

ACT Onco[®] + Report

| PATIENT | | |
|-----------------------------|-----------------------------|----------------------|
| Identifier: 林惠芳 | | Patient ID: 10371069 |
| Date of Birth: May 27, 1957 | | Gender: Female |
| Diagnosis: Sarcoma | | |
| ORDERING PHYSICIAN | | |
| Name: 顏厥全醫師 | | 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: S11149598A | Collection site: Lymph node | Type: FFPE tissue |
| Date received: Dec 02, 2022 | Lab ID: AA-22-07359 | 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 | |
| Not detected | | | |

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

| Genomic Alterations/Biomarkers | Possibly Sensitive | | Possibly Resistant |
|--------------------------------|---|--|-------------------------|
| | | | |
| FGFR1 Amplification | Erdafitinib, Infigratinib, Lenvatinib, Pazopanib, Ponatinib, Regorafenib, Sunitinib | | Palbociclib, Ribociclib |

Note:

- The above summary tables present genomic variants and biomarkers based on the three-tiered approach proposed by US FDA for reporting tumor profiling NGS testing. "Variants/biomarkers with evidence of clinical significance" refers to mutations that are widely recognized as standard-of-care biomarkers (FDA level 2/AMP tier 1). "Variants/biomarkers with potential clinical significance" refers to mutations that are not included in the standard of care but are informational for clinicians, which are commonly biomarkers used as inclusion 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 |
|--------------|-------------------|------------------|
| Not detected | | |

- Copy Number Alterations

| Chromosome | Gene | Variation | Copy Number |
|------------|---------------|-----------------------|-------------|
| Chr17 | TP53 | Homozygous deletion | 0 |
| Chr11 | ATM, CHEK1 | Heterozygous deletion | 1 |
| Chr13 | BRCA2 | Heterozygous deletion | 1 |
| Chr16 | PALB2, TSC2 | Heterozygous deletion | 1 |
| Chr17 | NF1 | Heterozygous deletion | 1 |
| Chr3 | ATR | Heterozygous deletion | 1 |
| Chr4 | FBXW7 | Heterozygous deletion | 1 |
| Chr9 | CDKN2A, PTCH1 | Heterozygous deletion | 1 |
| Chr8 | FGFR1 | Amplification | 8 |

- 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) | 1.3 muts/Mb |
| Microsatellite Instability (MSI) | Microsatellite stable (MSS) |

Note:

- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 64% 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 3B | | |
| FGFR1 Amplification | Erdafitinib, Infigratinib, Ponatinib, Regorafenib, Sunitinib | sensitive |
| Level 4 | | |
| FGFR1 Amplification | Lenvatinib, Pazopanib | sensitive |
| FGFR1 Amplification | Palbociclib, Ribociclib | resistant |

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

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

- Other Biomarkers with Potential Clinical Effects for ICIs

| Genomic Alterations | Potential Clinical Effects |
|---------------------|----------------------------|
| Not detected | |

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

CHEMOTHERAPIES

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

HORMONAL THERAPIES

| Genomic Alterations | Therapies | Effect | Level of Evidence | Cancer Type |
|------------------------|-----------|-----------|-------------------|---|
| 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

ATM Heterozygous deletion

Biological Impact

The ataxia-telangiectasia mutated protein kinase (ATM) gene encodes a PI3K-related serine/threonine protein kinase involved in genomic integrity maintenance and plays central roles in DNA double-strand break (DSB) repair, which can be induced by ionizing radiation, chemotherapy drugs, or oxidative stress^[1]. ATM is a well-characterized tumor suppressor gene, hereditary mutations and haploinsufficiency of ATM result in markedly increased susceptibility to a variety of cancer types^{[2][3][4][5][6]}. Results from a case-cohort study of colorectal cancer and cancer-free control individuals suggested that germline pathogenic mutations in ATM and PALB2 should be added to established CRC risk genes as part of standard tumor genetic testing panels^[7]. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies^{[8][9][10][11]} and a broad range of tumors such as prostate cancer^[12], head and neck squamous cell carcinoma (HNSCC)^[13], pancreatic cancer^[14], lung adenocarcinoma^[15], breast cancer^[16], and ovarian cancer^[3].

Therapeutic and prognostic relevance

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate (NCT02987543)^[17].

In a phase II trial (TOPARP-A; NCT01682772), 3 out of 4 metastatic prostate cancer patients harboring only ATM inactivating mutations responded to olaparib treatment^[18]. Also, the phase II TOPARP-B trial (NCT01682772) demonstrated that olaparib treatment resulted in a RECIST 1.1 or PSA50 response rate of 10.5% (2/12) and a composite overall response rate of 36.8% (7/19) in prostate cancer patients harboring deleterious ATM mutations^[19]. In another randomized, double-blind phase II trial in Asian patients with metastatic gastric cancer has shown that addition of olaparib to paclitaxel significantly increased the OS in both the overall population and patients with low or undetectable ATM protein expression (NCT01063517)^[20]. However, in the subsequent phase III trial (GOLD; NCT01924533), addition of olaparib to paclitaxel did not significantly improve OS in the overall or the ATM-negative population of Asian gastric cancer patients^[21]. Besides, in a phase II trial (TBCRC 048; NCT03344965), 7 metastatic breast cancer patients harboring only ATM mutations were not responded to olaparib treatment (SD: n=2, PD: n=5)^[22]. In a phase II trial (TRITON2; NCT02952534), 49 mCRPC patients harboring ATM alteration had limited response to rucaparib treatment. The radiographic response rate was 10.5% (n=2/19 evaluable patients), the prostate-specific antigen response rate was 4.1% (n=2/49), and the 6-month clinical benefit rate was 28.6% (n=12/42)^[23].

In preclinical studies, cells with ATM alternation were sensitive to olaparib, niraparib, and talazoparib treatment in vitro and in vivo^{[24][25][26][27]}.

In addition, ATM has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in breast cancer (NCT04053322) and advanced solid tumors (NCT03297606), rucaparib efficacy in ovarian cancer (NCT01968213)^[28] and prostate cancer (NCT02952534, NCT03533946)^[23], niraparib efficacy in pancreatic cancer (NCT03553004, NCT03601923), prostate cancer (NCT02854436), melanoma (NCT03925350), metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma (NCT03840967), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in advanced or metastatic cancer (NCT02286687), HER2-negative solid tumors (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

Also, a prospective study in muscle-invasive bladder cancer patients suggested that genomic alternations in the DNA repair genes ATMs, RB1 and FANCC could be recognized as biomarkers predictive of response to cisplatin-based neoadjuvant chemotherapy^[29]. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer^[30].

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A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer^[31].

ATR Heterozygous deletion

Biological Impact

Ataxia Telangiectasia and Rad3-related protein (ATR) gene encodes a serine/threonine kinase that is involved in the DNA damage response. ATR plays as a central coordinator of the DNA damage response (DDR) by responding to single-stranded regions of the DNA^{[32][33]} and the maintenance of genome stability^[34]. ATR has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^{[35][36]}. Germline mutation of ATR is associated with cancer predisposition and Seckel syndrome, a condition associated with CNS disorders^{[37][38]}. Somatic mutations of ATR are associated with microsatellite instability and are found in colorectal cancer^[39], urothelial cancer^[40], gastric cancer^[41], endometrial cancer^[42] and myelomas^[43].

Therapeutic and prognostic relevance

In a clinical study, a metastatic castration-resistant prostate cancer patient harboring deleterious mutation in the ATR gene (K2106fs) had a PSA remission of 62% and PSA-PFS of 13 months by olaparib treatment^[44].

ATR has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in ovarian cancer^[45] and advanced solid tumors (NCT03297606; CAPTUR trial), rucaparib efficacy in ovarian cancer^[28], niraparib efficacy in pancreatic cancer (NCT03553004), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative solid tumors (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair^[46]. BRCA2 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^[47]. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia^[48]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers^[49].

Therapeutic and prognostic relevance

The U.S. FDA has approved olaparib in advanced ovarian cancer under several settings including (1) first-line maintenance treatment for patients with deleterious or suspected deleterious germline or somatic BRCA mutation who are in complete or partial response to first-line platinum-based chemotherapy^[50]; (2) in combination with bevacizumab as first-line maintenance treatment for patients who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status^[51]; (3) maintenance treatment for patients with recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy^{[52][53]}. In addition, olaparib has also been approved in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative breast cancer who have been treated with chemotherapy in either neoadjuvant, adjuvant, or metastatic setting^[54] and germline BRCA-mutated metastatic pancreatic cancer^[55]. Of note, in May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate (NCT02987543)^[17].

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Rucaparib has been approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy^[28]. NCCN guidelines recommend rucaparib as recurrence therapy for patients with BRCA-mutated ovarian cancer, who have been treated with two or more lines of chemotherapies^[56]. In May 2020, the U.S. FDA also approved rucaparib to treat adult patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy (TRITON2, NCT02952534). Moreover, NCCN guidelines recommend rucaparib as maintenance therapy following prior platinum-based therapy for patients with metastatic pancreatic cancer harboring germline or somatic BRCA mutation.

The U.S. FDA has approved niraparib for the maintenance treatment of patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to first-line platinum-based chemotherapy and patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy^{[57][58]}. Besides, NCCN guidelines recommend niraparib as maintenance therapy for ovarian cancer patients with BRCA mutations. The U.S. FDA also approved talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer^[59].

CDKN2A Heterozygous 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^{[60][61][62]}. 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^[63]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation^{[64][65]}.

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors^{[66][67]}. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments^{[68][69][70]}. 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^{[71][72][73]}. 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)^{[74][75]}.

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^{[67][76][77]}.

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^[69]. 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^[78].

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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^[79].

CHEK1 Heterozygous deletion

Biological Impact

The checkpoint kinase 1 (CHEK1 or CHK1) gene encodes a protein kinase involved in transducing DNA damage signals and is required for both the intra-S phase and G2/M checkpoints^[80]. CHEK1 heterozygosity has been shown to cause haploinsufficient phenotypes that can contribute to tumorigenesis through inappropriate S phase entry, accumulation of DNA damage during replication, and failure to restrain mitotic entry^{[81][82]}. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors^[83], and CHEK1 mutations are extremely rare^[80]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer^[84], breast cancer^[85], colorectal cancer^[86], non-small cell lung (NSCLC) cancer^[87], and nasopharyngeal cancer^[88].

Therapeutic and prognostic relevance

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate (NCT02987543)^[17].

In addition, CHEK1 has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in advanced solid tumors (NCT03297606; CAPTUR trial), rucaparib efficacy in ovarian cancer (NCT01968213)^[28], prostate cancer (NCT03533946), niraparib efficacy in pancreatic cancer (NCT03553004), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in lung cancer (NCT03377556), respectively.

Selective inhibitors for CHEK1 and CHEK2 alone or in combination with other agents are currently being investigated in clinical trials^[89].

FBXW7 Heterozygous deletion

Biological Impact

The F-box/WD repeat-containing protein 7 (FBXW7) gene encodes a protein that belongs to the SCF (SKP1-CUL1-F-box protein) E3 ligase complex. FBXW7 is recognized as a tumor suppressor which is involved in the negative regulation of oncogenes such as c-Myc^{[90][91]}, c-Jun^[92], cyclin E^[93], Notch family members^{[94][95]}, Aurora-A^[96], mTOR^[97], KLF5^[98], and MCL-1^[99]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation^[100]. FBXW7 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^{[98][99][101]}.

Therapeutic and prognostic relevance

Clinical efficacy of mTOR inhibitors was seen in patients harboring aberrations in the FBXW7 gene (one patient with refractory fibrolamellar hepatocellular carcinoma, and one patient with lung adenocarcinoma)^{[102][103]}. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor^[97].

Preclinical studies suggested that mutations or loss of FBXW7 were associated with regorafenib and oxaliplatin resistance in CRC cell lines and gefitinib resistance in lung cancer cells^{[104][105][106][107]}.

Retrospective studies have indicated that a relatively low expression level of FBXW7 is an independent prognostic marker of poor survival for patients with hepatocellular carcinoma, lung adenocarcinoma and squamous cell carcinoma^{[108][106]}.

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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^{[109][110]}. Several studies have demonstrated that FGFR1 amplification correlates with FGFR1 overexpression^{[111][112][113][114][115][116]}. 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^{[117][118][119]}. Amplification of FGFR1 has been associated with early relapse, and poor survival, specifically in ER+ breast cancer^{[117][120]}, and may be associated with progression of breast cancer from in situ-to-invasive transition^[121].

FGFR1 amplifications have been reported in various types of cancer, including lung cancer^[122], breast cancer^[117], oral squamous cell carcinoma (OSCC)^[123], prostate cancer^[124], and esophageal cell carcinoma^[125]. Besides, activating mutations (C381R and N330I) have been identified in giant cell lesions of the jaw^[126].

Therapeutic and prognostic relevance

Non-selective TKI-targeting inhibitors such as pazopanib, regorafenib, and ponatinib are multi-kinase inhibitors with inhibitory activities towards FGFR1^{[127][128]}. 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^[129].

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^[130]. Another clinical study demonstrated that three patients with metastatic colorectal cancer achieved partial responses to regorafenib treatment, and all of them harbored FGFR1 amplification^[131].

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^[132]. 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^[133]. 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^[134].

In ER-positive breast cancer, FGFR1 amplification has been implicated as an acquired mechanism of resistance to endocrine therapies^[135], such as letrozole, 4-hydroxytamoxifen, and anastrozole-containing regimen^{[136][117][137]}. 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

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trial, ER-positive breast cancer patients with FGFR1 amplification exhibited a shorter progression-free survival when treated with letrozole plus ribociclib^[129].

Meanwhile, in non-small cell lung carcinoma (NSCLC), FGFR1 is considered as an alternative acquired mechanism of resistance to EGFR tyrosine kinase inhibitors^[138]. For example, upregulated FGFR1-FGF2 autocrine loop was identified in a gefitinib-resistant cell model^[139], and focal FGFR1 amplification was observed in an NSCLC patient who developed resistance to osimertinib treatment^[140].

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^{[141][142]}.

In preclinical study, thyroid cancer cell with FGFR1 amplification is sensitive to lenvatinib treatment^{[143][144]}. Ponatinib, a multi-targeted tyrosine kinase inhibitor, demonstrated anti-proliferative activity in lung cancer, breast cancer, and Ewing's sarcoma cells overexpressing FGFR1^{[145][127][146]}.

NF1 Heterozygous deletion

Biological Impact

The neurofibromin 1 (NF1) gene encodes a GTPase activating protein (GAP) which is an important negative regulator of the Ras cellular proliferation pathways^{[147][148][149][150]}. Besides, NF1 also physically interacts with the N-terminal domain of focal adhesion kinase (FAK) and involves in the regulation of cell adhesion, growth, and other pathways^{[151][152]}. NF1 is considered a classical haploinsufficient tumor suppressor gene with loss of one allele through inherited or acquired mutation may lead to reduced protein expression and is insufficient to execute normal cellular functions contributing to tumor development^{[153][154][155][156][157]}. NF1 syndrome is a germline condition resulting in a predisposition to several types of cancer such as neurofibromas, melanoma, lung cancer, ovarian cancer, breast cancer, colorectal cancer, hematological malignancies^{[158][159][160]}. Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types^[161], including myelodysplastic syndromes, melanomas, colon cancer^[162], glioblastomas^[163], lung cancer^[164], ovarian cancer, and breast cancer^[158].

Therapeutic and prognostic relevance

In April 2020, the U.S. FDA has approved selumetinib for pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN). A phase II trial (NCT02664935, NLMT) demonstrated that selumetinib in combination with docetaxel resulted in a confirmed ORR of 28.5% (4/14), durable clinical benefit (DCB) rate of 50% (7/14), and mPFS of 5.3 months in lung adenocarcinoma patients harboring NF1 loss^[165]. NF1 loss has been determined as an inclusion criterion for the trials evaluating selumetinib efficacies in lung cancer (NCT02664935) and NF1-associated tumors (NCT03326388).

NF1 depletion has been associated with drug resistance to RAF and EGFR inhibitors, tamoxifen, and retinoic acid^{[161][166]}. For example, loss of NF1 was identified in patients with lung adenocarcinomas or colorectal cancer who presented resistance to anti-EGFR treatment, including erlotinib, gefitinib, afatinib, and cetuximab, respectively^{[167][168][169]}. Loss of NF1 in patients with BRAF-mutated melanomas was also suggested conferring resistance to BRAF inhibitors^{[170][171][172][173]}.

Notably, preclinical studies further revealed that the addition of a MEK inhibitor could restore the sensitivity to erlotinib^[167]. Also, in a liquid biopsy-based ctDNA profiling study of HER2-positive metastatic gastric cancer, NF1 loss (either induced by mutation or deletion) was suggested as a novel mechanism contributes to trastuzumab resistance. The cell-based study also showed that the trastuzumab and lapatinib resistance could be overcome with a combination of HER2 and MEK/ERK inhibitors^[174]. A case study had reported that MEK inhibitor, trametinib, was effective in a treatment-refractory neurofibromatosis type I-associated glioblastoma^[175]. Various preclinical data had also supported

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the activity of MEK and mTOR inhibitors in NF1-deficient tumors^{[176][177][178][179][180][181]}. In an NGS-based study, patients harboring mutations in the mTOR pathway, including mTOR, TSC1, TSC2, NF1, PIK3CA, and PIK3CG responded to everolimus^[182].

PALB2 Heterozygous deletion

Biological Impact

The partner and localizer of BRCA2 (PALB2) gene encodes a protein that plays a critical role in homologous recombination repair (HRR) through its ability to interact with BRCA2 in nuclear foci, promoting its localization and stability in key nuclear structures^[183]. The Fanconi anemia complementation group (FANCA) which includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCI (also called BRIP1), FANCL, FANCM and FANCN (also called PALB2) are involved in the repair of DNA double-strand breaks (DSBs) by homologous recombination (HR)^{[184][185][186]}. PALB2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function^[187]. Biallelic germline loss-of-function mutations in PALB2 cause Fanconi anemia, whereas monoallelic loss-of-function mutations are associated with an increased risk of breast cancer and pancreatic cancer^[188]. Fanconi Anemia is an autosomal recessive disease characterized by hematological abnormalities, bone marrow failure, limb deformities, skin hyperpigmentation, and susceptibility to hematologic and solid malignancies, such as acute myeloid leukemia and head and neck carcinoma^{[189][190]}.

Therapeutic and prognostic relevance

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate^[17].

NCCN guideline for pancreatic cancer recommended that rucaparib as maintenance therapy following prior platinum-based therapy for patients with pancreatic adenocarcinoma harboring PALB2 mutations^[191].

In a Phase I trial, a pancreatic cancer patient harboring a PALB2 mutation had a partial response to talazoparib treatment^[192]. In a preclinical study, talazoparib demonstrated anti-tumor activity on a Wilms tumor cell line with a PALB2 truncating mutation in mice xenograft model^[193]. PALB2 loss of function mutation has been determined as an inclusion criterion for the trial evaluating rucaparib efficacy in ovarian cancer^[28] or prostate cancer^[23]; talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556); niraparib efficacy in pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), or any malignancy (except prostate) cancer (NCT03207347).

A case report demonstrated an exceptional response to mitomycin C and cisplatin treatment in a gemcitabine-resistant pancreatic cancer patient with biallelic inactivation of PALB2^[194].

PTCH1 Heterozygous deletion

Biological Impact

The PTCH1 (protein patched homolog 1) gene encodes a multi-pass transmembrane receptor for sonic hedgehog (shh), a tumor suppressor that acts to repress shh signaling in the absence of ligand^[195]. Inactivation of PTCH1 results in hedgehog ligand-independent activation of SMO, causing a downstream activation of the pathway and lead to the neoplastic growth^{[196][197]}. Recurrent PTCH1 mutations have been reported in sporadic basal cell carcinoma (BCCs) and medulloblastoma^{[198][199][200][201]}. Germline PTCH1 mutations are associated with the nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome), predisposing patients to basal cell carcinoma and medulloblastoma^[199]. PTCH1 is a haploinsufficient tumor suppressor gene with one copy loss may be sufficient to promote tumor development in

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mice^{[196][202]}.

Therapeutic and prognostic relevance

Vismodegib and sonidegib are small molecule inhibitors of SMO approved by the U.S. FDA for the treatment of patients with basal cell carcinoma^{[203][204][205][206]}. A heavily pretreated patient with metastatic medulloblastoma harboring loss-of-heterozygosity and somatic mutation of PTCH1 showed rapid regression of the tumor after treated with vismodegib^[207]. Furthermore, a phase II study demonstrated that vismodegib treatment results in extended progression-free survival (PFS) in patients with loss-of-heterozygosity, SHH-driven medulloblastoma^[208]. In the phase II MyPathway trial, three advanced solid tumors patients harboring PTCH1 loss-of-function mutations had partial responses to vismodegib treatment^[209]. In a clinical study, two patients with Sonic Hedgehog (SHH) activated medulloblastoma harboring PTCH1 loss-of-function mutations demonstrated partial responses to sonidegib treatment^[210].

TP53 Homozygous deletion

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[211]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[212].

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)^[213].

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^[214]. 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^[215].

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^{[216][217][218]}. 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)^[219]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[220][221]}. 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^[222].

TSC2 Heterozygous deletion

Biological Impact

The tuberous sclerosis complex 2 (TSC2) gene encodes a protein called tuberin, which interact with a protein called hamartin (encoded by the TSC1 gene). This hamartin-tuberin tumor suppressor complex plays a critical role in growth control as a negative regulator of the mammalian target of rapamycin (mTOR) pathway^{[223][224]}. Mutations in TSC1/TSC2 tumor suppressor genes that result in inactivation of the complex are commonly found in patients with tuberous sclerosis complex^{[225][226][227]}, while the loss of heterozygosity (LOH) in TSC1/TSC2 has been identified in head and neck squamous cell carcinoma (HNSCC)^[228] and endometrial cancer^[229]. TSC2 deletion, splicing-mutant, and inactivating mutations such as A1141T, G305V, S1514X, and R1032X, has been identified in TSC2-null hepatocellular carcinoma (HCC) cell lines, patient-derived xenograft, and primary tumors. Mutations in the TSC1 and TSC2 genes cause the

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autosomal dominant genetic disorder tuberous sclerosis complex (TSC)^[230].

Therapeutic and prognostic relevance

Genomic alterations with activating effects of the mTOR signaling pathway (including deletion/inactivation of TSC1/TSC2) have been shown to confer sensitivity to everolimus across multiple cancer types, such as bladder cancer, gastric cancer, sarcoma, thyroid cancer, hepatocellular carcinoma (HCC) as well as head and neck squamous cell carcinoma (HNSCC)^{[231][182][232]}. Results from one Phase II study of advanced endometrial cancer showed that mutations in AKT1, TSC1, and TSC2 might predict sensitivity to temsirolimus^[233]. Recent studies indicated that there are mTORC1-independent signaling pathways downstream of hamartin-tuberin, which may represent new therapeutic targets^[234].

Everolimus has been approved by the U.S. FDA for Tuberous Sclerosis Complex (TSC)-associated renal angiomyolipoma and Tuberous Sclerosis Complex (TSC)-associated subependymal giant cell astrocytoma (SEGA). This approval is based on the results from EXIST-1, EXIST-2, and Study 2485 trials (NCT00789828, NCT00790400, and NCT00411619).

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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 ^[235] 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 ^[77] NCT02107703 | Breast cancer (Approved on 2017/09/28) |
| | HR+/HER2- Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3] |
| MONARCH 1 ^[236] NCT02102490 | Breast cancer (Approved on 2017/09/28) |
| | HR+/HER2- Abemaciclib [ORR(%): 19.7 vs. 17.4] |

Binimetinib (MEKTOVI)

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

- FDA Approval Summary of Binimetinib (MEKTOVI)

| | |
|--|---|
| MEKTOVI ^[237] NCT01909453 | Melanoma (Approved on 2018/06/27) |
| | BRAF V600E/K Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3] |

Cobimetinib (COTELLIC)

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

- FDA Approval Summary of Cobimetinib (COTELLIC)

| | |
|---|---|
| coBRIM ^[238] NCT01689519 | Melanoma (Approved on 2015/11/10) |
| | BRAF V600E/K Cobimetinib + vemurafenib vs. Placebo + vemurafenib [PFS(M): 12.3 vs. 7.2] |

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Erdaftinib (BALVERSA)

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

- FDA Approval Summary of Erdaftinib (BALVERSA)

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

Everolimus (AFINITOR)

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

- FDA Approval Summary of Everolimus (AFINITOR)

| | |
|--|--|
| RADIANT-4 ^[239] NCT01524783 | Lung or gastrointestinal neuroendocrine tumor (Approved on 2016/02/26) |
| | - |
| | Everolimus vs. Placebo [PFS(M): 11 vs. 3.9] |
| BOLERO-2 ^[240] NCT00863655 | Breast cancer (Approved on 2012/07/20) |
| | ER+/HER2- |
| | Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2] |
| EXIST-2 NCT00790400 | Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma (Approved on 2012/04/26) |
| | - |
| | Everolimus vs. Placebo [ORR(%): 41.8 vs. 0] |
| RADIANT-3 ^[241] NCT00510068 | Pancreatic neuroendocrine tumor (Approved on 2011/05/05) |
| | - |
| | Everolimus vs. Placebo [PFS(M): 11 vs. 4.6] |
| EXIST-1 ^[242] NCT00789828 | Subependymal giant cell astrocytoma (Approved on 2010/10/29) |
| | - |
| | Everolimus vs. Placebo [ORR(%): 35.0] |
| RECORD-1 ^[243] NCT00410124 | Renal cell carcinoma (Approved on 2009/05/30) |
| | - |
| | Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9] |

Infgratinib (TRUSELTIQ)

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

- FDA Approval Summary of Infgratinib (TRUSELTIQ)

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

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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 ^[244] NCT01761266 | Hepatocellular carcinoma (Approved on 2018/08/16) |
| | - Lenvatinib vs. Sorafenib [OS(M): 13.6 vs. 12.3] |
| SELECT ^[245] NCT01136733 | Renal cell carcinoma (Approved on 2016/05/13) |
| | - Lenvatinib+ everolimus vs. Everolimus [PFS(M): 14.6 vs. 5.5] |
| SELECT ^[246] NCT01321554 | Thyroid cancer (Approved on 2015/02/13) |
| | - Lenvatinib vs. Placebo [PFS(M): 18.3 vs. 3.6] |

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 ^[58] 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):] |

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| | |
|--|---|
| PROfound ^[17] 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 ^[51] NCT02477644 | Ovarian cancer (Approved on 2020/05/08) |
| | HRD+ Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7] |
| POLO ^[55] 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 ^[50] 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 ^[54] NCT02000622 | Breast cancer (Approved on 2018/02/06) |
| | HER2-/gBRCA mutation Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2] |
| SOLO-2/ENGOT-Ov21 ^[247] 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 ^[248] 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 ^[249] NCT01740427 | Breast cancer (Approved on 2017/03/31) |
| | ER+/HER2- Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5] |
| PALOMA-3 ^[250] 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 ^[251] NCT00753688 | Sarcoma (Approved on 2016/04/26) |
| | - Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6] |

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| | |
|---|---|
| VEG105192 ^[252] 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 ^[253] NCT01207440 | Chronic phase chronic myeloid leukemia (Approved on 2014/03/12) |
| | - |
| | Ponatinib [MCyR(%): 55] |
| PACE ^[253] NCT01207440 | Accelerated phase chronic myeloid leukemia (Approved on 2014/03/12) |
| | - |
| | Ponatinib [MaHR(%): 57] |
| PACE ^[253] NCT01207440 | Blast phase chronic myeloid leukemia (Approved on 2014/03/12) |
| | - |
| | Ponatinib [MaHR(%): 31] |
| PACE ^[253] 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 ^[254] NCT01774344 | Hepatocellular carcinoma, Hepatocellular carcinoma (Approved on 2017/04/27) |
| | - |
| | Bsc vs. Placebo [OS(M): 10.6 vs. 7.8] |
| GRID ^[255] NCT01271712 | Gastrointestinal stromal tumor (Approved on 2013/02/25) |
| | - |
| | Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9] |
| CORRECT ^[256] NCT01103323 | Colorectal cancer (Approved on 2012/09/27) |
| | - |
| | Regorafenib vs. Placebo [OS(M): 6.4 vs. 5] |

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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^[76] 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^[28] NCT01968213 | Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2018/04/06) |
| | - |
| | Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4] |

Selumetinib (KOSELUGO)

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

- FDA Approval Summary of Selumetinib (KOSELUGO)

| | |
|------------------------------|---|
| SPRINT NCT01362803 | Plexiform neurofibromas (Approved on 2020/04/10) |
| | - |
| | Selumetinib [ORR(%): 66.0] |

Sonidegib (ODOMZO)

Sonidegib is a Hedgehog signaling pathway inhibitor by blocking its key component, smoothened (smo). Sonidegib is developed and marketed by Novartis under the trade name ODOMZO.

- FDA Approval Summary of Sonidegib (ODOMZO)

| | |
|--|--|
| BOLT^[205] NCT01327053 | Basal cell carcinoma (Approved on 2015/07/24) |
| | - |
| | Sonidegib [ORR(%): 58.0] |

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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)

| | |
|--------------------------------|--|
| [257][258][259] NCT00428597 | Pancreatic cancer (Approved on 2011/05/20) |
| | - Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4] |
| [260][261] NCT00083889 | Renal cell carcinoma (Approved on 2007/02/02) |
| | - Sunitinib vs. Ifn- α [PFS(W): 47.3 vs. 22] |
| [262][263][261] NCT00077974 | Renal cell carcinoma (Approved on 2007/02/02) |
| | - Sunitinib [ORR(%): 34.0] |
| [263][261] NCT00054886 | Renal cell carcinoma (Approved on 2007/02/02) |
| | - Sunitinib [ORR(%): 36.5] |
| [264] 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 ^[59] NCT01945775 | Breast cancer (Approved on 2018/10/16) |
| | HER2-/gBRCA mutation |
| | Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6] |

Temsirolimus (TORISEL)

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

- FDA Approval Summary of Temsirolimus (TORISEL)

| | |
|----------------------|---|
| [265] NCT00065468 | Renal cell carcinoma (Approved on 2007/05/30) |
| | - Temsirolimus vs. Ifn- α [OS(M): 10.9 vs. 7.3] |

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Trametinib (MEKINIST)

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

- FDA Approval Summary of Trametinib (MEKINIST)

| | |
|--|--|
| BRF117019, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060, NCT02124772 | Cancer (Approved on 2022/06/22) |
| | BRAF V600E |
| | Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0] |
| BRF117019 ^[266] NCT02034110 | Anaplastic thyroid cancer (Approved on 2018/05/04) |
| | BRAF V600E |
| | Dabrafenib + trametinib [ORR(%): 61.0] |
| BRF113928 ^[267] 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 ^[268] NCT01584648 | Melanoma (Approved on 2014/01/10) |
| | BRAF V600E/K |
| | Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8] |
| METRIC ^[269] NCT01245062 | Melanoma (Approved on 2013/05/29) |
| | BRAF V600E/K |
| | Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5] |

Vismodegib (ERIVEDGE)

Vismodegib is a cyclopamine-competitive antagonist and acts as a first-in-class Hedgehog signaling pathway inhibitor by blocking its key component smoothened (smo). Vismodegib is developed by Genentech and marketed by Roche under the trade name ERIVEDGE.

- FDA Approval Summary of Vismodegib (ERIVEDGE)

| | |
|---|--|
| ERIVANCE BCC ^[203] NCT00833417 | Basal cell carcinoma (Approved on 2012/01/30) |
| | - |
| | Vismodegib [ORR (mBCC)(%): 30.3, ORR (laBCC)(%): 42.9] |

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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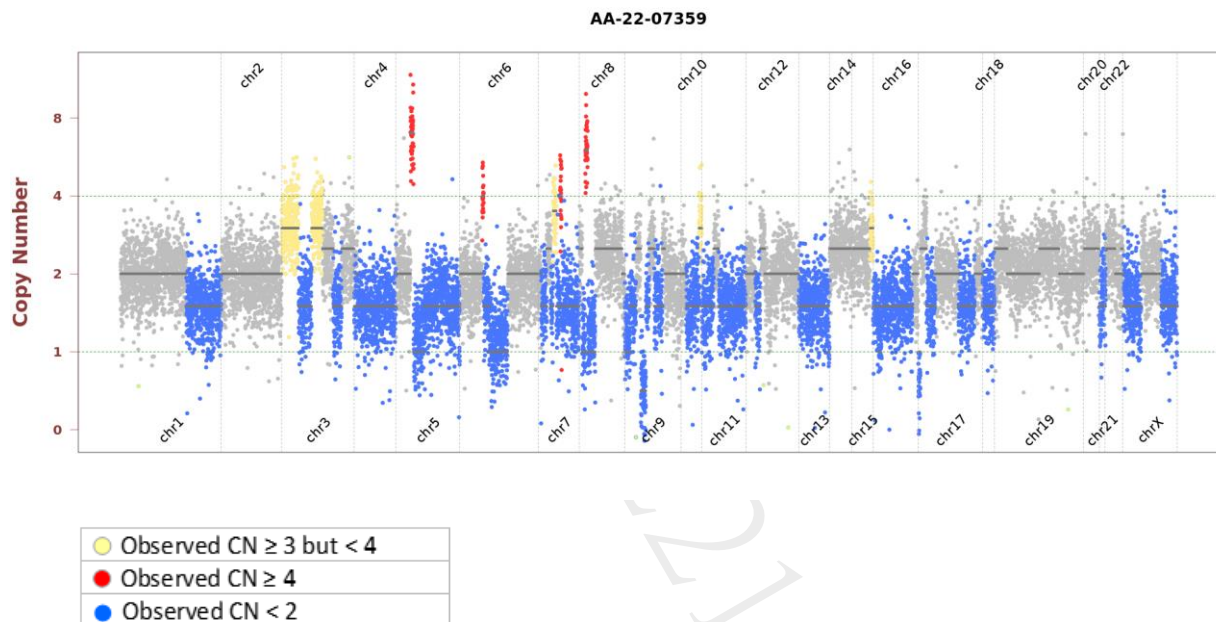
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

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

- Copy Number Alterations

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



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OTHER DETECTED VARIANTS

| Gene | Amino Acid Change | Exon | cDNA Change | Accession Number | COSMIC ID | Allele Frequency | Coverage |
|--------|-------------------|------|-------------|------------------|-------------|------------------|----------|
| ARID1A | Splice region | - | c.3866+8T>A | NM_006015 | - | 34.8% | 883 |
| ARID2 | Q192R | 5 | c.575A>G | NM_152641 | - | 16.6% | 638 |
| CARD11 | A581T | 13 | c.1741G>A | NM_032415 | COSM3663142 | 23.2% | 796 |
| FGFR4 | Splice region | - | c.2016-5T>G | NM_213647 | - | 75.8% | 95 |
| FLCN | R527Q | 14 | c.1580G>A | NM_144997 | COSM976078 | 14.5% | 2250 |
| FLT4 | A804T | 17 | c.2410G>A | NM_182925 | - | 77.7% | 754 |
| IRS1 | H831Q | 1 | c.2493T>A | NM_005544 | COSM3046893 | 32.5% | 240 |
| LRP1B | V216I | 6 | c.646G>A | NM_018557 | COSM3961243 | 44.4% | 99 |
| MUC16 | Q11913P | 5 | c.35738A>C | NM_024690 | - | 47.9% | 1033 |
| MUC16 | G6182V | 3 | c.18545G>T | NM_024690 | - | 17.6% | 1258 |
| MUC16 | I5861V | 3 | c.17581A>G | NM_024690 | - | 47.2% | 1150 |
| NOTCH3 | V237M | 5 | c.709G>A | NM_000435 | - | 53.2% | 442 |
| SYNE1 | Q6294L | 101 | c.18881A>T | NM_182961 | - | 39.5% | 1019 |
| TET1 | Q1332E | 4 | c.3994C>G | NM_030625 | - | 18.9% | 428 |
| TSC1 | A414V | 12 | c.1241C>T | NM_000368 | - | 18.2% | 685 |
| VEGFB | V150L | 6 | c.448G>C | NM_003377 | - | 21.6% | 1148 |

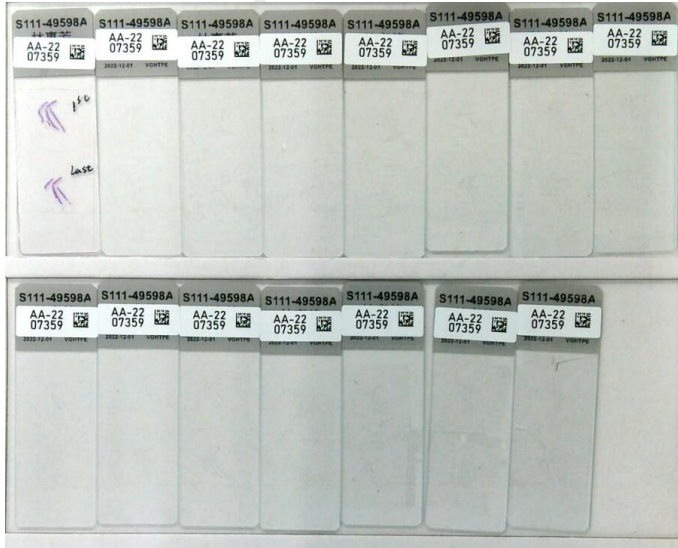
Note:

- 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: Nov 28, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11149598A
- Collection site: Lymph node
- Examined by: Dr. Chien-Ta Chiang
- 1. The percentage of viable tumor cells in total cells in the whole slide (%): 70%
- 2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 70%
- 3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
- 4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
- 5. Additional comment: NA
- Manual macrodissection: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco[®]+

DNA test

- Mean Depth: 923x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 122

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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 $\geq 5\%$ 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).

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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 $\geq 10\%$; (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 |
| ADAMTS11 | 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* | SLC1B1* |
| SLC1B3* | 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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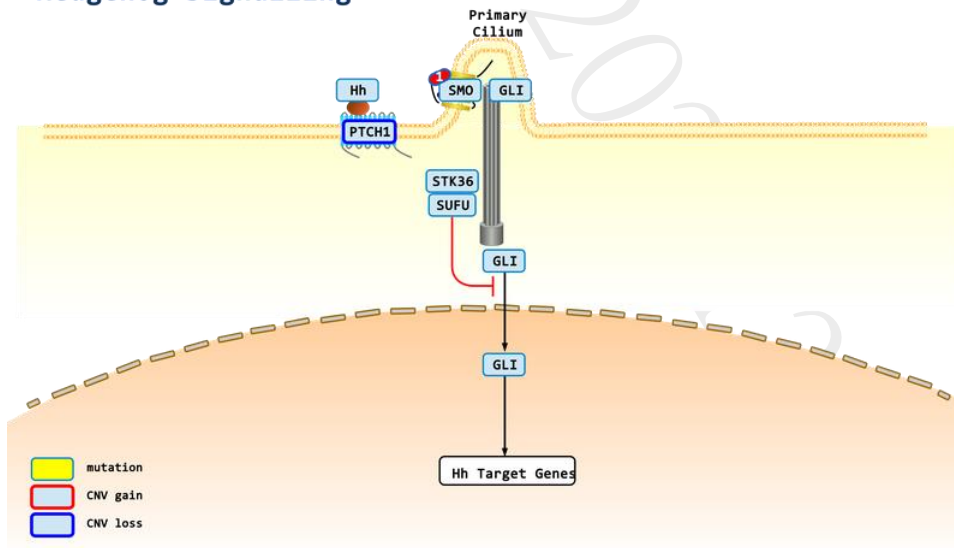
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

| Gene | Therapies | Possible effect |
|--------|--|------------------|
| CDKN2A | Abemaciclib, Palbociclib, Ribociclib | sensitive |
| NF1 | Binimetinib, Cobimetinib, Trametinib, Selumetinib, Everolimus, Temsirolimus | sensitive |
| FBXW7 | Everolimus, Temsirolimus | sensitive |
| TSC2 | Everolimus, Temsirolimus | sensitive |
| ATM | Niraparib, Olaparib, Rucaparib, Talazoparib | sensitive |
| ATR | Niraparib, Olaparib, Rucaparib, Talazoparib | sensitive |
| BRCA2 | Niraparib, Olaparib, Rucaparib, Talazoparib | sensitive |
| CHEK1 | Niraparib, Olaparib, Rucaparib, Talazoparib | sensitive |
| PALB2 | Niraparib, Olaparib, Rucaparib, Talazoparib | sensitive |
| PTCH1 | Sonidegib, Vismodegib | sensitive |
| NF1 | Afatinib, Erlotinib, Gefitinib, Lapatinib, Vemurafenib, Cetuximab, Trastuzumab | resistant |
| FBXW7 | Gefitinib, Regorafenib | resistant |

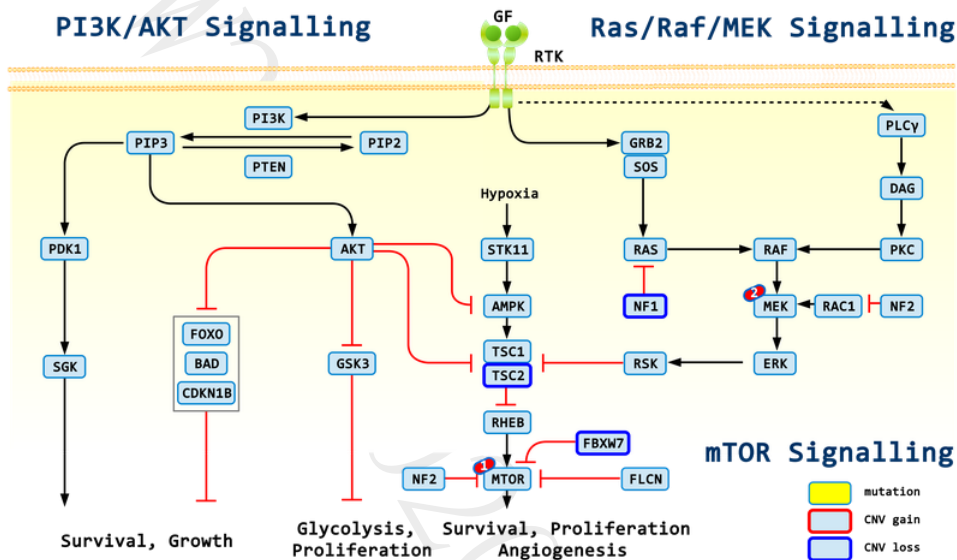
SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

Hedgehog Signalling

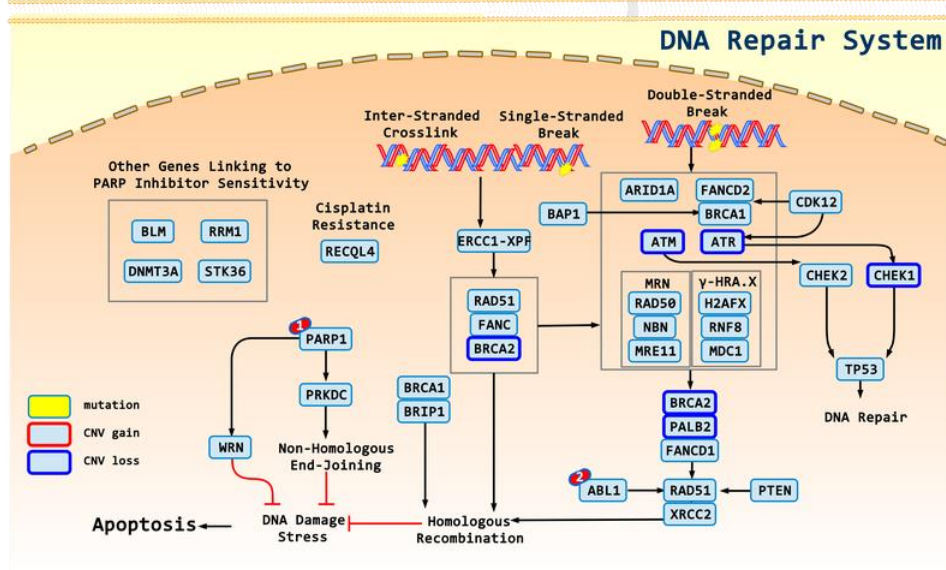


1: Sonidegib, Vismodegib

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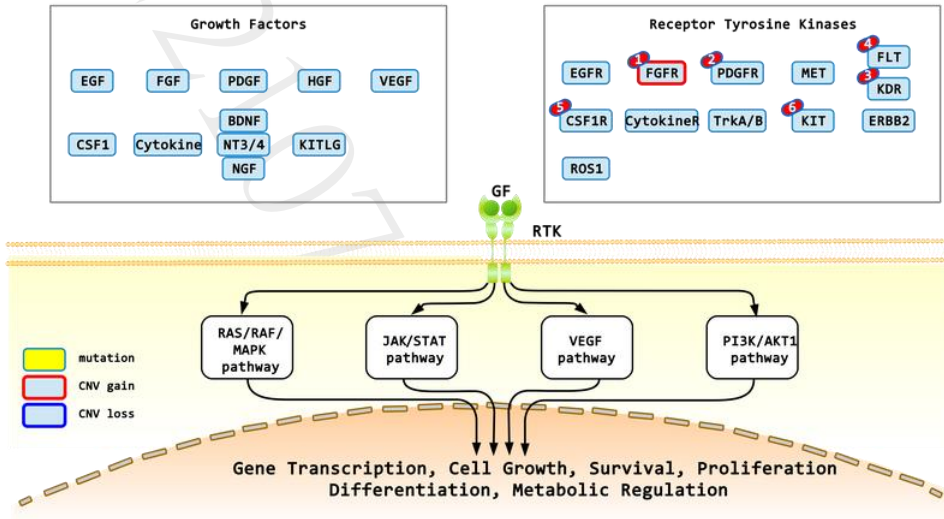
1: Everolimus, Temsirolimus; 2: Trametinib, Selumetinib, Binimetinib, Cobimetinib



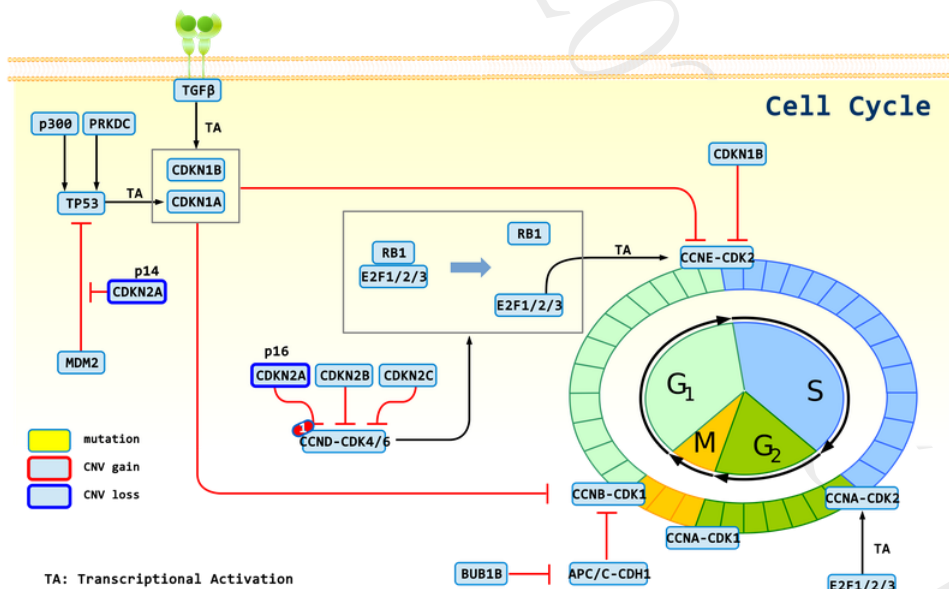
1: Olaparib, Niraparib, Rucaparib, Talazoparib; 2: Ponatinib

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Receptor Tyrosine Kinase/Growth Factor Signalling



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



1: Palbociclib, Ribociclib, Abemaciclib

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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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