS proteins cycle between an active (GTP-bound) and an inactive (GDP-bound) state, to activate the downstream oncogenic pathways, including the PI3K/AKT/mTOR and MAPK pathways[1]. KRAS mutations occur primarily in three hotspots G12, G13 and Q61, and less frequently in codon A146[1][2]. These are activating mutations that lead to constitutive activation and persistent stimulation of the downstream signaling pathways[3][4]. Mutations in KRAS have been reported in a diverse spectrum of human malignancies, including pancreatic carcinomas (>80%)[1][5], colon carcinomas (40-50%)[6][7], and lung carcinomas (30-50%)[8][9], but are also present in biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer, liver cancer, myeloid leukemia and breast cancer[2].

KRAS G12V is a hotspot mutation that has been shown to result in the increased activation of downstream signaling pathways[10].

Therapeutic and prognostic relevance

Except for KRAS G12C, other KRAS mutants are not currently targetable, but the downstream MEK serves as a potential target[11]. MEK inhibitors trametinib, cobimetinib, and binimetinib were approved by the U.S. FDA for patients with advanced metastatic melanoma whose tumors harbor BRAF V600 mutations[12][13][14][15].

There are case reports indicated that patients harboring a KRAS mutation may benefit from MEK inhibitor treatment. A patient with small cell neuroendocrine carcinoma (SCNEC) of the cervix harboring a KRAS G12D mutation showed significant response with trametinib[16]. Another low-grade serous carcinoma case with KRAS G12D also has sustained response to trametinib (Am J Clin Exp Obstet Gynecol 2015;2(3):140-143). In addition, a low-grade serous ovarian cancer patient harboring KRAS G12V mutation showed stable disease after 8 weeks of binimetinib treatment, and demonstrated a partial response after another 26 weeks of treatment[17]. However, trametinib did not demonstrate superiority to docetaxel in KRAS-mutant non-small cell lung cancer (NSCLC) patients, based on results from a randomized Phase II study[18].

Both clinical and preclinical studies demonstrated a limited response to monotherapy using MEK inhibitors[19]. Moreover, several clinical trials are in progress to evaluate the combination of MEK and mTOR inhibition as a new potential therapeutic strategy in CRC[20], and in patient-derived xenografts of RAS-mutant CRC, inhibition of MEK and mTOR suppressed tumor growth, but not tumor regression[21]. A study using the CRC patient-derived xenograft (PDX) model showed that the combination of trametinib, a MEK inhibitor, and palbociclib, a CDK4/6 inhibitor, was well tolerated and resulted in objective responses in all KRAS mutant models[22].

KRAS mutation has been determined as an inclusion criterion for the trials evaluating MEK inhibitors efficacies in various types of solid tumors (NCT03704688, NCT02399943, NCT02285439, NCT03637491, NCT04214418).

Cetuximab and panitumumab are two EGFR-specific antibodies approved by the U.S. FDA for patients with KRAS wild-type metastatic colorectal cancer (NCT00154102, NCT00079066, NCT01412957, NCT00364013). Results from the PRIME and FIRE-3 trials indicated that panitumumab and cetuximab did not benefit patients with KRAS or NRAS mutations and may even have a detrimental effect in these patients[23]. Taken together, the National Comprehensive Cancer Network (NCCN) recommended that, cetuximab and panitumumab should only be used if both KRAS and NRAS genes are normal (NCCN guidelines)[24][25]. Numerous studies have demonstrated the presence of KRAS or NRAS mutations at exon 2, 3 or 4 as a predictor of resistance to anti-EGFR therapies[26][27][28][29][30][31][32].

Sorafenib, a multi-kinase inhibitor, has been shown to be beneficial in KRAS-mutant CRC[33], KRAS-mutant NSCLC[34],

and KRAS-amplified melanoma[35].

There has been conflicting data on the effect of KRAS mutation on the efficacy of bevacizumab in metastatic CRC patients(J Clin Oncol 34, 2016 (suppl; abstr 3525))[36][37].

In NCCN guidelines for NSCLC, KRAS mutations have been suggested as an emerging biomarker for EGFR TKIs in NSCLC patients. KRAS mutations are associated with a lack of efficacy of EGFR TKIs, including erlotinib, gefitinib, afatinib, and osimertinib, in NSCLC patients[38][39][40].

Studies have shown that KRAS mutation, especially those occurs in exon 2 (codon 12 or 13) and codon 61 indicated a poor prognosis for patients with CRC[41].

In low-grade serous carcinoma of the ovary or peritoneum, patients with KRAS or BRAF mutations (n=21) had a significantly better OS than those with wild-type KRAS or BRAF (n=58) (106.7 months vs 66.8 months), respectively[42]. In ovarian serous borderline tumor with recurrent low-grade serous carcinoma, patient harboring KRAS G12V mutation appeared to have shorter survival time[43].

In patients with metastatic colorectal cancer treated with bevacizumab, the shortest survival was observed in patients with tumors harboring G12V or G12A KRAS mutation, and the PFS and OS for patients with G12V/A KRAS mutation was 6.6 and 16.8 compared to 11.6 and 23.6 months for patients with tumors harboring other KRAS mutation type[44]. In another retrospective study, Patients with KRAS G12V exhibited worse OS and higher recurrence incidences compared with the entire cohort (OS: 26 months vs 60 months; DFS: 15 months vs 24 months) in lung adenocarcinoma[45].

Metastatic colorectal cancer patients harboring KRAS amplification were resistant to anti-EGFR therapy such as cetuximab and panitumumab[46][47].

Some in vitro studies showed that activation of the RAS, due to either KRAS/NRAS mutations or to KRAS amplification, rendered lung cancer cells resistant to ROS1 inhibition by crizotinib[48][49][50].

PIK3R1 S83*

Biological Impact

The PIK3R1 gene encodes the PI3K regulatory subunit p85α, which exerts tumor-suppressive roles by regulating the p110α subunit of PI3K[51]. Approximately 90% of PIK3R1 mutations occur in nSH2 and iSH2 domains, relieving the inhibitory effect on p110 and leading to constitutive activation of the AKT-mTOR pathway[52][53]. PIK3R1 is somatically mutated in glioblastoma, colorectal cancer, pancreatic cancer, breast cancer, and endometrial cancer[54][55][56].

S83* mutation results in a premature truncation of the PIK3R1 protein at amino acid 83 (UniProtKB). This mutation is predicted to lead to a loss of PIK3R1 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

In a clinical study, low expression of PIK3R1 was observed in breast tumors and associated with poor metastasis-free survival[57].

Knockout of PIK3R1 in breast cancer cell lines led to MAPK pathway activation and sensitized PIK3R1-null cells to trametinib[58]. In another preclinical study, loss-of-function RNAi-based screening assay showed that silencing PIK3R1 enhances the sensitivity of breast cancer cell lines to rapamycin, an MTOR inhibitors[59].

SMAD4 V407fs

Biological Impact

The SMAD family member 4 (SMAD4) gene encodes a transcription factor that acts as a downstream effector in the TGF-β signaling pathway. Upon phosphorylated and activated by serine-threonine receptor kinase, Smad4 is the Co-Smad which recruits other activated R-Smad proteins to the Smad transcriptional complex and regulate TGF-β-targeted genes[60]. Smad4 has been identified as a haploinsufficient gene with one copy loss may lead to a weak protein expression and is insufficient to execute its original physiological function[61]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)[62][63][64][65]. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer[66], colorectal cancer (CRC)[64][67][68], and less frequently seen in other cancers such as lung adenocarcinoma[69], head and neck cancer[70][71], and cutaneous squamous cell carcinoma[72].

V407fs mutation results in a change in the amino acid sequence beginning at 407, likely to cause premature truncation of the functional SMAD4 protein (UniProtKB). This mutation is predicted to lead to a loss of SMAD4 protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

In Chinese patients with metastatic colorectal cancer, SMAD4 or NF1 mutations are suggested as a potential biomarker for poor prognosis to cetuximab-based therapy[73]. Preclinical data demonstrated that depletion of SMAD4 by shRNA knockdown increased clonogenic survival and cetuximab resistance in HPV-negative head and neck squamous cell carcinoma cells[74].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)[75][76]. CRC patients with normal SMAD4 diploidy exhibited three-fold higher benefit of 5-FU/mitomycin-based adjuvant therapy when compared with those with SMAD4 deletion[77].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis[78][79][80][81][82][83][84][85]. In cervical cancer patients, weak cytoplasmic SMAD4 expression and absent nuclear SMAD4 expression were shown to be significantly associated with poor disease-free and overall 5-year survival[86].

TP53 Splice donor

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[87]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[88].

TP53 c.919+2T>A is a variant located at the splice donor region, which may result in the exon skipping.

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)[89].

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[90]. 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[91].

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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[92][93][94]. 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)[95]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[96][97]. 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[98].

AKT2 Amplification

Biological Impact

The v-akt murine thymoma viral oncogene homolog 2 (AKT2 , also known as HIHGHH, PRKBB, PKBBETA, RAC-BETA, PKBB) gene encodes an AKT family of serine/threonine protein kinases, including AKT1 and AKT3 isoforms, that act as a downstream effector of the pro-oncogenic PI3-kinase signaling pathway[99][100][101][102][103]. Whereas somatic AKT2 mutations have been described rarely in cancer, germline autosomal dominant mutations in AKT2 are associated with familial diabetes mellitus in humans[104].

Therapeutic and prognostic relevance

A preclinical study demonstrated that an AKT2-amplified pancreatic cancer cell line exhibited resistance to erlotinib. Besides, amplification of AKT2 was predominantly expressed across pancreatic cancer patients in TCGA datasets and correlated with high mRNA expression. Patients with a high AKT2 expression tended to have poor response to erlotinib plus gemcitabine[105].

CDK6 Amplification

Biological Impact

CDK6 encodes the cyclin-dependent kinase 6, a serine/threonine kinase that controls the checkpoint at G1-S phase. Binding of CDK4/6 to cyclin D is negatively regulated by p16INK4a, a cyclin-dependent kinase inhibitor encoded by CDKN2A[106][107]. As CDK4 and CDK6 play overlapping and redundant physiological roles in the regulation of cell cycle, increased CDK6 activity could also promote tumorigenesis in a way similar to CDK4[108]. Amplification of CDK6 has been observed in esophageal carcinoma[109][110][111], leukemia and lymphoma[112][113][114].

Therapeutic and prognostic relevance

CDK6 amplification has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in several types of solid tumors (NCT02693535).

Results from two cohort studies (n=45 and n=46) showed that CDK6 overexpression was correlated with shorter median time to progression in ER+ breast cancer patients who had received fulvestrant (2.5 vs. 8.2 months and 3.4 vs. 8.9 months for CDK6 overexpression vs. normal expression) but was not correlated with other lines of treatment (N=68, tamoxifen or endocrine therapy). In vitro study further confirmed that cells exhibiting upregulation of CDK6 were resistant to fulvestrant[115].

In a case report, a patient with CDK6-amplified osteosarcoma was treated with ribociclib in combination with gemcitabine and resulted in stable disease for 10 cycles of the treatment[116]. However, a preclinical study showed that transformed cells harboring acquired CDK6 amplification were resistant to abemaciclib, as demonstrated by reduced response of the CDK4/6 target, phospho-Rb (pRb)[117].

CDKN1B Amplification

Biological Impact

The CDKN1B gene encodes cyclin-dependent kinase (CDK) inhibitor 1B, also called p27, which is a member of the Cip/Kip protein family. The p27 protein is ubiquitously expressed and located both in the nucleus and in the cytoplasm. Nuclear p27 functions as a tumor suppressor by controlling cell cycle progression from G1 to S phase, specifically by inhibiting the binding of cyclin A and E to CDK2[118]. It has been demonstrated that haploinsufficiency of CDKN1B contributed to leukemogenesis in T-cell prolymphocytic leukemia[119].

Therapeutic and prognostic relevance

Low CDKN1B levels due to increased protein degradation are prevalent in several different types of epithelial tumors and are commonly correlated with aggressive tumor growth and poor clinical outcome[120][121][122]. Loss of p27 expression is associated with poor prognosis in a variety of tumors, including pancreatic cancer[123], colorectal cancer[124], gastroenteropancreatic neuroendocrine tumors[125], and breast cancer[126].

In vitro data demonstrated that Src inhibitors could increase p27 stability and restore tamoxifen sensitivity in tamoxifen-resistant breast cancer cells[127].

CDKN1B amplification has been found to correlate with poor prognosis in gastric cancer[128].

FGFR1 Amplification

Biological Impact

The fibroblast growth factor receptor 1 (FGFR1) gene encodes a receptor tyrosine kinase that plays crucial roles in cellular proliferation, survival, migration and angiogenesis[129][130]. Several studies have demonstrated that FGFR1 amplification correlates with FGFR1 overexpression[131][132][133][134][135][136]. Overexpression of FGFR1 has also been shown to enhance both ligand-dependent, and independent activation of downstream signaling pathways such as the phosphoinositide-3 kinase (PI3K) and the extracellular signal-regulated kinase 1/2 (ERK1/2) cascades[137][138][139]. Amplification of FGFR1 has been associated with early relapse, and poor survival, specifically in ER+ breast cancer[137][140], and may be associated with progression of breast cancer from in situ-to-invasive transition[141].

FGFR1 amplifications have been reported in various types of cancer, including lung cancer[142], breast cancer[137], oral squamous cell carcinoma (OSCC)[143], prostate cancer[144], and esophageal cell carcinoma[145]. Besides, activating mutations (C381R and N330I) have been identified in giant cell lesions of the jaw[146].

Therapeutic and prognostic relevance

Non-selective TKI-targeting inhibitors such as pazopanib, regorafenib, and ponatinib are multi-kinase inhibitors with inhibitory activities towards FGFR1[147][148].FGFR1 mutations, amplifications, and fusions, have been determined as an inclusion criteria for a trial examining pemigatinib efficacies in advanced malignancies including solid tumor, endometrial carcinoma, gastric carcinoma, multiple myeloma, myeloproliferative neoplasm, squamous cell lung carcinoma, and urothelial carcinoma (FIGHT-101; NCT02393248).

To date, Erdafitinib (BALVERSATM), is the first and only pan-FGFR kinase inhibitor approved by U.S. FDA, for the treatment of patients with locally advanced or metastatic bladder cancer with FGFR3 mutations or FGFR2/FGFR3 fusions. Addition of the erdafitinib to palbociclib/fulvestrant induced complete responses of FGFR1-amplified/ER+ patient-derived-xenografts[149].

In a phase II clinical trial (TAPUR; NCT02693535), heavily pre-treated patients with metastatic breast cancer harboring FGFR1 amplification and/or mutation were treated with sunitinib, resulting in two partial responses (ORR=7%) and five stable diseases at 16+ weeks, with a disease control rate of 29% (Cancer Res (2021) 81 (13_Supplement): CT173.).

A case report of a patient with HR+, HER2- breast cancer harboring FGFR1 amplification responded well to pazopanib[150]. Another clinical study demonstrated that three patients with metastatic colorectal cancer achieved partial responses to regorafenib treatment, and all of them harbored FGFR1 amplification[151].

FGFR1 amplification has been selected as an inclusion criteria for the trial examining erdafitinib, ponatinib, regorafenib, sunitinib, and infigratinib efficacies in multiple tumor types (NCT03390504, NCT03473743, NCT03238196, NCT02272998, NCT02795156, NCT02693535, NCT04233567, NCT02150967).

Several small molecule FGFR inhibitors such as AZD-4547 and NVP-BGJ398 (Infigratinib) are under clinical evaluation, although mainly in the early stages of trials[152]. Infigratinib has shown antitumor activity and manageable safety profile in patients with a variety of solid tumors, including FGFR1-amplified squamous cell lung cancer (sqNSCLC) and FGFR3-mutant bladder/urothelial cancers[153]. Meanwhile, Dovitinib, a potent FGFR inhibitor, in combination with fulvestrant showed promising clinical activity in the FGF pathway-amplified postmenopausal patients with HR+, HER2- advanced breast cancer[154].

In ER-positive breast cancer, FGFR1 amplification has been implicated as an acquired mechanism of resistance to endocrine therapies[155], such as letrozole, 4-hydroxytamoxifen, and anastrozole-containing regimen[156][137][157]. Besides, FGFR1/2 amplification or activating mutations were detected in ctDNA from post-progression ER-positive breast cancer patients after the fulvestrant plus palbociclib treatment. According to the subgroup analysis from MONALEESA-2 clinical trial, ER-positive breast cancer patients with FGFR1 amplification exhibited a shorter progression-free survival when treated with letrozole plus ribociclib[149].

Meanwhile, in non-small cell lung carcinoma (NSCLC), FGFR1 is considered as an alternative acquired mechanism of resistance to EGFR tyrosine kinase inhibitors[158]. For example, upregulated FGFR1-FGF2 autocrine loop was identified in a gefitinib-resistant cell model[159], and focal FGFR1 amplification was observed in an NSCLC patient who developed resistance to osimertinib treatment[160].

The BOLERO-2 clinical trial (everolimus plus exemestane) suggested that FGFR1 amplification and CCND1 amplification may be correlated with lessened progression-free survival (PFS) with the mTOR inhibitor everolimus[161][162].

In preclinical study, thyroid cancer cell with FGFR1 amplification is sensitive to lenvatinib treatment[163][164]. Ponatinib, a multi-targeted tyrosine kinase inhibitor, demonstrated anti-proliferative activity in lung cancer, breast cancer, and Ewing's sarcoma cells overexpressing FGFR1[165][147][166].

KDM5A Amplification

Biological Impact

KDM5A (lysine demethylase 5A) gene encodes a histone demethylase for histone 3 lysine 4 (H3K4)[167]which regulates cell cycle progression and cellular differentiation by chromatin remodeling and transcriptional silencing[168][169][170][171]. KDM5A gene amplification has been reported in breast cancer, glioblastoma, and head and neck cancer[172][173][174]which is associated with angiogenesis, tumor progression, and treatment resistance[175][176][177]. Rearrangements of KDM5A with NUP98 has been reported in acute leukemia patients[178].

Therapeutic and prognostic relevance

Several in vitro studies have reported that amplification of KDM5A was correlated with drug resistance such as temozolomide in glioblastoma[173], gefitinib in NSCLC[177], and erlotinib in breast cancer[172].

RAD51 Heterozygous deletion

Biological Impact

The RAD51 gene encodes a recombinase that is crucial for homologous recombination (HR)-mediated repair of double-strand DNA breaks (DSBs) by forming complexes with known tumor suppressors including BRCA1, BRCA2, and PALB2[179][180][181]. RAD51 has been characterized as a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[182]. Overexpression of RAD51 has been observed in many cancer cells, including pancreatic cancer and breast cancer and its hyperexpression is implicated in drug resistance[183][184][185][186][187][188][189]. Germline mutations in RAD51 are associated with increased susceptibility to breast cancer[190][191][192][193].

Therapeutic and prognostic relevance

RAD51 loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer[194]; rucaparib efficacy in solid tumor (NCT04171700); talazoparib efficacy in lung cancer (NCT03377556); niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate cancer) (NCT03207347).

Preclinical studies showed that decreased RAD51 expression could sensitize cells to olaparib-induced tumor cell cytotoxicity[195][196].

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US FDA-APPROVED DRUG(S)

Erdafitinib (BALVERSA)

Erdafitinib is a kinase inhibitor that binds to and inhibits enzymatic activity of FGFR1, FGFR2, FGFR3 and FGFR4 based on in vitro data. Erdafitinib also binds to RET, CSF1R, PDGFRA, PDGFRB, FLT4, KIT, and VEGFR2. Erdafitinib is developed and marketed by Janssen under the trade name BALVERSA.

- FDA Approval Summary of Erdafitinib (BALVERSA)

Study BLC2001 NCT02365597	**Bladder urothelial carcinoma** (Approved on 2019/04/12)
	FGFR2/3 fusion or FGFR3 mutation
	Erdafitinib [ORR(%): 32.2]

Infigratinib (TRUSELTIQ)

Infigratinib a kinase inhibitor. Infigratinib is developed and marketed by QED Therapeutics, Inc. under the trade name TRUSELTIQ.

- FDA Approval Summary of Infigratinib (TRUSELTIQ)

CBGJ398X2204 NCT02150967	**Cholangiocarcinoma** (Approved on 2021/05/28)
	FGFR2 fusion
	Infigratinib [ORR(%): 23.0, DOR(M): 5]

Lenvatinib (LENVIMA)

Lenvatinib is a multiple kinase inhibitor against the VEGFR1, VEGFR2 and VEGFR3. Lenvatinib is marketed by Eisai Inc. under the trade name LENVIMA.

- FDA Approval Summary of Lenvatinib (LENVIMA)

KEYNOTE-775 (Study 309) NCT03517449	**Endometrial carcinoma** (Approved on 2021/07/22)
	MSS/pMMR
	Pembrolizumab + lenvatinib vs. Investigator's choice of doxorubicin or paclitaxel [PFS(M): 6.6 vs. 3.8, OS(M): 17.4 vs. 12]
KEYNOTE-146 NCT02501096	**Endometrial carcinoma** (Approved on 2019/09/17)
	MSS/pMMR
	Pembrolizumab + lenvatinib [ORR(%): 38.3, DOR(M): NR]
REFLECT[197] NCT01761266	**Hepatocellular carcinoma** (Approved on 2018/08/16)
	-
	Lenvatinib vs. Sorafenib [OS(M): 13.6 vs. 12.3]
SELECT[198] NCT01136733	**Renal cell carcinoma** (Approved on 2016/05/13)
	-
	Lenvatinib+ everolimus vs. Everolimus [PFS(M): 14.6 vs. 5.5]
SELECT[199] NCT01321554	**Thyroid cancer** (Approved on 2015/02/13)
	-
	Lenvatinib vs. Placebo [PFS(M): 18.3 vs. 3.6]

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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[200] 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[201] 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[202] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[203] 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[204] 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[205] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[206] 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[207] 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[208] NCT00753688	**Sarcoma** (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]
VEG105192[209] NCT00334282	**Renal cell carcinoma** (Approved on 2009/10/19)
	-
	Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]

Ponatinib (ICLUSIG)

Ponatinib is an oral, small molecule, multi-kinase inhibitor designed to inhibit the activity of the tyrosine kinase ABL, including the T315I mutated ABL as well. Ponatinib is developed and marketed by ARIAD under the trade name ICLUSIG.

- FDA Approval Summary of Ponatinib (ICLUSIG)

PACE[210] NCT01207440	**Chronic phase chronic myeloid leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MCyR(%): 55]
PACE[210] NCT01207440	**Accelerated phase chronic myeloid leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MaHR(%): 57]
PACE[210] NCT01207440	**Blast phase chronic myeloid leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MaHR(%): 31]
PACE[210] NCT01207440	**Philadelphia-positive acute lymphoblastic leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MaHR(%): 41]

Regorafenib (STIVARGA)

Regorafenib is a multi-kinase inhibitor which targets angiogenic, stromal and oncogenic receptor tyrosine kinases (RTKs). Regorafenib is developed and marketed by Bayer HealthCare Pharmaceuticals under the trade name STIVARGA.

- FDA Approval Summary of Regorafenib (STIVARGA)

RESORCE[211] NCT01774344	**Hepatocellular carcinoma, Hepatocellular carcinoma** (Approved on 2017/04/27)
	-
	Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]

GRID[212] NCT01271712	**Gastrointestinal stromal tumor** (Approved on 2013/02/25)
	-
	Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]
CORRECT[213] NCT01103323	**Colorectal cancer** (Approved on 2012/09/27)
	-
	Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

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[214] 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[215] NCT00984282	**Differentiated thyroid carcinoma** (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
SHARP[216] NCT00105443	**Hepatocellular carcinoma** (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]
TARGET[217] 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)

[218][219][220] NCT00428597	**Pancreatic cancer** (Approved on 2011/05/20)
	-
	Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]
[221][222] NCT00083889	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib vs. Ifn-α [PFS(W): 47.3 vs. 22]
[223][224][222] NCT00077974	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 34.0]
[224][222] NCT00054886	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 36.5]
[225] 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[226] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

Trametinib (MEKINIST)

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

- FDA Approval Summary of Trametinib (MEKINIST)

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

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BRF117019[227] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[228] NCT01336634	**Non-small cell lung cancer** (Approved on 2017/06/22)
	BRAF V600E
	Trametinib + dabrafenib vs. Dabrafenib [ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9]
COMBI-d[12] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[13] 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

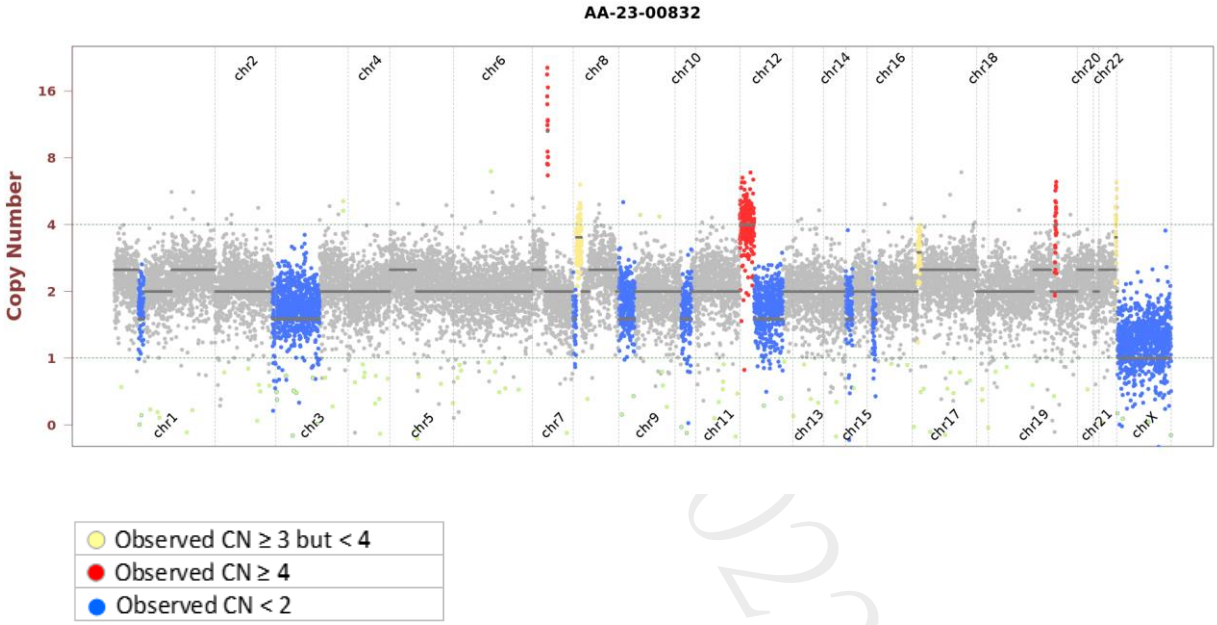
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
KRAS	G12V	2	c.35G>T	NM_004985	COSM520	52.5%	3624
PIK3R1	S83*	2	c.248C>A	NM_181523	-	11.4%	1231
SMAD4	V407fs	10	c.1214_1217dup	NM_005359	-	25.9%	781
TP53	Splice donor	-	c.919+2T>A	NM_000546	COSM45779	30.7%	654

- 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
ADAMTS9	P1665R	32	c.4994C>G	NM_182920	-	64.7%	720
ADAMTSL1	R1322G	22	c.3964A>G	NM_001040272	-	66.4%	241
ADGRA2	T777M	15	c.2330C>T	NM_032777	-	28.2%	582
BRD4	V228I	5	c.682G>A	NM_058243	-	46.4%	470
CSF1R	T75I	3	c.224C>T	NM_005211	-	50.7%	668
DNMT3A	F732del	19	c.2193_2195del	NM_175629	COSM99742	5.0%	462
FANCD2	K156R	7	c.467A>G	NM_001018115	-	8.1%	259
FGFR3	Splice region	-	c.1959+7C>T	NM_000142	-	58.6%	152
FGFR3	Splice region	8	c.933G>A	NM_000142	-	54.0%	150
MUC6	R1059H	24	c.3176G>A	NM_005961	-	53.7%	175
SOCS1	V183M	2	c.547G>A	NM_003745	-	57.4%	312
SPOP	P10L	3	c.29C>T	NM_001007229	-	48.9%	882
USH2A	Splice region	-	c.6958-5C>T	NM_206933	-	61.1%	321
USH2A	R2175H	34	c.6524G>A	NM_206933	-	34.8%	333
USH2A	V2228E	35	c.6683T>A	NM_206933	-	62.6%	1302

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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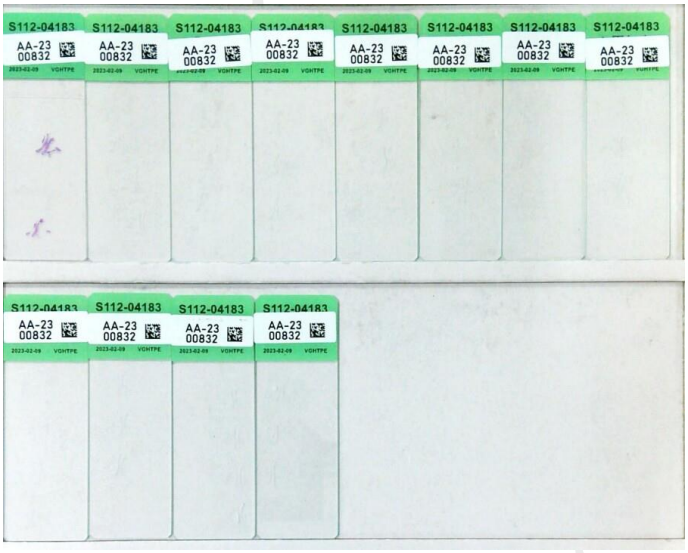
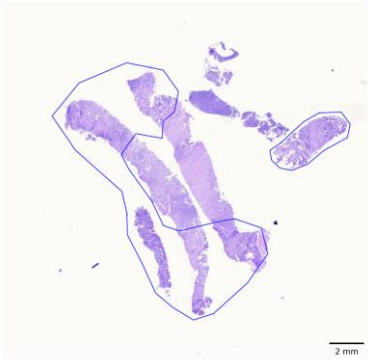
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: Feb 04, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11204183A
- Collection site: Liver
- Examined by: Dr. Yun-An Chen
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 10%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 30%
    3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 40%
    4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 20%
    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: 713x
- Target Base Coverage at 100x: 93%

RNA test

- Average unique RNA Start Sites per control GSP2: 144

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LIMITATIONS

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

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RNA test

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

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

DATABASE USED

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

Variant Analysis:
醫檢師張筑芃 博士
Chu-Yuan Chang Ph.D.
檢字第 020115 號

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

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GENE LIST

SNV & CNV

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

*Analysis of copy number alterations NOT available.

FUSION

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

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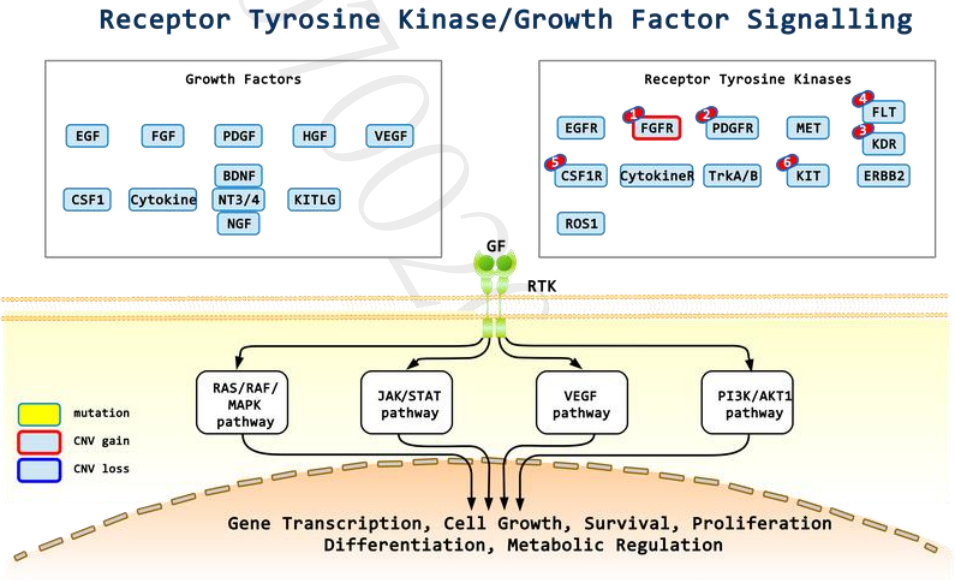
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
RAD51	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Ponatinib, Lenvatinib, Erdafitinib, Infigratinib, Pazopanib; 2: Ponatinib, Pazopanib, Erdafitinib, Sunitinib, Regorafenib; 3: Ponatinib, Lenvatinib, Pazopanib, Erdafitinib, Sunitinib; 4: Ponatinib, Sunitinib, Lenvatinib, Pazopanib, Erdafitinib; 5: Sunitinib; 6: Ponatinib, Regorafenib, Lenvatinib, Pazopanib, Erdafitinib, Sunitinib, Sorafenib

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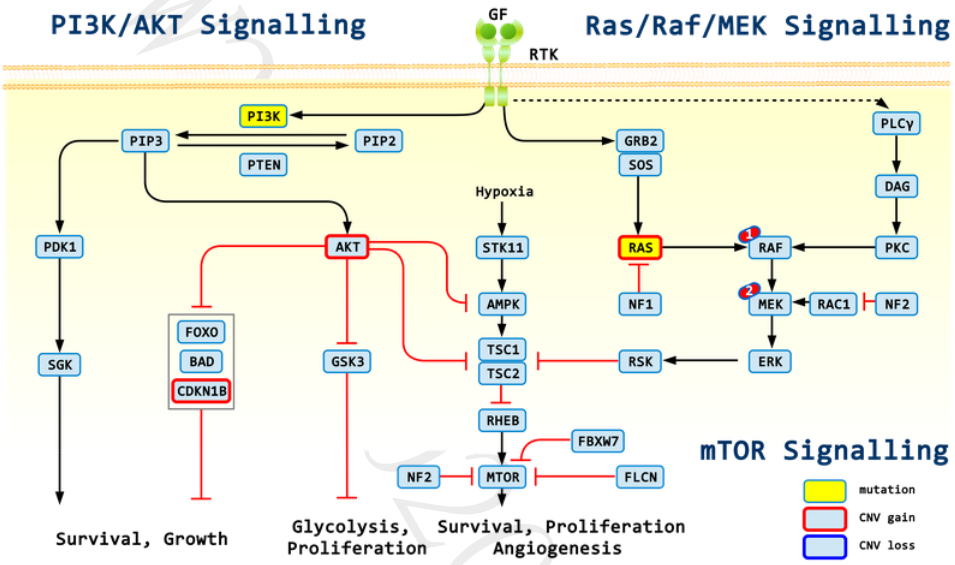
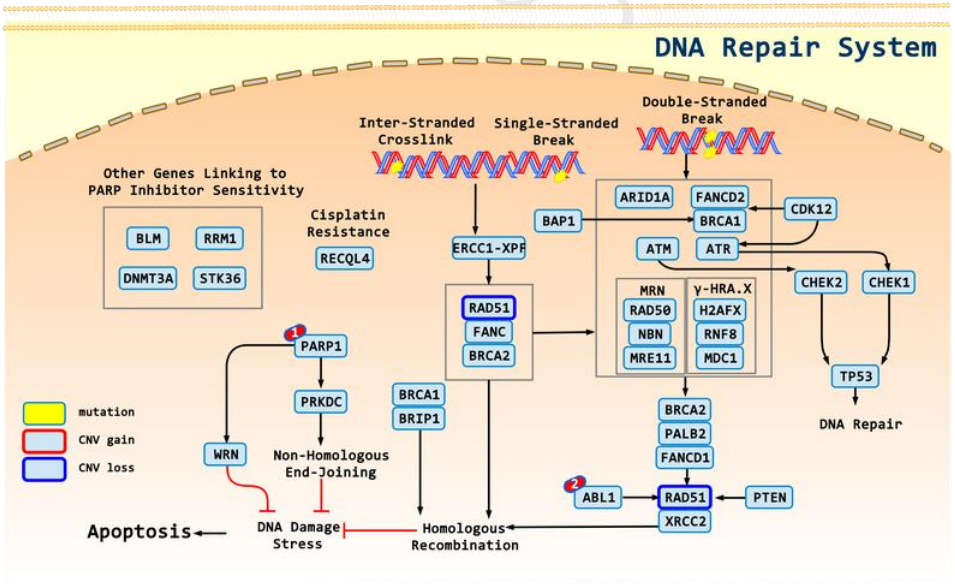


1: Sorafenib; 2: Trametinib



1: Olaparib, Niraparib, Rucaparib, Talazoparib; 2: Ponatinib

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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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