

ACT Onco[®] + Report

PATIENT		
Name: 關貴玲		Patient ID: 48384129
Date of Birth: Nov 26, 1957		Gender: Female
Diagnosis: Pancreatic cancer		
ORDERING PHYSICIAN		
Name: 姜乃榕醫師		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: S11179292A	Collection site: Pancreas	Type: FFPE tissue
Date received: Aug 30, 2022	Lab ID: AA-22-05067	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
ARID1A M384fs	Dasatinib, Olaparib, Rucaparib, Talazoparib	-
KRAS Q61K	-	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib, Panitumumab, Cetuximab
PTPRT Splice acceptor	-	Bevacizumab
CDKN2A Homozygous deletion	Abemaciclib, 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
ARID1A	M384fs	30.3%
KRAS	Q61K	30.8%
PIK3C2G	Y1103fs	47.5%
PTPRT	Splice acceptor	23.4%
TP53	Splice acceptor	47.5%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr9	CDKN2A	Homozygous deletion	0
Chr10	PTEN	Heterozygous deletion	1
Chr11	ATM, CHEK1, MRE11	Heterozygous deletion	1
Chr13	RB1	Heterozygous deletion	1
Chr15	RAD51	Heterozygous deletion	1
Chr16	PALB2, TSC2	Heterozygous deletion	1
Chr17	FLCN, RAD51C, TP53	Heterozygous deletion	1
Chr18	SMAD4	Heterozygous deletion	1
Chr19	STK11	Heterozygous deletion	1
Chr22	CHEK2, NF2	Heterozygous deletion	1
Chr3	BAP1, MLH1	Heterozygous deletion	1

- Fusions

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

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	1.9 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:

- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 55% 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 Q61K	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib, Panitumumab, Cetuximab	resistant
Level 3B		
ARID1A M384fs	Olaparib	sensitive
CDKN2A Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	sensitive
Level 4		
ARID1A M384fs	Dasatinib, Rucaparib, Talazoparib	sensitive
PTPR Splice acceptor	Bevacizumab	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
ARID1A M384fs	Platinum-based regimens	Less sensitive	Clinical	Ovarian cancer
PIK3C2G Y1103fs	Oxaliplatin	Resistant	Clinical	Colorectal cancer

HORMONAL THERAPIES

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

OTHERS

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

Note:

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

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VARIANT INTERPRETATION

ARID1A M384fs

Biological Impact

The AT-rich interactive domain 1A (ARID1A) gene encodes the BAF250A protein, a component of the SWI/SNF chromatin remodeling complex that plays a role in various cellular functions, including DNA repair, DNA synthesis, and transcription^{[1][2]}. Haploinsufficiency of ARID1A is associated with tumor formation in some cancers^[3]. Inactivation of ARID1A is commonly observed in ovarian, endometrial, uterine, and, gastric cancers^{[4][5][6][7][8]}.

M384fs mutation results in a change in the amino acid sequence beginning at 384, likely to cause premature truncation of the functional ARID1A protein (UniProtKB). This mutation is predicted to lead to a loss of ARID1A protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

ARID1A is the most frequently mutated genes in ovarian clear cell carcinoma and several synthetic lethality hypothesis-based therapeutic targets in ARID1A mutated cancer are in development. For examples, 1) EZH2 inhibitor^{[9][10]}; 2) AKT-inhibitors MK-2206 and perifosine, as well as PI3K-inhibitor buparlisib^[11]; 3) multiple kinase inhibitor, dasatinib^[12].

Some preclinical evidences suggested that reduced ARID1A expression confers resistance to several HER2/PI3K/mTOR signaling cascade inhibitors such as AZD8055 and trastuzumab, through activation of annexin A1 expression^[13]. Loss or decreased expression of ARID1A has been reported to associate with resistance to platinum-based chemotherapies, shorter overall survival and lower complete response rate in ovarian cancer patients^{[14][15]}.

Low expression of ARID1A is a significant and independent prognostic factor for poor disease-free and overall survival in breast cancer patients^{[16][17]}. Besides, loss of ARID1A expression was more frequently seen in mismatch repair (MMR)-deficient colorectal cancers, predominantly in tumor with MLH1 promoter hypermethylation^[18]. Positive ARID1A expression could independently predict worse overall survival in stage IV CRC patients compared with negative ARID1A expression^[19].

ARID1A mutation has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in metastatic biliary tract cancer (NCT04042831), and niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), or any malignancy, except prostate cancer (NCT03207347).

The preclinical study discovered that ARID1A deficiency sensitized some tumors to PARP inhibitor drugs, such as olaparib, rucaparib, talazoparib, and veliparib, which block DNA damage repair pathways^[20].

KRAS Q61K

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^[21]. KRAS mutations occur primarily in three hotspots G12, G13 and Q61, and less frequently in codon A146^{[21][22]}. These are activating mutations that lead to constitutive activation and persistent stimulation of the downstream signaling pathways^{[23][24]}. Mutations in KRAS have been reported in a diverse spectrum of human malignancies, including pancreatic carcinomas (>80%)^{[21][25]}, colon carcinomas (40-50%)^{[26][27]}, and lung carcinomas (30-50%)^{[28][29]}, but are also present in biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer, liver cancer, myeloid leukemia and breast cancer^[22].

KRAS codon 61 is a residue located in the GTP-binding region of the KRAS protein and frequently mutated in a variety

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of cancers. Although other alterations at codon 61 (Q61H/L/R) are known to be oncogenic, Q61K has not been functionally characterized; therefore, the function of KRAS Q61K remains unknown.

Therapeutic and prognostic relevance

Except for KRAS G12C, other KRAS mutants are not currently targetable, but the downstream MEK serves as a potential target^[30]. 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^{[31][32][33][34]}.

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^[35]. 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^[36]. 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^[37].

Both clinical and preclinical studies demonstrated a limited response to monotherapy using MEK inhibitors^[38]. Moreover, several clinical trials are in progress to evaluate the combination of MEK and mTOR inhibition as a new potential therapeutic strategy in CRC^[39], and in patient-derived xenografts of RAS-mutant CRC, inhibition of MEK and mTOR suppressed tumor growth, but not tumor regression^[40]. 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^[41].

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^[42]. 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)^{[43][44]}. 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^{[45][46][47][48][49][50][51]}.

Sorafenib, a multi-kinase inhibitor, has been shown to be beneficial in KRAS-mutant CRC^[52], KRAS-mutant NSCLC^[53], and KRAS-amplified melanoma^[54].

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))^{[55][56]}.

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^{[57][58][59]}.

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^[60].

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^[61].

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In ovarian serous borderline tumor with recurrent low-grade serous carcinoma, patient harboring KRAS G12V mutation appeared to have shorter survival time^[62].

The National Comprehensive Cancer Network recommendation indicates that colorectal cancer patients with any KRAS or NRAS mutation, including those of Q61 and A146, will not benefit from anti-EGFR therapy^[63].

A retrospective study indicated that a patient with advanced lung cancer harboring KRAS Q61K mutation had longer PFS (6.2m) than the median PFS in the KRAS-mutant cohort (1.5m) after nivolumab plus chemotherapy treatment^[64]. Furthermore, there is another retrospective study of patients with pancreatic carcinoma demonstrated that patients with KRAS Q61 mutations showed significantly improved survival^[65].

In a case report, a NSCLC patient harboring EML4-ALK and ALK A1200_G1201delinsW developed progressive disease after 4 months of brigatinib treatment, and the acquisition of KRAS Q61K and disappearance of ALK A1200_G1201delinsW were subsequently identified in post-treatment biopsy^[66].

PIK3C2G Y1103fs

Biological Impact

The PIK3C2G gene encodes a protein contains a lipid kinase catalytic domain as well as a C-terminal C2 domain, a characteristic of the class II phosphoinositide 3-kinases (PI3Ks). C2 domains act as calcium-dependent phospholipid binding motifs that mediate translocation of proteins to membranes, and may also mediate protein-protein interactions^{[67][68]}. PIK3C2G plays roles in the regulation of protein trafficking signaling pathways and glycogen synthase^[69]. Inactivating mutations of PIK3C2G are found in melanomas^[70].

Y1103fs mutation results in a change in the amino acid sequence beginning at 1103, likely to cause premature truncation of the functional PIK3C2G protein (UniProtKB). This mutation is predicted to lead to a loss of PIK3C2G protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

Low copy number of PIK3C2G has been reported to associate with shorter overall survival and recurrence-free survival in stage III colorectal cancer patients treated with oxaliplatin-based chemotherapy^[71].

PTPRT Splice acceptor

Biological Impact

PTPRT encodes the enzyme Protein tyrosine phosphatases rho (PTPp), regulating a plethora of cellular processes and cell-cell adhesion^{[72][73][74]}. PTPRT has been recognized as a tumor suppressor gene by dephosphorylating proteins involved in cell proliferation, migration, growth, and survival^[75]. It is the most frequently mutated PTPR in human cancers, including colorectal, lung, gastric cancer and hematologic malignancies^{[76][73][77][78]}. Hypermethylation of the PTPRT promoter was found associated with downregulation of PTPRT gene expression in HNSCC^[79].

PTPRT c.3982-2A>C is a variant located at the splice acceptor region, which may result in the exon skipping.

Therapeutic and prognostic relevance

Deleterious PTPRT/PTPRD alternations, including missense variants and truncating variants, have been shown associated with bevacizumab-resistance in metastatic colorectal cancer and lead to shortened survival in bevacizumab-treated patients compared to those without deleterious PTPRT/PTPRD alternations (Median PFS: 8.6 v.s. 13.1 months)^[80]. Moreover, clinical studies demonstrated that PTPRT mutation conferred to high tumor mutation burden and improved survival in ICI-treated pan-cancer patients, especially in NSCLC and melanoma patients^[81](doi: 10.1200/JCO.2020.38.15_suppl.e15112).

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TP53 Splice acceptor, Heterozygous deletion

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[82]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[83].

TP53 c.560-2A>T is a variant located at the splice acceptor region, which may result in the exon skipping. Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

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)^[84].

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^[85]. 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^[86].

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^{[87][88][89]}. 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)^[90]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[91][92]}. 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^[93].

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^[94]. 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^{[95][96][97][98][99]}. 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^[100]. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies^{[101][102][103][104]} and a board range of tumors such as prostate cancer^[105], head and neck squamous cell carcinoma (HNSCC)^[106], pancreatic cancer^[107], lung adenocarcinoma^[108], breast cancer^[109], and ovarian cancer^[96].

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)^[110].

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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^[111]. 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^[112]. 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)^[113]. 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^[114]. 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)^[115]. 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)^[116].

In preclinical studies, cells with ATM alternation were sensitive to olaparib, niraparib, and talazoparib treatment in vitro and in vivo^{[117][118][119][120]}.

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)^[121] and prostate cancer (NCT02952534, NCT03533946)^[116], 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^[122]. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer^[123].

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer^[124].

BAP1 Heterozygous deletion

Biological Impact

Breast cancer type 1 susceptibility protein (BRCA1)-associated protein (BAP1) encodes an enzyme with ubiquitin carboxyl hydrolase activity involved in the regulation of cell cycle, transcription, and double-strand DNA repair^{[125][126][127]}. BAP1 acts as a tumor suppressor by forming a complex with BRCA1^[128]. BAP1 is a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is related to renal cell carcinoma (RCC)^[129]. Inactivating mutations of BAP1 were frequently observed in uveal melanoma with high metastatic risk, malignant mesothelioma and other carcinoma types, including a subtype of renal cell carcinoma and intrahepatic cholangiocarcinoma^{[126][130][131][132][133][134][135]}.

Therapeutic and prognostic relevance

In a Phase II trial (MiST1; NCT03654833), rucaparib demonstrated manageable toxicity and clinical activity in patients with relapsed malignant mesothelioma that were negative for BAP1 (n=23), BRCA1 (n=13), or both (n=10), resulting in a 12-week disease control rate (DCR) of 58% (15/26), a 24-week DCR of 23% (6/26), and an objective response rate of 11.5% (3/26)^[136]. The loss of BAP1 was shown to be associated with increased sensitivity to PARP inhibitor, olaparib, in renal cell carcinoma (RCC)^[132] and mesothelioma cell lines^[137]. However, no difference in sensitivity to the

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PARP inhibitor niraparib (MK4827) was observed between BAP1-mutant and wild-type mesothelioma cell^[126]. BAP1 deficiency was also linked to a high tumor grade and was correlated with metastasis development in uveal melanoma^[130].

An open-label, non-randomized, Phase II study (NCT03207347) has been initiated, aimed at investigating the use of niraparib in mesothelioma, uveal melanoma, renal cell carcinoma, and cholangiocarcinoma patients with tumors known to have mutations in BAP1 and other selected DNA double-strand break repair pathway genes. BAP1 loss of function mutation has been selected as an inclusion criteria for the trial examining olaparib in urothelial cancer (NCT03375307) and malignant mesothelioma (NCT04515836).

CDKN2A Homozygous deletion

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53^{[138][139][140]}. 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^[141]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation^{[142][143]}.

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors^{[144][145]}. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments^{[146][147][148]}. 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^{[149][150][151]}. 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).

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^{[145][152][153]}.

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^[147]. 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^[154].

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^[155].

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^[156]. 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^{[157][158]}. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors^[159], and CHEK1 mutations are

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extremely rare^[156]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer^[160], breast cancer^[161], colorectal cancer^[162], non-small cell lung (NSCLC) cancer^[163], and nasopharyngeal cancer^[164].

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)^[110].

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)^[121], 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^[165].

CHEK2 Heterozygous deletion

Biological Impact

The checkpoint kinase 2 (CHEK2 or CHK2) gene encodes a serine/threonine protein kinase involved in transducing DNA damage signals that are required for both the intra-S phase and G2/M checkpoints^[166]. CHEK2 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^{[157][158]}. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers^{[167][168][169][170][171]}.

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)^[110].

In a phase II trial (TBCRC 048; NCT03344965), 7 metastatic breast cancer patients harboring only germline mutations in CHEK2 were not responded to olaparib treatment (SD: n=3, PD: n=4)^[115]. Furthermore, in another phase II trial (TRITON2; NCT02952534), 12 mCRPC patients harboring CHEK2 alteration had limited response to rucaparib treatment. One patient with co-occurring ATM alteration had a radiographic partial response (n=1/9 evaluable patients). The prostate-specific antigen response rate was 16.7% (n=2/12), and the 6-month clinical benefit rate was 37.5% (n=3/8)^[116].

In addition, CHEK2 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)^[121], and prostate cancer (NCT02952534, NCT03533946)^[116], niraparib efficacy in metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma (NCT03840967), melanoma (NCT03925350), pancreatic cancer (NCT03553004, NCT03601923), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative solid tumors (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

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FLCN Heterozygous deletion

Biological Impact

The FLCN gene encodes the tumor suppressor, Folliculin, a GTPase activating protein (GAP) for RagC/D GTPase proteins involved in amino acid sensing and signaling to mTORC1^[172]. FLCN 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^{[173][174]}. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling^{[175][176]}. Germline mutation of the FLCN gene causes the Birt-Hogg-Dubé syndrome, a rare disorder that is characterized by benign hamartomatous skin lesions and an increased risk of pneumothorax and renal tumors^[177].

Therapeutic and prognostic relevance

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTC) patients who had PI3K/mTOR/AKT alterations, including TSC2, FLCN or NF1, showed impressive progression-free survival (PFS) of 15.2 months after receiving everolimus^[178]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting^[179].

MLH1 Heterozygous deletion

Biological Impact

The MutL protein homolog 1 (MLH1) gene encodes a tumor suppressor that dimerizes with PMS2 protein to form a component of the DNA mismatch repair (MMR) system^[180]. Deletion of one copy of the MLH1 gene resulted in haploinsufficiency in the correction of small insertions/deletions (indels), and could be a driving force in pancreatic and renal carcinogenesis^[181]. Genetic alterations such as mutation, loss of heterozygosity or epigenetic silencing could lead to inactivation of MLH1 and are associated with a broad spectrum of cancers, including a subset of sporadic colon, gastric and endometrial cancers, as well as the hereditary non-polyposis colon cancer (HNPCC, also known as Lynch syndrome)^{[182][183][184]}.

Therapeutic and prognostic relevance

Currently, there are no FDA-approved medications specifically targeting MLH1. A screening test for microsatellite instability (MSI) is commonly used to identify an MMR-deficient tumor in the clinic^{[185][186]}. Pembrolizumab (KEYTRUDA), an inhibitor targeting programmed cell death 1 (PD-1), has been approved by the U.S. FDA for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient cancer. Down-regulation of genes involved in the MMR pathway such as MLH1, MSH2 and, MSH6 in high-grade serous epithelial ovarian cancer cell lines rendered cells sensitive to PARP inhibitors^[187].

MRE11 Heterozygous deletion

Biological Impact

The MRE11 gene encodes a protein that forms the MRE11-RAD50-NBS (MRN) complex involved in sensing and repairing DNA double-strand breaks via homologous recombination and non-homologous end joining^{[188][189]}. MRE11 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 function^[188]. The carrier of MRE11 mutation may confer elevated risks for numerous types of cancers including breast cancer, ovarian cancer, endometrial cancer, colorectal cancer, and lymphoid cancer^{[188][189][190][191][192][193][194]}.

Therapeutic and prognostic relevance

In a Phase II clinical trial (n=50), one castration-resistant prostate cancer patient harboring an MRE11 inactivating mutation responded to olaparib^[111]. Preclinically, loss of MRE11 also predicted sensitivity to PARP inhibitor talazoparib and ABT-888 in endometrial cancer^[195] and microsatellite unstable colorectal cancer (CRC) cell lines^[196].

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CRC patients with tumor deficient of MRE11 showed initially reduced disease-free survival (DFS) and overall survival (OS) but improved long-term DFS and OS compared with patients with an intact MRE11^[197].

NF2 Heterozygous deletion

Biological Impact

The neurofibromin (NF2) gene encodes the protein Merlin, a tumor suppressor that functions as a negative regulator of the PI3K/AKT/mTOR pathway^{[198][199][200]}. NF2 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^[201]. Inactivation germline mutations in the NF2 are associated with the hereditary neurofibromatosis type 2, a disorder characterized by the growth of noncancerous tumors in the nervous system^{[198][202]}. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas^[126], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers^[203].

Therapeutic and prognostic relevance

Genomic alterations with activating effects on the mTOR signaling pathway have been identified to confer sensitivity to everolimus across multiple cancer types^{[204][205][206][207]}. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer and urothelial carcinoma^{[208][209]}, both harboring NF2 truncating mutations. Preclinical evidence has shown the efficacy of MEK1/2 inhibitor selumetinib in KRAS-mutant thyroid cancer model with NF2 loss^[210].

Analysis of afatinib-plus-cetuximab-resistant biopsy specimens revealed a loss-of-function alteration in genes that modulate mTOR signaling pathway, including NF2 and TSC1^[211].

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^[212]. The Fanconi anemia complementation group (FANC) which includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM and FANCN (also called PALB2) are involved in the repair of DNA double-strand breaks (DSBs) by homologous recombination (HR)^{[213][214][215]}. 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^[216]. 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^[217]. 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^{[218][219]}.

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^[110].

NCCN guideline for pancreatic cancer recommended that rucaparib as maintenance therapy following prior platinum-based therapy for patients with pancreatic adenocarcinoma harboring PALB2 mutations^[220].

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In a Phase I trial, a pancreatic cancer patient harboring a PALB2 mutation had a partial response to talazoparib treatment^[221]. In a preclinical study, talazoparib demonstrated anti-tumor activity on a Wilms tumor cell line with a PALB2 truncating mutation in mice xenograft model^[222]. PALB2 loss of function mutation has been determined as an inclusion criterion for the trial evaluating rucaparib efficacy in ovarian cancer^[121] or prostate cancer^[116]; 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^[223].

PTEN Heterozygous deletion

Biological Impact

The phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene encodes a lipid/protein phosphatase that is important for the regulation of cell proliferation, survival, homologous recombination and maintenance of genomic integrity^{[224][225]}. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway^[226]. PTEN is a haploinsufficient tumor suppressor gene, in which having only one copy of the wild-type allele does not produce enough protein product to execute wild-type functions^{[83][227][228]}. Germline loss-of-function PTEN mutations are found in approximately 80% of patients with Cowden syndrome, a disorder that is associated with high-penetrance breast and thyroid cancer^{[229][230][231]}. Somatic mutations or monoallelic loss of PTEN is regularly observed in a significant fraction of human cancers, including sporadic breast cancer, colon cancer, endometrial cancer, prostate cancer, and glioblastoma^{[232][233][234][235][236]}.

Therapeutic and prognostic relevance

Somatic loss of PTEN results in aberrant activation of PI3K/AKT/mTOR signaling pathway and provides a mechanistic rationale for PI3K pathway inhibitors treatment^{[237][238]}. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes^{[239][240][241][242][243][244]}. Moreover, early clinical data also indicated that PTEN loss was associated with improved response and longer PFS in patients with advanced breast cancer^[204], advanced pancreatic neuroendocrine tumors^[245], and metastatic castration-resistant prostate cancer treated with mTORC1 inhibitor, everolimus^[246].

Several groups found that PTEN loss was generally associated with poor response to trastuzumab therapy, whether this agent was administered in the neoadjuvant, adjuvant, or metastatic settings^{[247][248][249][250][251]}.

Loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab^{[252][253][254][255][256][48]}. However, encouraging anti-tumor activity of the combination of an EGFR antibody and a mTORC1 inhibitor (everolimus or temsirolimus) have been reported in early-phase clinical studies (J Clin Oncol. 2011;29 (suppl): abstr 3587; J Clin Oncol. 2013;31 (suppl): abstr 608). Ongoing phase I/II studies testing combinations of EGFR antibodies and PI3K/AKT/mTOR pathway inhibitors (e.g., NCT01816984, NCT01252628, NCT01719380) will provide larger numbers of patients to assess the role of PTEN status in therapeutic response.

Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib^{[257][258]}. Inhibition of the PI3K/AKT/mTOR signal pathway has been shown to be an effective strategy to radiosensitize NSCLC cells harboring the EGFR activating mutation that acquires resistance to both TKIs due to PTEN loss or inactivation mutations^[259].

Loss or biallelic inactivation of PTEN is associated with resistance to anti-PD-1 checkpoint blockade therapies, including pembrolizumab and nivolumab in melanoma and leiomyosarcoma patients^{[260][261][262]}.

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PTEN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in metastatic biliary tract cancer (NCT04042831); talazoparib efficacy in HER2-negative breast cancer (NCT02401347), and niraparib efficacy in breast cancer (NCT04508803) or any malignancy (except prostate) cancer (NCT03207347). Clinical data also suggested that PTEN deficient cancers may be sensitive to olaparib^[263].

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^{[264][265][266]}. 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^[267]. Overexpression of RAD51 has been observed in many cancer cells, including pancreatic cancer and breast cancer and its hyperexpression is implicated in drug resistance^{[268][269][270][271][272][273][274]}. Germline mutations in RAD51 are associated with increased susceptibility to breast cancer^{[275][276][277][278]}.

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^[279]; 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^{[280][281]}.

RAD51C Heterozygous deletion

Biological Impact

The RAD51C (RAD51 paralog C) encodes a member of the RAD51 protein family involved in the late phase of homologous recombination DNA repair. Germline mutations in RAD51C have been shown to confer increased susceptibility to ovarian cancer and head and neck squamous cell carcinoma (HNSCC)^{[282][283][284][285][286]}. Amplification of RAD51C has been implicated in tumor progression^{[287][288]}. RAD51C is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function^[289].

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^[110].

A preclinical study using gastric cancer xenograft model showed that RAD51C deficiency caused sensitivity to PARP inhibitor olaparib^[290].

RAD51C loss of function mutation has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer^{[121][116]}; talazoparib efficacy in HER2-negative breast cancer (NCT02401347) or prostate cancer (NCT03148795), and niraparib efficacies in pancreatic cancer (NCT03553004).

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RB1 Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication^[291]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis^[292]. RB1 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^{[293][294][295]}. Deletion or inactivating mutation of RB1 is found in a number of tumors, including lung, prostate, bladder, breast cancers and sarcomas. RB1 mutations are found in approximately half of all retinoblastoma cases^[296].

Therapeutic and prognostic relevance

A deleterious mutation in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response and better overall survival to cisplatin-based chemotherapy for muscle-invasive bladder cancer patients^[122]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytosine (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy^[297].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer^{[298][299]}.

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment^[300]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib^[301].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)^{[302][303]}. Analyses of repeat biopsy samples from patients with EGFR-mutant adenocarcinoma that had transformed to the SCLC subtype have revealed that 100% of these patients have loss of RB1 and may be the alteration that induces this non-small-cell to small-cell transformation^{[299][304]}.

SMAD4 Heterozygous deletion

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^[305]. 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^[306]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)^{[307][308][309][310]}. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer^[311], colorectal cancer (CRC)^{[309][312][313]}, and less frequently seen in other cancers such as lung adenocarcinoma^[314], head and neck cancer^{[315][316]}, and cutaneous squamous cell carcinoma^[317].

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^[318]. 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^[319].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)^{[320][321]}. 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^[322].

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Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis^{[323][324][325][326][327][328][329][330]}. 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^[331].

STK11 Heterozygous deletion

Biological Impact

The serine/threonine kinase 11 (STK11, also known as LKB1) gene encodes the multifunctional serine/threonine kinase, a tumor suppressor that functions as an inhibitor for the mTOR signaling pathway^{[332][333]}. STK11 is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^{[334][335]}. In the mouse model, loss of STK11 promotes aggressive endometrial and squamous cell carcinomas^{[336][337]}. Mutations in STK11 have been found in lung, breast, cervical, testicular, and liver cancers, as well as malignant melanoma, pancreatic and biliary carcinoma^[338]. Germline mutations in STK11 are found in 30-70% of Peutz-Jeghers syndrome^[339].

Therapeutic and prognostic relevance

A clinical study in a pancreatic cancer patient with Peutz-Jeghers syndrome whose tumor harboring an STK11 D194E mutation coupled with the loss of heterozygosity of the other STK11 allele displayed partial response to the everolimus treatment^[340]. In another clinical case study, an adrenocorticotrophic pituitary carcinoma patient whose tumor bearing an STK11 inactivating mutation responded to a combination of everolimus and radiotherapy^[341].

Preclinical data suggested that lung cancer cell lines with STK11 inactivating mutations may confer increased sensitivity to the MEK-1 and MEK-2 inhibitor, trametinib^[342].

Inactivating mutations of STK11 was shown to be associated with resistance to immune checkpoint blockade in KRAS-mutant lung adenocarcinoma (LUAC) and NSCLC (DOI: 10.1200/JCO.2017.35.15_suppl.9016)^{[343][344][345]}. It was proposed that loss of STK11 negatively impacts the number and function of tumor-infiltrating T cells (TILs) and PD-L1 expression on tumor cells and therefore results in an ineffective response to PD-1-targeting antibodies^[346].

TSC2 Heterozygous deletion

Biological Impact

The tuberous sclerosis complex 2 (TSC2) gene encodes a protein called tuberlin, which interact with a protein called hamartin (encoded by the TSC1 gene). This hamartin-tuberlin tumor suppressor complex plays a critical role in growth control as a negative regulator of the mammalian target of rapamycin (mTOR) pathway^{[347][348]}. Mutations in TSC1/TSC2 tumor suppressor genes that result in inactivation of the complex are commonly found in patients with tuberous sclerosis complex^{[349][350][351]}, while the loss of heterozygosity (LOH) in TSC1/TSC2 has been identified in head and neck squamous cell carcinoma (HNSCC)^[352] and endometrial cancer^[353]. 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 autosomal dominant genetic disorder tuberous sclerosis complex (TSC)^[354].

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)^{[208][207][355]}. Results from one Phase II study of advanced endometrial cancer showed that mutations in AKT1, TSC1, and TSC2 might predict sensitivity to temsirolimus^[356]. Recent studies indicated that there are mTORC1-independent signaling pathways downstream of hamartin-tuberlin, which may represent new therapeutic

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targets^[357].

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 ^[358] 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 ^[153] NCT02107703	Breast cancer (Approved on 2017/09/28)
	HR+/HER2- Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1 ^[359] 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 ^[34] 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 ^[360] 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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Dasatinib (SPRYCEL)

Dasatinib is an oral Bcr-Abl tyrosine kinase inhibitor (inhibits the "Philadelphia chromosome") and Src family tyrosine kinase inhibitor. Dasatinib is produced by Bristol-Myers Squibb and sold under the trade name SPRYCEL.

- FDA Approval Summary of Dasatinib (SPRYCEL)

DASISION ^[361] NCT00481247	Chronic myeloid leukemia (Approved on 2010/10/28)
	- Dasatinib vs. Imatinib [ORR(%): 76.8 vs. 66.2]
^[362] NCT00123474	Chronic myeloid leukemia (Approved on 2007/11/08)
	- Dasatinib [ORR(%): 63.0]
^[363] NCT00123487	Acute lymphocytic leukemia (Approved on 2006/06/28)
	- Dasatinib [ORR(%): 38.0]

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 ^[364] NCT01524783	Lung or gastrointestinal neuroendocrine tumor (Approved on 2016/02/26)
	- Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2 ^[365] 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 ^[245] NCT00510068	Pancreatic neuroendocrine tumor (Approved on 2011/05/05)
	- Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1 ^[366] NCT00789828	Subependymal giant cell astrocytoma (Approved on 2010/10/29)
	- Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1 ^[367] NCT00410124	Renal cell carcinoma (Approved on 2009/05/30)
	- Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

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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]
QUADRA ^[368] NCT02354586	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2019/10/23)
	HRD+ Niraparib [ORR(%): 24.0, DOR(M): 8.3]
NOVA ^[369] 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 ^[110] 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 ^[370] NCT02477644	Ovarian cancer (Approved on 2020/05/08)
	HRD+ Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO ^[371] 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 ^[372] 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 ^[373] NCT02000622	Breast cancer (Approved on 2018/02/06)
	HER2-/gBRCA mutation Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21 ^[374] 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]

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Study19 ^[375] NCT00753545	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]
Study 42 ^[376] NCT01078662	Ovarian cancer (Approved on 2014/12/19)
	gBRCA mutation
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

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 ^[377] NCT01740427	Breast cancer (Approved on 2017/03/31)
	ER+/HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3 ^[378] NCT01942135	Breast cancer (Approved on 2016/02/19)
	ER+/HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

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 ^[152] 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 ^[121] NCT01968213	Ovarian 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]

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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 ^[379] 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)

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

Trametinib (MEKINIST)

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

- FDA Approval Summary of Trametinib (MEKINIST)

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 ^[381] NCT02034110	Anaplastic thyroid cancer (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928 ^[382] 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 ^[31] NCT01584648	Melanoma (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC ^[32] 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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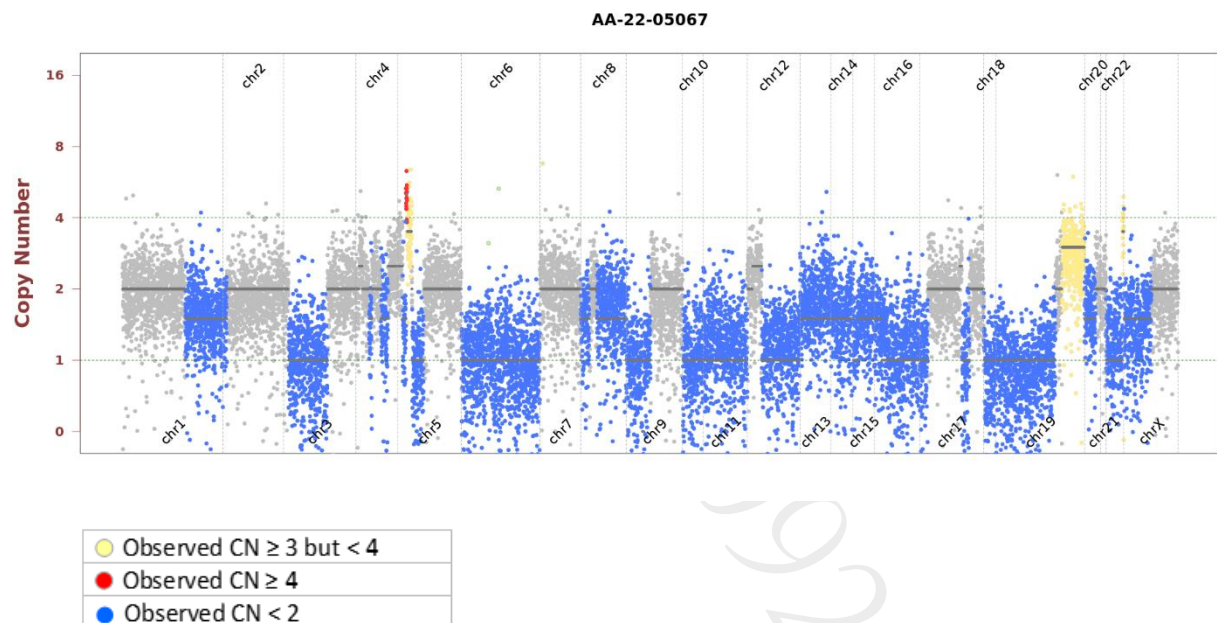
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ARID1A	M384fs	2	c.1148_1149insCGTCC	NM_006015	-	30.3%	565
KRAS	Q61K	3	c.180_181delinsAA	NM_004985	COSM87298	30.8%	1053
PIK3C2G	Y1103fs	24	c.3299_3306dup	NM_004570	COSM2003816	47.5%	688
PTPRT	Splice acceptor	-	c.3982-2A>C	NM_007050	-	23.4%	111
TP53	Splice acceptor	-	c.560-2A>T	NM_000546	COSM45026	47.5%	478

- 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
BRCA1	M669T	10	c.2006T>C	NM_007294	-	52.5%	444
CREBBP	A2419V	31	c.7256C>T	NM_004380	COSM6914370	20.8%	759
EP300	Splice region	-	c.4026-7T>C	NM_001429	-	26.8%	567
EP300	R1305H	24	c.3914G>A	NM_001429	-	73.0%	2063
EPHA5	G591S	8	c.1771G>A	NM_001281765	-	24.0%	1125
HNF1A	A568T	8	c.1702G>A	NM_000545	-	30.4%	230
MSH6	G354L	4	c.1060_1061delinsTT	NM_000179	-	42.8%	1408
MTOR	V1119I	22	c.3355G>A	NM_004958	-	54.0%	907
NTRK1	V99M	3	c.295G>A	NM_002529	-	51.5%	771
POLD1	P404L	10	c.1211C>T	NM_001256849	-	31.2%	721
RECQL4	A1122T	20	c.3364G>A	NM_004260	-	54.2%	559
SETD2	R402Q	3	c.1205G>A	NM_014159	-	25.6%	1768
SMARCA4	M42I	3	c.126G>A	NM_001128844	-	81.1%	275

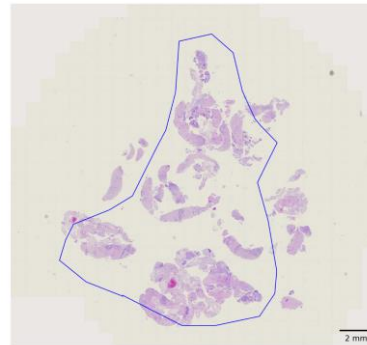
Note:

- 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: Jul 21, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11179292A
- Collection site: Pancreas
- Examined by: Dr. Chien-Ta Chiang
- 1. The percentage of viable tumor cells in total cells in the whole slide (%): 25%
- 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 (%): 20%
- 4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 10%
- 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: 816x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 27

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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
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*	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	SOC1*	SOX2*	SOX9	SPEN	SPOP
SRC	STAG2	STAT3	STK11	SUFU	SYK	SYNE1	TAF1	TAP1	TAP2	TAPBP	TBX3
TEK	TERT	TET1	TET2	TGFBR2	TMSB4X*	TNF	TNFAIP3	TNFRSF14	TNFSF11	TOP1	TP53
TPMT*	TSC1	TSC2	TSHR	TYMS	U2AF1	UBE2A*	UBE2K	UBR5	UGT1A1*	USH2A	VDR*
VEGFA	VEGFB	VHL	WT1	XIAP	XPO1	XRCC2	ZNF217				

*Analysis of copy number alterations NOT available.

FUSION

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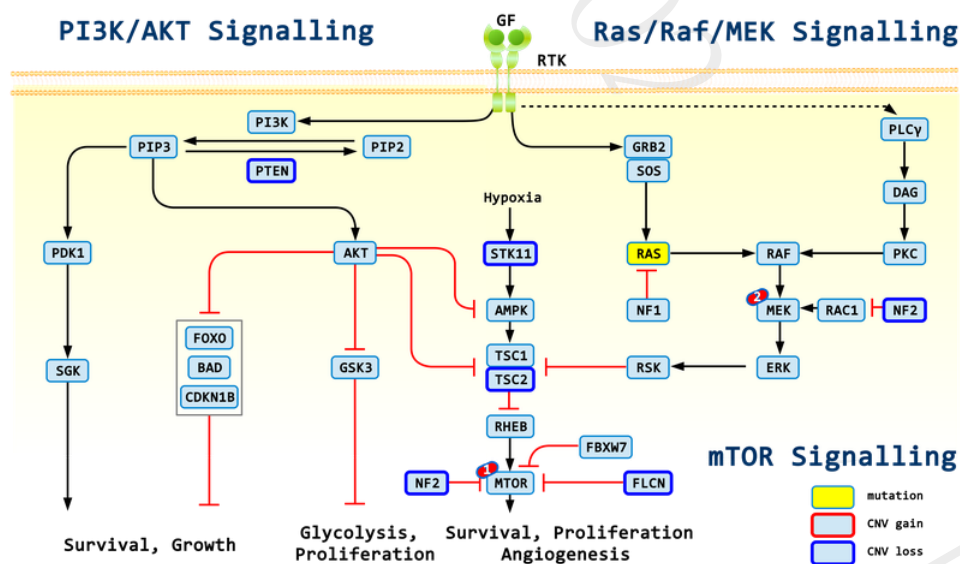
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

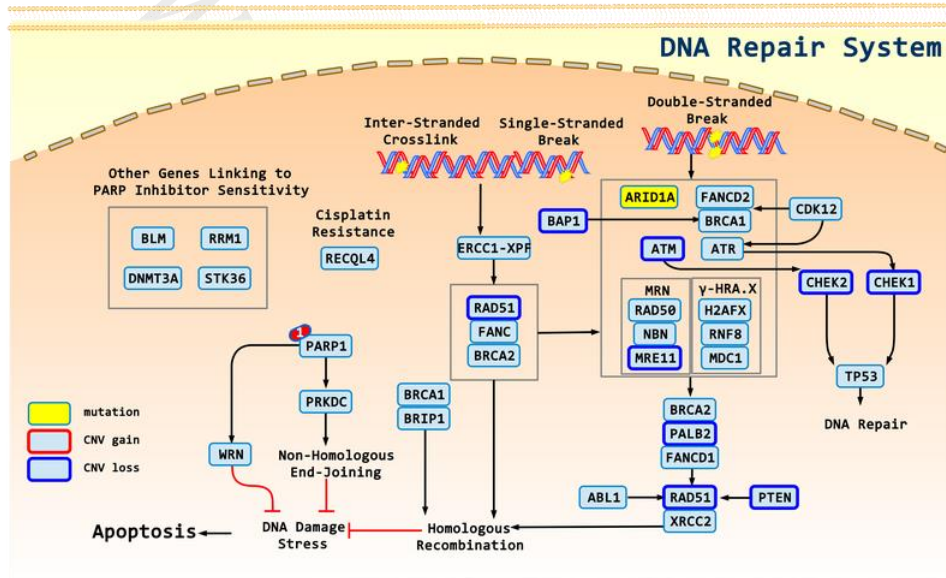
Gene	Therapies	Possible effect
STK11	Binimetinib, Cobimetinib, Trametinib, Everolimus, Temsirolimus	sensitive
PTEN	Everolimus, Temsirolimus, Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
FLCN	Everolimus, Temsirolimus	sensitive
NF2	Everolimus, Temsirolimus	sensitive
TSC2	Everolimus, Temsirolimus	sensitive
ATM	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
BAP1	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
CHEK1	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
CHEK2	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
MLH1	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
MRE11	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
PALB2	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
RAD51	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
RAD51C	Olaparib, Rucaparib	sensitive
RB1	Abemaciclib, Palbociclib, Ribociclib	resistant
SMAD4	Cetuximab	resistant
PTEN	Erlotinib, Gefitinib, Panitumumab, Cetuximab, Trastuzumab	resistant

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

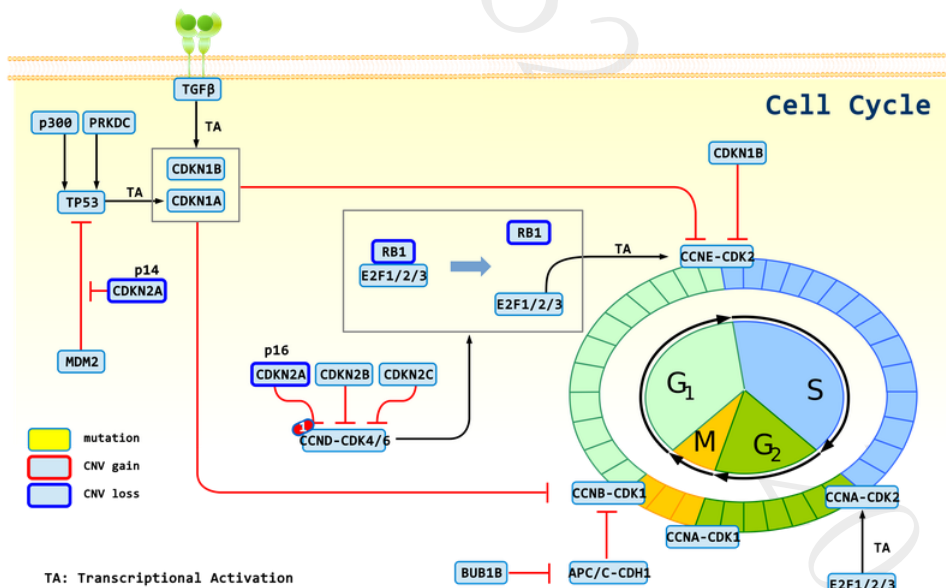


1: Everolimus, Temsirolimus; 2: Trametinib, Cobimetinib, Binimetinib

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1: Olaparib, Niraparib, Rucaparib, Talazoparib



1: Abemaciclib, Palbociclib, Ribociclib

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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。

責任

本檢驗報告僅提供專業醫療參考，本公司及其員工不對任何由使用本報告之內容引起的直接、間接、特殊、連帶或衍生的損失或損害承擔責任。

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