

# ACT Onco<sup>®</sup> + Report

PATIENT		
Identifier: 陳*卿		Patient ID: ***05713
Date of Birth: Nov **, 1955		Gender: Female
Diagnosis: Retroperitoneal carcinoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11305498A	Collection site: Retroperitoneal	Type: FFPE tissue
Date received: Feb 15, 2024	Lab ID: AA-24-00873	D/ID: NA

## ABOUT ACT Onco<sup>®</sup>+

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) ( $\leq 15$  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	
PIK3CA C420R	-	-	Alpelisib, Capivasertib, Everolimus
SDHB R90*	-	-	Pazopanib, Regorafenib, Sunitinib
TMB-High	Dostarlimab-gxly, Pembrolizumab	-	Atezolizumab, Avelumab, Cemiplimab-rwlc, Durvalumab, Ipilimumab, Nivolumab, Toripalimab-tpzi, Tremelimumab

### VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
ARID1A S964fs	Dasatinib, Olaparib, Rucaparib, Talazoparib	-
PIK3CA C420R	Temsirolimus	-
FBXW7 R479Q	Everolimus, Temsirolimus	Gefitinib, Regorafenib
KRAS G13C	-	Cetuximab, Panitumumab

#### Note:

- The above summary tables present genomic variants and biomarkers based on the three-tiered approach proposed by US FDA for reporting tumor profiling NGS testing. "Variants/biomarkers with evidence of clinical significance" refers to mutations that are widely recognized as standard-of-care biomarkers (FDA level 2/AMP tier 1). "Variants/biomarkers with potential clinical significance" refers to mutations that are not included in the standard of care but are informational for clinicians, which are commonly biomarkers used as inclusion criteria for clinical trials (FDA level 3/AMP tier 2).
- The therapeutic agents and possible effects to a given drug are based on mapping the variants/biomarkers with ACT Genomics clinical knowledge database. The mapping results only provide information for reference, but not medical recommendation.
- Please refer to corresponding sections for more detailed information about genomic alteration and clinical relevance listed above.

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## TESTING RESULTS

### VARIANT(S) WITH CLINICAL RELEVANCE

#### - Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
ARID1A	S964fs	25.3%
B2M	L15fs	19.1%
CTCF	E464*	21.7%
FBXW7	R479Q	17.0%
KRAS	G13C	18.2%
PIK3CA	C420R	25.9%
POLD1	Splice acceptor	17.5%
PRKDC	Splice donor	6.7%
SDHB	R90*	17.6%

#### - Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Not detected			

#### - 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)	44.6 muts/Mb (TMB-High)
Microsatellite Instability (MSI)	Pending

#### 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 30% tumor purity.
- 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  $\geq 7.5$  mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is  $< 30\%$ .

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## SUPPLEMENTARY INFORMATION FOR THERAPEUTIC IMPLICATIONS TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
<b>Level 3A</b>		
<b>PIK3CA</b> C420R	Alpelisib, Capivasertib, Everolimus	<b>sensitive</b>
<b>SDHB</b> R90*	Pazopanib, Regorafenib, Sunitinib	<b>sensitive</b>
<b>KRAS</b> G13C	Cetuximab, Panitumumab	<b>resistant</b>
<b>Level 3B</b>		
<b>PIK3CA</b> C420R	Temsirolimus	<b>sensitive</b>
<b>ARID1A</b> S964fs	Olaparib	<b>sensitive</b>
<b>Level 4</b>		
<b>FBXW7</b> R479Q	Everolimus, Temsirolimus	<b>sensitive</b>
<b>ARID1A</b> S964fs	Dasatinib, Rucaparib, Talazoparib	<b>sensitive</b>
<b>FBXW7</b> R479Q	Gefitinib, Regorafenib	<b>resistant</b>

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

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## IMMUNE CHECKPOINT INHIBITORS (ICIs)

Genomic Alterations	Approved for Patient's Cancer Type	Approved for Other Cancer Type
<b>TMB-High</b> (44.6 muts/Mb)	Dostarlimab-gxly, Pembrolizumab	Atezolizumab, Avelumab, Cemiplimab-rwlc, Durvalumab, Ipilimumab, Nivolumab, Toripalimab-tpzi, Tremelimumab

TMB, Tumor Mutational Burden; Muts/Mb, mutations per megabase

## - 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
<b>ARID1A</b> S964fs	Platinum-based regimens	<b>Less sensitive</b>	Clinical	Ovarian cancer

## HORMONAL THERAPIES

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

## OTHERS

### Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AA	Irinotecan-based regimens	Level 1B
<b>Clinical Interpretation:</b> Patients with the AA genotype and cancer who are treated with irinotecan-based regimens may have an increased risk of diarrhea and neutropenia as compared to patients with the AG or GG genotype. Other genetic and clinical factors may also influence a patient's risk of diarrhea and neutropenia.				

\* Level of evidence was defined by PharmGKB (<https://www.pharmgkb.org/page/clinAnnLevels>)

**Level 1A:** Clinical annotations describe variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation.

**Level 1B:** Clinical annotations describe variant-drug combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label.

**Level 2A:** Variants in Level 2A clinical annotations are found in PharmGKB's Tier 1 Very Important Pharmacogenes (VIPs). These variants are in known pharmacogenes, implying causation of drug phenotype is more likely.

#### Note:

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

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## VARIANT INTERPRETATION

### Tumor mutational burden (TMB): High (44.6 mutations / Mb)

High TMB is a potential biomarker that predicts response to immune checkpoint inhibitors, including anti-CTLA-4 and anti-PD-1 in melanoma, anti-PD-1 in non-small cell lung cancer (NSCLC) and colorectal cancer (CRC), cutaneous squamous cell carcinoma (CSCC), and anti-PD-L1 therapy in bladder cancer<sup>[1][2][3][3][4][5][6][7][8]</sup>. Of note, the U.S. FDA has approved tumor mutational burden-high (TMB-H) as a predictive biomarker for pembrolizumab in adult and pediatric patients with unresectable or metastatic solid tumor who have progressed following prior treatment and have no satisfactory alternative treatment options. CRCs with defects in mismatch-repair (MMR) are more susceptible to PD-1 blockade<sup>[6]</sup>. High mutation load is associated with shorter overall survival in lung cancer and breast cancer patients<sup>[9][10]</sup>.

### ARID1A S964fs

#### 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<sup>[11][12]</sup>. Haploinsufficiency of ARID1A is associated with tumor formation in some cancers<sup>[13]</sup>. Inactivation of ARID1A is commonly observed in ovarian, endometrial, uterine, and, gastric cancers<sup>[14][15][16][17][18]</sup>.

S964fs mutation results in a change in the amino acid sequence beginning at 964, 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<sup>[19][20]</sup>; 2) AKT-inhibitors MK-2206 and perifosine, as well as PI3K-inhibitor buparlisib<sup>[21]</sup>; 3) multiple kinase inhibitor, dasatinib<sup>[22]</sup>.

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<sup>[23]</sup>. 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<sup>[24][25]</sup>.

Low expression of ARID1A is a significant and independent prognostic factor for poor disease-free and overall survival in breast cancer patients<sup>[26][27]</sup>. Besides, loss of ARID1A expression was more frequently seen in mismatch repair (MMR)-deficient colorectal cancers, predominantly in tumor with MLH1 promoter hypermethylation<sup>[28]</sup>. Positive ARID1A expression could independently predict worse overall survival in stage IV CRC patients compared with negative ARID1A expression<sup>[29]</sup>.

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<sup>[30]</sup>.

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## B2M L15fs

### Biological Impact

The Beta-2-Microglobulin (B2M) gene encodes a component of MHC class I molecules, which is required for HLA class I folding and transport cell surface expressing protein<sup>[31]</sup>. Mutations of B2M could lead to loss of HLA class I antigen expression and lack of CD8 T cell recognition. B2M also acts as a growth factor and signaling molecule implicated in breast cancer and leukemia<sup>[32][33][34]</sup>.

L15fs mutation results in a change in the amino acid sequence beginning at 15, likely to cause premature truncation of the functional B2M protein (UniProtKB). This mutation is predicted to lead to a loss of B2M protein function, despite not being characterized in the literature.

### Therapeutic and prognostic relevance

Several studies found evidence and proposed that melanoma patients who initially responded to immunotherapies might have developed acquired resistance through the loss of B2M<sup>[35][36][37]</sup>. Later, similar phenomena occurred in other types of cancer like colorectal cancer and lung cancer<sup>[38][39]</sup>. However, a retrospective study has demonstrated that most immunotherapy-naïve patients with B2M-mutant or deficient MSI-H CRC obtain clinical benefit from ICI treatment<sup>[40]</sup>.

## CTCF E464\*

### Biological Impact

CCCTC-binding factor (CTCF) is a transcription factor and has been reported to active or repress gene transcription by different cofactors<sup>[41][42]</sup>. CTCF mutation usually caused truncated protein and mainly found in carcinomas of the endometrium, digestive tract and breast<sup>[43][44][45]</sup>. CTCF haploinsufficiency has been demonstrated to alter gene methylation pattern and predispose mice to a range of cancers<sup>[46]</sup>.

E464\* mutation results in a premature truncation of the CTCF protein at amino acid 464 (UniProtKB). This mutation is predicted to lead to a loss of CTCF function, despite not having been characterized in the literature.

### Therapeutic and prognostic relevance

Reduction of CTCF copy number was associated with poor survival in endometrial cancer<sup>[46][47]</sup>.

## FBXW7 R479Q

### 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<sup>[48][49]</sup>, c-Jun<sup>[50]</sup>, cyclin E<sup>[51]</sup>, Notch family members<sup>[52][53]</sup>, Aurora-A<sup>[54]</sup>, mTOR<sup>[55]</sup>, KLF5<sup>[56]</sup>, and MCL-1<sup>[57]</sup>. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation<sup>[58]</sup>. 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<sup>[56][57][59]</sup>.

FBXW7 R479Q is a missense mutation lies within the WD repeat 3 of the FBW7 protein (UniProtKB). FBW7 R479Q was demonstrated as a loss-of-function mutant which is defective in NOTCH binding, leading to the stabilization of NOTCH1 and MYC proteins and contribute to the transformation in leukemias<sup>[60]</sup>.



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## 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)<sup>[61][62]</sup>. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor<sup>[55]</sup>.

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<sup>[63][64][65][66]</sup>.

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<sup>[67][65]</sup>.

A retrospective study showed that patients with colorectal cancer and harbored FBXW7 hotspot mutations like R465H, R465C, and R479Q have higher 5-year overall survival rate when compared with patients carrying other FBXW7 mutant types<sup>[68]</sup>.

## KRAS G13C

### 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<sup>[69]</sup>. KRAS mutations occur primarily in three hotspots G12, G13 and Q61, and less frequently in codon A146<sup>[69][70]</sup>. These are activating mutations that lead to constitutive activation and persistent stimulation of the downstream signaling pathways<sup>[71][72]</sup>. Mutations in KRAS have been reported in a diverse spectrum of human malignancies, including pancreatic carcinomas (>80%)<sup>[69][73]</sup>, colon carcinomas (40-50%)<sup>[74][75]</sup>, and lung carcinomas (30-50%)<sup>[76][77]</sup>, but are also present in biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer, liver cancer, myeloid leukemia and breast cancer<sup>[70]</sup>.

KRAS G13C is a hotspot mutation lies within the GTP-binding region of the KRAS protein (UniProtKB). G13C mutation results in decreased KRAS GTPase activity and activation of downstream signaling in vitro<sup>[78][79]</sup>.

## Therapeutic and prognostic relevance

Cetuximab and panitumumab are FDA-approved for treating RAS wild-type metastatic colorectal cancer. The NCCN for CRC recommends that patients with any known KRAS or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab.

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).

KRAS mutations are associated with a lack of efficacy of EGFR TKIs<sup>[80][81][82]</sup>. Some case reports suggest that MEK inhibitors may benefit patients with KRAS mutations, as shown in cervical and ovarian cancer cases (Am J Clin Exp Obstet Gynecol 2015;2(3):140-143)<sup>[83][84]</sup>. However, a randomized Phase II study did not find trametinib to be superior to docetaxel in KRAS-mutant non-small cell lung cancer patients<sup>[85]</sup>. MEK inhibitors as a monotherapy have limited response<sup>[86]</sup>.

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Combining MEK and mTOR inhibitors is being evaluated as a potential strategy in RAS-mutant CRC<sup>[87][88]</sup>. The combination of trametinib and palbociclib has resulted in objective responses in KRAS mutant models<sup>[89]</sup>.

Sorafenib has been shown to be beneficial in KRAS-mutant CRC/NSCLC, and KRAS-amplified melanoma<sup>[90][91][92]</sup>. KRAS mutations in exon 2 (codon 12 or 13) and codon 61 have been associated with poor prognosis in CRC<sup>[93]</sup>.

Patients with KRAS or BRAF mutations in low-grade serous carcinoma of the ovary or peritoneum had better overall survival than those with wild-type genes<sup>[94]</sup>. In ovarian serous borderline tumor, KRAS G12V mutation was linked to shorter survival time<sup>[95]</sup>.

## **PIK3CA C420R**

### **Biological Impact**

The PIK3CA gene encodes the catalytic subunit (p110α) of phosphatidylinositol 3-kinase (PI3K) that plays a key role in the PI3K/AKT signaling pathway and is involved in the regulation of cellular functions such as proliferation, metabolism and protein synthesis, angiogenesis and apoptosis. PIK3CA has long been described as an oncogene and the PIK3CA gene amplification, deletion, and mutations have been reported in a wide range of cancers, including colorectal, breast, brain, liver, ovarian, stomach and lung cancers<sup>[96][97][98][99]</sup>. Mutations located in the exon 9 that encodes the PI3K helical (like E542K, E545K) and the exon 20 that encodes the catalytic/kinase domain (like H1047R, H1047L, H1047Y) have been shown to result in the constitutively activated mutant, which could enhance downstream signaling and oncogenic transformation in vitro and in vivo<sup>[97][100][101][102]</sup>.

PIK3CA C420R is located in the C2 domain of the PIK3CA protein<sup>[103]</sup>. This is a gain-of-function mutation which had been shown to lead to constitutive phosphorylation of the downstream targets AKT and S6, increased cell proliferation, migration, and cell transformation in vitro<sup>[103][104][105]</sup>.

### **Therapeutic and prognostic relevance**

Alpelisib in combination with fulvestrant is FDA-approved for treating HR+, HER2-, PIK3CA-mutated, advanced breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. FDA also approved capivasertib with fulvestrant for HR+, HER2-, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

In NCCN guidelines for breast cancer, alpelisib plus fulvestrant has been recommended for HR-positive/HER2-negative breast cancer patients with PIK3CA activating mutation. Also, the NCCN guidelines for histiocytic neoplasms has recommended everolimus for patients with PIK3CA mutation.

PIK3CA mutation has been determined as an inclusion criterion for the trials evaluating everolimus, temsirolimus, and alpelisib efficacies in various types of solid tumors (NCT03805399, NCT03203525, NCT04251533).

Everolimus has shown clinical benefit when added to trastuzumab for patients with HER2-overexpressing metastatic breast cancer, particularly in those with PIK3CA mutations, PTEN loss, or hyperactive PI3K pathway<sup>[106]</sup>. The addition of everolimus to trastuzumab plus vinorelbine has also prolonged PFS in patients with trastuzumab-resistant and taxane-pretreated, HER2-positive, advanced breast cancer. However, adverse events should be taken into consideration<sup>[107]</sup>. Patients with PIK3CA mutations have shown a favorable response to mTOR inhibitors-containing monotherapy or in combination with doxorubicin and bevacizumab. Combining PI3K-targeted agents with endocrine therapy is suggested<sup>[108][109][110][111]</sup>.



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Hyperactivation of the PI3K signaling pathway is associated with resistance to endocrine and HER2-targeting therapies in advanced breast cancer patients<sup>[112][113][114][115]</sup>. PIK3CA mutations also occur in 5% of EGFR-mutated lung cancers that developed resistance to EGFR TKI therapy<sup>[116][117]</sup>.

In CRC patients, PIK3CA mutation and wild-type KRAS/BRAF showed fair responses to anti-EGFR therapies<sup>[118]</sup>. PIK3CA mutations are significantly correlated with better recurrence-free survival in unsorted breast cancer patients, according to two meta-analyses involving five studies<sup>[119][120][121]</sup>. However, in patients with advanced EGFR- or KRAS-mutant lung adenocarcinoma, a concurrent PIK3CA mutation is a poor prognostic factor<sup>[122]</sup>.

## POLD1 Splice acceptor

### Biological Impact

DNA polymerase delta 1 (POLD1) encodes the catalytic subunit of DNA polymerase delta, which contains both polymerase and exonuclease activity<sup>[123]</sup>. POLD1 is involved in DNA synthesis of the lagging strand during DNA replication, proofreading activity during polymerization, and DNA repair<sup>[124][125][126]</sup>. Functional studies have demonstrated that reduced expression of POLD1 was associated with genomic instability and a high frequency of chromosomal aberrations<sup>[127][128]</sup>. Germline loss-of-function mutations in the proofreading domains of POLD1 and POLE were reported to predispose oligo-adenomatous polyposis, early-onset colorectal cancer, endometrial cancer, breast cancer, and brain tumors<sup>[129]</sup>.

POLD1 c.3121-1G>T is a variant located at the splice acceptor region, which may result in the exon skipping.

### Therapeutic and prognostic relevance

In a study of pembrolizumab in non-small cell lung carcinoma, loss-of-function mutation in POLD1 gene and nonsense mutation in BRCA2 or deleterious mutation in MSH2 were detected in two patients with high tumor mutation burden, respectively. One of whom had a partial response, and the other had stable disease after pembrolizumab treatment, and both of them had progression-free survival for eight months<sup>[5]</sup>. POLD1 has been selected as an inclusion criterion for the trial examining niraparib in any malignancy, except prostate (NCT03207347).

## PRKDC Splice donor

### Biological Impact

PRKDC (Protein Kinase, DNA-Activated, Catalytic Polypeptide) gene encodes a catalytic subunit of DNA-dependent protein kinase which plays essential roles in DNA double-strand break repair and recombination<sup>[130][131]</sup>. Furthermore, PRKDC also participates in cell cycle regulation<sup>[132]</sup>. PRKDC mutations are frequently detected in bladder cancer, colorectal cancer, lung cancer, and endometrial cancer<sup>[133]</sup>. Up-regulation of PRKDC has been reported in colorectal cancer<sup>[134]</sup>, nasopharyngeal cancer<sup>[135]</sup>, and breast cancer<sup>[136]</sup>.

PRKDC c.966+2T>C is a variant located at the splice donor region, which may result in the exon skipping.

### Therapeutic and prognostic relevance

PRKDC mutation is significantly associated with high mutation load in a variety of cancer types. Loss-of-function mutations of PRKDC have been observed in gastric cancer, lung cancer and melanoma patients who responded to immunologic checkpoint inhibitors ([ascopubs.org/doi/abs/10.1200/JCO.2017.35.15\\_suppl.3022](https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.3022)). PRKDC has been selected as an inclusion criterion for the trial examining niraparib in any malignancy (except prostate) (NCT03207347).

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## SDHB R90\*

### Biological Impact

Succinate dehydrogenase complex, subunit B (SDHB) encodes a catalytic subunit of SDH localized in the inner mitochondrial membrane<sup>[137]</sup>. It is involved in catalyzing the oxidation of succinate to fumarate in the tricarboxylic acid (TCA) cycle and is coupled with the reduction of ubiquinone in the electron transport chain for ATP production<sup>[138]</sup>. Functional inactivation of the SDH complex, including loss-of-function mutations in the SDH gene subunits or loss of SDHB protein expression, were identified in a majority of the gastrointestinal stromal tumors (GISTs) lacking KIT and PDGFRA mutations. Germline mutations in SDHB are associated with hereditary paraganglioma/pheochromocytoma, renal clear cell carcinoma and gastrointestinal stromal tumors (GISTs)<sup>[139][140][141]</sup>.

R90\* mutation results in a premature truncation of the SDHB protein at amino acid 90 (UniProtKB). This mutation is predicted to lead to a loss of SDHB function, despite not having been characterized in the literature.

### Therapeutic and prognostic relevance

In NCCN guidelines for GIST, imatinib is not indicated for use in patients with SDH-deficient GISTs. The guidelines recommend consideration of sunitinib, regorafenib, and pazopanib as options for unresectable SDH-deficient GISTs<sup>[142]</sup>.

In a retrospective study, 7 of 38 patients with SDH-deficient GISTs had an objective response (1 complete, 3 partial, and 3 mixed responses) by sunitinib treatment<sup>[143]</sup>. In another retrospective study, 4 patients with SDH-deficient GISTs had disease progression during imatinib treatment, but all 4 patients regained disease control with PFS of 26 months, 11 months, RFS of 24 months, and 9 months when the treatment was changed to sunitinib, respectively<sup>[144]</sup>.

In a phase II study (NCT01068769), all 6 patients with SDH-deficient GISTs benefited from regorafenib treatment, the clinical benefit rate was 100%, and the mPFS was 10 months<sup>[145]</sup>. In another phase II study, a SDH-deficient GIST patient had a partial response by pazopanib treatment<sup>[146]</sup>.

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## US FDA-APPROVED DRUG(S)

### Alpelisib (PIQRAY)

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3K $\alpha$ . Gain-of-function mutations in the gene encoding the catalytic  $\alpha$ -subunit of PI3K (PIK3CA) lead to activation of PI3K $\alpha$  and Akt-signaling, cellular transformation and the generation of tumors in vitro and in vivo models. Alpelisib is developed and marketed by Novartis under the trade name PIQRAY.

### - FDA Approval Summary of Alpelisib (PIQRAY)

<b>SOLAR-1</b> <sup>[147]</sup> NCT02437318	<b>Hr-positive, her2-negative breast cancer</b> (Approved on 2019/05/24)
	<b>PIK3CA mutation</b>
	Alpelisib plus fulvestrant vs. Placebo plus fulvestrant [PFS(M): 11 vs. 5.7]

### Atezolizumab (TECENTRIQ)

Atezolizumab is a humanized, anti-programmed cell death-ligand 1 (PD-L1) monoclonal antibody of the IgG1 isotype, which can lead to the reactivation of immune cells that might recognize and attack tumor cells. Atezolizumab is developed and marketed by Genentech/Roche under the trade name TECENTRIQ.

### - FDA Approval Summary of Atezolizumab (TECENTRIQ)

<b>ML39345</b> NCT03141684	<b>Alveolar soft part sarcoma</b> (Approved on 2022/12/09)
	-
	Atezolizumab [ORR(%): 24.0]
<b>IMpower010</b> NCT02486718	<b>Non-small cell lung carcinoma</b> (Approved on 2021/10/15)
	<b>PD-L1</b>
	Atezolizumab vs. Best supportive care (bsc) [DFS (PD-L1 TC $\geq$ 1%)(M): not reached vs. 35.3]
<b>IMspire150</b> NCT02908672	<b>Melanoma</b> (Approved on 2020/07/30)
	<b>BRAF V600 mutation</b>
	Atezolizumab + cobimetinib + vemurafenib vs. Placebo + cobimetinib + vemurafenib [PFS(M): 15.1 vs. 10.6]
<b>IMbrave150</b> NCT03434379	<b>Hepatocellular carcinoma</b> (Approved on 2020/05/29)
	-
	Atezolizumab plus bevacizumab vs. Sorafenib [PFS(M): 6.8 vs. 4.3, OS(M): NR vs. 13.2]
<b>IMpower133</b> <sup>[148]</sup> NCT02763579	<b>Small cell lung cancer</b> (Approved on 2019/03/18)
	-
	Atezolizumab plus carboplatin and etoposide vs. Carboplatin and etoposide [PFS(M): 5.2 vs. 4.3, OS(M): 12.3 vs. 10.3]
<b>OAK</b> <sup>[149]</sup> NCT02008227	<b>Non-small cell lung carcinoma</b> (Approved on 2016/10/18)
	<b>PD-L1</b>
	Atezolizumab vs. Docetaxel [OS(M): 13.8 vs. 9.6]
<b>POPLAR</b> <sup>[150]</sup> NCT01903993	<b>Non-small cell lung carcinoma</b> (Approved on 2016/10/18)
	<b>PD-L1</b>
	Atezolizumab vs. Docetaxel [OS(M): 12.6 vs. 9.7]

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## Avelumab (BAVENCIO)

Avelumab is fully human monoclonal programmed death ligand-1 (PD-L1) antibody, belonging to the group of immune checkpoint blockade cancer therapies. Avelumab is developed and marketed by Merck KGaA and Pfizer under the trade name BAVENCIO.

### - FDA Approval Summary of Avelumab (BAVENCIO)

<b>JAVELIN Renal 101</b> <sup>[151]</sup> NCT02684006	<b>Renal cell carcinoma</b> (Approved on 2019/05/14)
	- Avelumab plus axitinib vs. Sunitinib [ORR(%): 51.4 vs. 25.7, PFS(M): 13.8 vs. 8.4]
<b>JAVELIN Solid Tumor</b> NCT01772004	<b>Bladder urothelial carcinoma</b> (Approved on 2017/05/09)
	- Avelumab [ORR(13W)(%): 13.6, ORR(6M)(%): 16.1]
<b>JAVELIN Merkel 200</b> <sup>[152]</sup> NCT02155647	<b>Merkel cell carcinoma</b> (Approved on 2017/03/23)
	- Avelumab [ORR(%): 33.0, DOR(M): 2.8 to 23.3+]

## Capivasertib (TRUQAP)

Capivasertib is developed and marketed by AstraZeneca Pharmaceuticals under the trade name TRUQAP.

### - FDA Approval Summary of Capivasertib (TRUQAP)

<b>CAPitello-291</b> NCT04305496	<b>Her2-receptor negative breast cancer</b> (Approved on 2023/11/16)
	<b>PIK3CA/AKT1/PTEN-alterations</b> Capivasertib + fulvestrant vs. Placebo + fulvestrant [investigator-assessed PFS(M): 7.3 vs. 3.1]

## Cemiplimab-rwlc (LIBTAYO)

Cemiplimab-rwlc is a recombinant human IgG4 monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2. Cemiplimab-rwlc is developed and marketed by Sanofi and Regeneron under the trade name LIBTAYO.

### - FDA Approval Summary of Cemiplimab-rwlc (LIBTAYO)

<b>Study 16113</b> NCT03409614	<b>Lung non-small cell carcinoma</b> (Approved on 2022/11/08)
	- Platinum-based chemotherapy [OS(M): 21.9 vs. 13.0]
<b>Study 1624</b> NCT03088540	<b>Non-small lung cancer</b> (Approved on 2021/02/22)
	<b>PD-L1</b> Cemiplimab-rwlc vs. Platinum-based chemotherapy [PFS(M): 6.2 vs. 5.6, OS(M): 22.1 vs. 14.3]
<b>Study 1620</b> NCT03132636	<b>Locally advanced basal cell carcinoma (labcc)</b> (Approved on 2021/02/09)
	- Cemiplimab-rwlc [ORR(%): 29.0, DOR(M): NR]
<b>Study 1620</b> NCT03132636	<b>Metastatic basal cell carcinoma (mbcc)</b> (Approved on 2021/02/09)
	- Cemiplimab-rwlc [ORR(%): 21.0, DOR(M): NR]

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Study 1423, Study 1540 <sup>[7]</sup> NCT02383212, NCT02760498	cutaneous squamous cell carcinoma (Approved on 2018/09/28)
	-
	Cemiplimab-rwlc [ORR(%): 47.2]

## 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 <sup>[153]</sup> NCT00481247	Chronic myeloid leukemia (Approved on 2010/10/28)
	-
	Dasatinib vs. Imatinib [ORR(%): 76.8 vs. 66.2]
<sup>[154]</sup> NCT00123474	Chronic myeloid leukemia (Approved on 2007/11/08)
	-
	Dasatinib [ORR(%): 63.0]
<sup>[155]</sup> NCT00123487	Acute lymphocytic leukemia (Approved on 2006/06/28)
	-
	Dasatinib [ORR(%): 38.0]

## Dostarlimab-gxly (JEMPERLI)

Dostarlimab-gxly is a programmed death receptor-1 (PD-1)-blocking antibody. Dostarlimab-gxly is developed and marketed by GlaxoSmithKline LLC under the trade name JEMPERLI.

### - FDA Approval Summary of Dostarlimab-gxly (JEMPERLI)

RUBY NCT03981796	Endometrial carcinoma (Approved on 2023/07/31)
	dMMR/MSI-H
	Dostarlimab-gxly with carboplatin and paclitaxel, followed by dostarlimab-gxly vs. Placebo with carboplatin and paclitaxel, followed by placebo [mPFS(M): 30.3 vs. 7.7]
GARNET NCT02715284	Cancer (Approved on 2021/08/17)
	dMMR
	Dostarlimab [ORR(%): 41.6, DoR(M): 34.7]
GARNET (Cohort A) NCT02715284	Endometrial carcinoma (Approved on 2021/04/22)
	dMMR
	Dostarlimab-gxly [ORR(%): 42.3, DOR(M): NR]



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## Durvalumab (IMFINZI)

Durvalumab is a programmed death ligand-1 (PD-L1)-blocking antibody. Durvalumab is developed and marketed by AstraZeneca under the trade name IMFINZI.

### - FDA Approval Summary of Durvalumab (IMFINZI)

<b>HIMALAYA</b> NCT03298451	<b>Hepatocellular carcinoma</b> (Approved on 2022/10/21)
	- Durvalumab + tremelimumab vs. Durvalumab + sorafenib [OS(M): 16.4 vs. 13.9]
<b>TOPAZ-1</b> NCT03875235	<b>Biliary tract cancer</b> (Approved on 2022/09/02)
	- Durvalumab [OS(M): 12.8 vs. 11.5]
<b>CASPIAN</b> <sup>[156]</sup> NCT03043872	<b>Extensive-stage small cell lung cancer</b> (Approved on 2020/03/27)
	- Durvalumab + etoposide + carboplatin or durvalumab + etoposide + cisplatin vs. Etoposide + carboplatin or etoposide + cisplatin [OS(M): 13 vs. 10.3]
<b>PACIFIC</b> <sup>[157]</sup> NCT02125461	<b>Non-small cell lung carcinoma</b> (Approved on 2018/02/16)
	- Durvalumab vs. Placebo [PFS(M): 16.8 vs. 5.6]

## 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)

<b>RADIANT-4</b> <sup>[158]</sup> NCT01524783	<b>Lung or gastrointestinal neuroendocrine tumor</b> (Approved on 2016/02/26)
	- Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
<b>BOLERO-2</b> <sup>[159]</sup> NCT00863655	<b>Breast cancer</b> (Approved on 2012/07/20)
	<b>ER+/HER2-</b> Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
<b>EXIST-2</b> NCT00790400	<b>Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma</b> (Approved on 2012/04/26)
	- Everolimus vs. Placebo [ORR(%): 41.8 vs. 0]
<b>RADIANT-3</b> <sup>[160]</sup> NCT00510068	<b>Pancreatic neuroendocrine tumor</b> (Approved on 2011/05/05)
	- Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
<b>EXIST-1</b> <sup>[161]</sup> NCT00789828	<b>Subependymal giant cell astrocytoma</b> (Approved on 2010/10/29)
	- Everolimus vs. Placebo [ORR(%): 35.0]
<b>RECORD-1</b> <sup>[162]</sup> NCT00410124	<b>Renal cell carcinoma</b> (Approved on 2009/05/30)
	- Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

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## Ipilimumab (YERVOY)

Ipilimumab is a fully human monoclonal antibody against the cytotoxic T-lymphocyte associated protein 4 (CTLA-4), an immune checkpoint protein receptor, to reactivate the immune responses. Ipilimumab is developed by Medarex and Bristol-Myers Squibb, and marketed by the latter under the trade name YERVOY.

### - FDA Approval Summary of Ipilimumab (YERVOY)

<b>CHECKMATE-648</b> NCT03143153	<b>Esophagus squamous cell carcinoma</b> (Approved on 2022/05/27)
	- Nivolumab and ipilimumab vs. Chemotherapy [OS(M): 12.8 vs. 10.7]
<b>CHECKMATE-743</b> NCT02899299	<b>Pleural mesothelioma</b> (Approved on 2020/10/02)
	- Nivolumab + ipilimumab vs. Pemetrexed + cisplatin [OS(M): 18.1 vs. 14.1]
<b>CHECKMATE-9LA</b> NCT03215706	<b>Non-small cell lung carcinoma</b> (Approved on 2020/05/26)
	- Nivolumab + ipilimumab + platinum-doublet chemotherapy vs. Platinum-doublet chemotherapy [OS(M): 14.1 vs. 10.7]
<b>CHECKMATE-227</b> NCT02477826	<b>Non-small cell lung carcinoma</b> (Approved on 2020/05/15)
	<b>PD-L1</b> Nivolumab + ipilimumab vs. Platinum-doublet chemotherapy [OS(M): 17.1 vs. 14.9]
<b>CHECKMATE-040</b> NCT01658878	<b>Hepatocellular carcinoma</b> (Approved on 2020/03/10)
	- Nivolumab + ipilimumab [ORR(%): 33.0]
<b>CHECKMATE-142</b> <sup>[163]</sup> NCT02060188	<b>Colorectal cancer</b> (Approved on 2018/07/10)
	<b>MSI-H or dMMR</b> Ipilimumab plus nivolumab vs. Nivolumab [ORR(%): 49.0 vs. 32.0]
<b>CHECKMATE-214</b> <sup>[164]</sup> NCT02231749	<b>Renal cell carcinoma</b> (Approved on 2018/04/16)
	- Nivolumab plus ipilimumab vs. Sunitinib [OS(M): 67.1 vs. 55.5]
<b>EORTC 18071</b> <sup>[165]</sup> NCT00636168	<b>Melanoma</b> (Approved on 2015/10/28)
	- Ipilimumab vs. Placebo [RFS(M): 26 vs. 17]
<b>MDX010-20</b> <sup>[166]</sup> NCT00094653	<b>Melanoma</b> (Approved on 2011/03/25)
	- Ipilimumab vs. Peptide vaccine with incomplete freund's adjuvant (gp100) [OS(M): 10 vs. 6]

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## Nivolumab (OPDIVO)

Nivolumab is a programmed death receptor-1 (PD-1)-blocking antibody. Nivolumab is developed and marketed by Bristol-Myers Squibb under the trade name OPDIVO.

### - FDA Approval Summary of Nivolumab (OPDIVO)

<b>CheckMate 76K</b> NCT04099251	<b>Melanoma</b> (Approved on 2023/10/13)
	- Nivolumab vs. Placebo [RFS(M): NR (95% CI: 28.5, NR) vs. NR (95% CI: 21.6, NR)]
<b>CHECKMATE-648</b> NCT03143153	<b>Esophagus squamous cell carcinoma</b> (Approved on 2022/05/27)
	- Nivolumab and ipilimumab vs. Chemotherapy [OS(M): 12.8 vs. 10.7]
<b>CHECKMATE-648</b> NCT03143153	<b>Esophagus squamous cell carcinoma</b> (Approved on 2022/05/27)
	- Nivolumab, fluorouracil, and cisplatin vs. Chemotherapy [OS(M): 13.2 vs. 10.7]
<b>CHECKMATE-816</b> NCT02998528	<b>Non-small cell lung cancer (nscic)</b> (Approved on 2022/03/04)
	- Nivolumab plus platinum-doublet chemotherapy vs. Platinum-chemotherapy [EFS(M): 31.6 vs. 20.8]
<b>CHECKMATE-274</b> NCT02632409	<b>Bladder urothelial carcinoma</b> (Approved on 2021/08/19)
	- Nivolumab [DFS (all randomized)(M): 20.8 vs. 10.8, DFS (PD-L1 ≥ 1%)(M): NR vs. 8.4]
<b>CHECKMATE-577</b> NCT02743494	<b>Gastroesophageal junction adenocarcinoma</b> (Approved on 2021/05/20)
	- Nivolumab vs. Placebo every 4 weeks beginning at week 17 for up to one year of treatment [DFS(M): 22.4 vs. 11]
<b>CHECKMATE-649</b> NCT02872116	<b>Gastroesophageal junction adenocarcinoma, Gastric adenocarcinoma</b> (Approved on 2021/04/16)
	- Nivolumab + chemotherapy (xelox or folfox) vs. Chemotherapy (xelox or folfox) [PFS(M): 7.7 vs. 6, OS(M): 14.4 vs. 11.1]
<b>CHECKMATE-9ER</b> NCT03141177	<b>Renal cell carcinoma</b> (Approved on 2021/01/22)
	- Nivolumab + cabozantinib vs. Sunitinib [ORR(%): 55.7 vs. 27.1, PFS(M): 16.6 vs. 8.3, OS(M): NR vs. NR]
<b>CHECKMATE-743</b> NCT02899299	<b>Pleural mesothelioma</b> (Approved on 2020/10/02)
	- Nivolumab + ipilimumab vs. Pemetrexed + cisplatin [OS(M): 18.1 vs. 14.1]
<b>CHECKMATE-9LA</b> NCT03215706	<b>Non-small cell lung carcinoma</b> (Approved on 2020/05/26)
	- Nivolumab + ipilimumab + platinum-doublet chemotherapy vs. Platinum-doublet chemotherapy [OS(M): 14.1 vs. 10.7]
<b>CHECKMATE-227</b> NCT02477826	<b>Non-small cell lung carcinoma</b> (Approved on 2020/05/15)
	<b>PD-L1</b> Nivolumab + ipilimumab vs. Platinum-doublet chemotherapy [OS(M): 17.1 vs. 14.9]

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<b>CheckMate 040</b> NCT01658878	<b>Hepatocellular carcinoma</b> (Approved on 2020/03/10)
	-
<b>CheckMate 142</b> NCT02060188	<b>Colorectal cancer</b> (Approved on 2017/07/31)
	<b>MSI-H or dMMR</b>
<b>CheckMate 141</b> <sup>[167]</sup> NCT02105636	<b>Squamous cell carcinoma of the head and neck cancer</b> (Approved on 2016/11/10)
	-
<b>CheckMate 205</b> <sup>[168]</sup> NCT02181738	<b>Hodgkin's lymphoma</b> (Approved on 2016/05/17)
	-
<b>CheckMate 039</b> <sup>[169]</sup> NCT01592370	<b>Hodgkin's lymphoma</b> (Approved on 2016/05/17)
	-
<b>CheckMate 067</b> <sup>[170]</sup> NCT01844505	<b>Melanoma</b> (Approved on 2016/01/23)
	-
<b>CheckMate 066</b> <sup>[171]</sup> NCT01721772	<b>Melanoma</b> (Approved on 2015/11/24)
	<b>BRAF V600 wild-type</b>
<b>CheckMate 025</b> <sup>[172]</sup> NCT01668784	<b>Renal cell carcinoma</b> (Approved on 2015/11/23)
	-
<b>CheckMate 057</b> <sup>[173]</sup> NCT01673867	<b>Non-small cell lung carcinoma</b> (Approved on 2015/10/09)
	-
<b>CheckMate 017</b> <sup>[174]</sup> NCT01642004	<b>Non-small cell lung carcinoma</b> (Approved on 2015/03/04)
	-
<b>CheckMate 037</b> <sup>[175]</sup> NCT01721746	<b>Melanoma</b> (Approved on 2014/12/22)
	-
	Nivolumab vs. Dacarbazine or carboplatin + paclitaxel [ORR(%): 32.0]

## 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)

<b>PROpel</b> NCT03732820	<b>Prostate cancer</b> (Approved on 2023/05/31)
	<b>BRCA mutation</b>
	Olaparib + abiraterone + prednisone vs. Placebo + abiraterone + prednisone [rPFS(M): not reached vs. 8]

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<b>OlympiA</b> NCT02032823	<b>Her2-negative high-risk early breast cancer</b> (Approved on 2022/03/11)
	<b>HER2-/gBRCA mutation</b>
	Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M): ]
<b>PROfound</b> <sup>[176]</sup> NCT02987543	<b>Prostate cancer</b> (Approved on 2020/05/19)
	<b>HRR genes mutation</b>
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
<b>PAOLA-1</b> <sup>[177]</sup> NCT02477644	<b>Ovarian cancer</b> (Approved on 2020/05/08)
	<b>HRD+</b>
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
<b>POLO</b> <sup>[178]</sup> NCT02184195	<b>Pancreatic adenocarcinoma</b> (Approved on 2019/12/27)
	<b>gBRCA mutation</b>
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
<b>SOLO-1</b> <sup>[179]</sup> NCT01844986	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2018/12/19)
	<b>gBRCA mutation or sBRCA mutation</b>
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
<b>OlympiAD</b> <sup>[180]</sup> NCT02000622	<b>Breast cancer</b> (Approved on 2018/02/06)
	<b>HER2-/gBRCA mutation</b>
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
<b>SOLO-2/ENGOT-Ov21</b> <sup>[181]</sup> NCT01874353	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2017/08/17)
	<b>gBRCA mutation</b>
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
<b>Study19</b> <sup>[182]</sup> NCT00753545	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

## Pazopanib (VOTRIENT)

Pazopanib is an oral, small molecule, multi-kinase inhibitor that targets receptor tyrosine kinase including vascular endothelial growth factor receptor-1, -2, -3 (VEGFR-1, -2, -3), platelet-derived growth factor receptor- $\alpha$ , - $\beta$  (PDGFR- $\alpha$ , - $\beta$ ), 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)

<b>PALETTE</b> <sup>[183]</sup> NCT00753688	<b>Sarcoma</b> (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]
<b>VEG105192</b> <sup>[184]</sup> NCT00334282	<b>Renal cell carcinoma</b> (Approved on 2009/10/19)
	-
	Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]



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## Pembrolizumab (KEYTRUDA)

Pembrolizumab is a programmed death receptor-1 (PD-1)-blocking antibody. Pembrolizumab is developed and marketed by Merck under the trade name KEYTRUDA.

## - FDA Approval Summary of Pembrolizumab (KEYTRUDA)

<b>KEYNOTE-859</b> NCT03675737	<b>Gastroesophageal junction adenocarcinoma</b> (Approved on 2023/11/16)
	- Pembrolizumab + chemotherapy vs. Placebo + chemotherapy [OS(M): 12.9 vs. 11.5]
<b>KEYNOTE-811</b> NCT03615326	<b>Gastric adenocarcinoma</b> (Approved on 2023/11/07)
	<b>HER2+</b> Pembrolizumab + trastuzumab + chemotherapy vs. Placebo + trastuzumab + chemotherapy [ORR(%): 74.0 vs. 52.0]
<b>KEYNOTE-966</b> NCT04003636	<b>Biliary tract cancer</b> (Approved on 2023/10/31)
	- Pembrolizumab + gemcitabine + cisplatin vs. Placebo + gemcitabine + cisplatin [OS(M): 12.7 vs. 10.9]
<b>KEYNOTE-671</b> NCT03425643	<b>Lung non-small cell carcinoma</b> (Approved on 2023/10/16)
	- Pembrolizumab vs. Placebo [OS(M): NR (95% CI: NR, NR) vs. 52.4 (95% CI: 45.7, NR)]
<b>KEYNOTE-091</b> NCT02504372	<b>Lung non-small cell carcinoma</b> (Approved on 2023/01/26)
	- Pembrolizumab vs. Placebo [DFS(M): 58.7 vs. 34.9]
<b>KEYNOTE-158</b> NCT02628067	<b>Endometrial carcinoma</b> (Approved on 2022/03/21)
	<b>MSI-H or dMMR</b> Pembrolizumab [ORR(%): 46.0, DoR(M): NR]
<b>KEYNOTE-716</b> NCT03553836	<b>Melanoma</b> (Approved on 2021/12/03)
	- Pembrolizumab [RFS(M): Not reached vs. Not reached]
<b>KEYNOTE-564</b> NCT03142334	<b>Renal cell carcinoma</b> (Approved on 2021/11/17)
	- Pembrolizumab vs. Placebo [DFS(M): NR vs. NR, OS(M): NR vs. NR]
<b>KEYNOTE-826</b> NCT03635567	<b>Cervical cancer</b> (Approved on 2021/10/13)
	<b>PD-L1</b> Pembrolizumab + paclitaxel + cisplatin with or without bevacizumab vs. Placebo + paclitaxel + cisplatin with or without bevacizumab [OS (PD-L1, CPS ≥1)(M): Not reached vs. 16.3, PFS(M): 10.4 vs. 8.2]
<b>CLEAR (Study 307/KEYNOTE-581)</b> NCT02811861	<b>renal cell carcinoma</b> (Approved on 2021/08/11)
	- Pembrolizumab + lenvatinib vs. Sunitinib [PFS(M): 23.9 vs. 9.2, OS(M): NR vs. NR, ORR(%): 71.0 vs. 36.0]
<b>KEYNOTE-522</b> NCT03036488	<b>Triple-receptor negative breast cancer</b> (Approved on 2021/07/26)
	- Pembrolizumab + chemotherapy as neoadjuvant treatment vs. Placebo in combination with chemotherapy [pCR(%): 63.0 vs. 56.0, EFS(): 123 vs. 93]

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<b>KEYNOTE-775 (Study 309)</b> NCT03517449	<b>Endometrial carcinoma</b> (Approved on 2021/07/22)
	<b>MSS/pMMR</b> Pembrolizumab + lenvatinib vs. Investigator's choice of doxorubicin or paclitaxel [PFS(M): 6.6 vs. 3.8, OS(M): 17.4 vs. 12]
<b>KEYNOTE-811</b> NCT03615326	<b>Gastroesophageal junction adenocarcinoma</b> (Approved on 2021/05/05)
	<b>HER2+</b> Pembrolizumab 200 mg every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin vs. Placebo every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin [ORR(%): 74.0 vs. 52.0, DOR(M): 10.6 vs. 9.5]
<b>KEYNOTE-590</b> NCT03189719	<b>Esophageal cancer, Gastroesophageal junction adenocarcinoma</b> (Approved on 2021/03/22)
	- Pembrolizumab in combination with cisplatin and fluorouracil vs. Placebo with cisplatin and fluorouracil [PFS(M): 6.3 vs. 5.8, OS(M): 12.4 vs. 9.8]
<b>KEYNOTE-355</b> NCT02819518	<b>Triple-receptor negative breast cancer</b> (Approved on 2020/11/13)
	<b>PD-L1</b> Pembrolizumab + paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin vs. Placebo + paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin [PFS(M): 9.7 vs. 5.6]
<b>KEYNOTE-204</b> NCT02684292	<b>Hodgkin's lymphoma</b> (Approved on 2020/10/14)
	- Pembrolizumab vs. Brentuximab vedotin [PFS(M): 13.2 vs. 8.3]
<b>KEYNOTE-158</b> NCT02628067	<b>Cancer</b> (Approved on 2020/06/17)
	<b>TMB-H</b> Pembrolizumab (tmb-h) vs. Pembrolizumab (non-tmb-h) [ORR(%): 29.0 vs. 6.0]
<b>KEYNOTE-146</b> NCT02501096	<b>Endometrial carcinoma</b> (Approved on 2019/09/17)
	<b>MSS/pMMR</b> Pembrolizumab + lenvatinib [ORR(%): 38.3, DOR(M): NR]
<b>KEYNOTE-426<sup>[185]</sup></b> NCT02853331	<b>Renal cell carcinoma</b> (Approved on 2019/04/19)
	- Pembrolizumab + axitinib vs. Sunitinib [ORR(%): 59.3 vs. 35.7, PFS(M): 15.1 vs. 11.1]
<b>KEYNOTE-017<sup>[186]</sup></b> NCT02267603	<b>Merkel cell carcinoma</b> (Approved on 2018/12/19)
	- Pembrolizumab [ORR(%): 56.0]
<b>KEYNOTE-224<sup>[187]</sup></b> NCT02702414	<b>Hepatocellular carcinoma</b> (Approved on 2018/11/09)
	- Pembrolizumab [ORR(%): 17.0]
<b>KEYNOTE-407<sup>[188]</sup></b> NCT02775435	<b>Squamous non-small cell lung carcinoma</b> (Approved on 2018/10/30)
	- Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. Carboplatin + paclitaxel/nab-paclitaxel [ORR(%): 58.0 vs. 35.0, PFS(M): 6.4 vs. 4.8]
<b>KEYNOTE-189<sup>[188]</sup></b> NCT02578680	<b>Nonsquamous non-small cell lung carcinoma</b> (Approved on 2018/08/20)
	- Pembrolizumab + pemetrexed + platinum vs. Pemetrexed + platinum [PFS(M): 8.8 vs. 4.9, OS(M): NR vs. 11.3]

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<b>KEYNOTE-158</b> NCT02628067	<b>Cervical cancer</b> (Approved on 2018/06/13)
	-
	Pembrolizumab [ORR(%): 14.3]
<b>KEYNOTE-170</b> NCT02576990	<b>Mediastinal large b-cell lymphoma</b> (Approved on 2018/06/13)
	-
	Pembrolizumab [ORR(%): 45.0]
<b>KEYNOTE-059</b> NCT02335411	<b>Gastroesophageal junction adenocarcinoma</b> (Approved on 2017/09/22)
	-
	Pembrolizumab [ORR(%): 13.3]
<b>KEYNOTE-028</b> <sup>[189][190]</sup> NCT02054806	<b>Cancer</b> (Approved on 2017/05/23)
	<b>MSI-H or dMMR</b>
	Pembrolizumab [ORR(%): 39.6]
<b>KEYNOTE-012</b> <sup>[191][192][193][194]</sup> NCT01848834	<b>Cancer</b> (Approved on 2017/05/23)
	<b>MSI-H or dMMR</b>
	Pembrolizumab [ORR(%): 39.6]
<b>KEYNOTE-164</b> NCT02460198	<b>Cancer</b> (Approved on 2017/05/23)
	<b>MSI-H or dMMR</b>
	Pembrolizumab [ORR(%): 39.6]
<b>KEYNOTE-016</b> <sup>[6]</sup> NCT01876511	<b>Cancer</b> (Approved on 2017/05/23)
	<b>MSI-H or dMMR</b>
	Pembrolizumab [ORR(%): 39.6]
<b>KEYNOTE-158</b> NCT02628067	<b>Cancer</b> (Approved on 2017/05/23)
	<b>MSI-H or dMMR</b>
	Pembrolizumab [ORR(%): 39.6]
<b>KEYNOTE-045</b> <sup>[195]</sup> NCT02256436	<b>Urinary bladder urothelial carcinoma</b> (Approved on 2017/05/18)
	-
	Pembrolizumab vs. Chemotherapy [ORR(%): 21.0 vs. 11.0]
<b>KEYNOTE-052</b> NCT02335424	<b>Urinary bladder urothelial carcinoma</b> (Approved on 2017/05/18)
	-
	Pembrolizumab [ORR(%): 29.0]
<b>KEYNOTE-087</b> <sup>[196]</sup> NCT02453594	<b>Hodgkin's lymphoma</b> (Approved on 2017/03/14)
	-
	Pembrolizumab [ORR(%): 69.0]
<b>KEYNOTE-024</b> <sup>[197]</sup> NCT02142738	<b>Non-small cell lung carcinoma</b> (Approved on 2016/10/24)
	<b>PD-L1</b>
	Pembrolizumab vs. Chemotherapy [PFS(M): 10.3 vs. 6]
<b>KEYNOTE-012</b> <sup>[192]</sup> NCT01848834	<b>Head and neck squamous cell carcinoma</b> (Approved on 2016/08/05)
	-
	Pembrolizumab [ORR(%): 16.0]
<b>KEYNOTE-006</b> <sup>[198]</sup> NCT01866319	<b>Melanoma</b> (Approved on 2015/12/18)
	-
	Pembrolizumab vs. Ipilimumab (3mg/kg every 3 weeks) [OS(M): NR vs. 16]
<b>KEYNOTE-010</b> <sup>[199]</sup> NCT01905657	<b>Non-small cell lung carcinoma</b> (Approved on 2015/10/02)
	<b>PD-L1</b>
	Pembrolizumab [OS(M): 10.4 vs. 8.5]

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KEYNOTE-002 <sup>[200]</sup> NCT01704287	Melanoma (Approved on 2014/09/24)
	-
	Pembrolizumab vs. Chemotherapy [PFS(M): 2.9 vs. 2.7]

## 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 <sup>[201]</sup> NCT01774344	Hepatocellular carcinoma, Hepatocellular carcinoma (Approved on 2017/04/27)
	-
	Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]
GRID <sup>[202]</sup> NCT01271712	Gastrointestinal stromal tumor (Approved on 2013/02/25)
	-
	Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]
CORRECT <sup>[203]</sup> NCT01103323	Colorectal cancer (Approved on 2012/09/27)
	-
	Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

## Rucaparib (RUBRACA)

Rucaparib is an inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1, -2 and -3 (PARP-1, -2, -3). Rucaparib is developed and marketed by Clovis Oncology under the trade name RUBRACA.

### - FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	Prostate cancer (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3 <sup>[204]</sup> 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]

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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- $\alpha$ , - $\beta$  (PDGFR- $\alpha$ , - $\beta$ ), 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)

[205][206][207] NCT00428597	<b>Pancreatic cancer</b> (Approved on 2011/05/20)
	-
	Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]
[208][209] NCT00083889	<b>Renal cell carcinoma</b> (Approved on 2007/02/02)
	-
	Sunitinib vs. Ifn- $\alpha$ [PFS(W): 47.3 vs. 22]
[210][211][209] NCT00077974	<b>Renal cell carcinoma</b> (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 34.0]
[211][209] NCT00054886	<b>Renal cell carcinoma</b> (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 36.5]
[212] NCT00075218	<b>Gastrointestinal stromal tumor</b> (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)

<b>TALAPRO-2</b> NCT03395197	<b>Prostate cancer</b> (Approved on 2023/06/20)
	<b>HRR genes mutation</b>
	Talazoparib + enzalutamide vs. Placebo + enzalutamide [rPFS(M): Not reached vs. 13.8]
<b>EMBRACA</b> <sup>[213]</sup> NCT01945775	<b>Breast cancer</b> (Approved on 2018/10/16)
	<b>HER2-/gBRCA mutation</b>
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]



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## 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)

[214] NCT00065468	<b>Renal cell carcinoma</b> (Approved on 2007/05/30)
	-
	Temsirolimus vs. Ifn- $\alpha$ [OS(M): 10.9 vs. 7.3]

## Toripalimab-tpzi (LOQTORZ)

LOQTORZI is a programmed death receptor-1 (PD-1)- blocking antibody. Toripalimab-tpzi is developed and marketed by Coherus BioSciences, Inc. under the trade name LOQTORZ.

### - FDA Approval Summary of Toripalimab-tpzi (LOQTORZ)

<b>POLARIS-02</b> NCT02915432	<b>Nasopharynx carcinoma</b> (Approved on 2023/10/27)
	-
	Toripalimab-tpzi [ORR(%): 21.0, DOR(M): 14.9]
<b>JUPITER-02</b> NCT03581786	<b>Nasopharynx carcinoma</b> (Approved on 2023/10/27)
	-
	Toripalimab-tpzi + cisplatin + gemcitabine vs. Placebo + cisplatin + gemcitabine [PFS(M): 11.7 vs. 8.0]

## Tremelimumab (IMJUDO)

Tremelimumab a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody. Tremelimumab is developed and marketed by AstraZeneca under the trade name IMJUDO.

### - FDA Approval Summary of Tremelimumab (IMJUDO)

<b>POSEIDON</b> NCT03164616	<b>Lung non-small cell carcinoma</b> (Approved on 2022/11/10)
	-
	Durvalumab and platinum-based chemotherapy [PFS(M): 6.2 vs. 4.8, OS(M): 14 vs. 11.7]
<b>HIMALAYA</b> NCT03298451	<b>Hepatocellular carcinoma</b> (Approved on 2022/10/21)
	-
	Tremelimumab + durvalumab vs. Tremelimumab + sorafenib [OS(M): 16.4 vs. 13.9]

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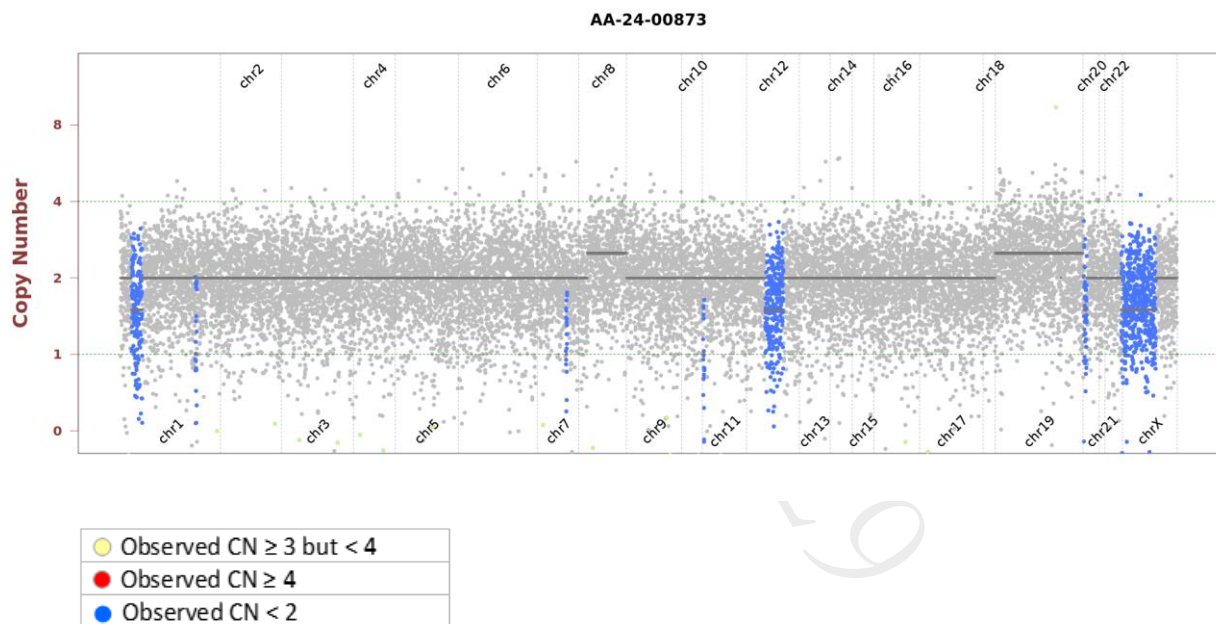
## SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

### - Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ARID1A	S964fs	10	c.2892_2905del	NM_006015	-	25.3%	601
B2M	L15fs	1	c.43_44del	NM_004048	COSM144579	19.1%	429
CTCF	E464*	8	c.1390G>T	NM_006565	-	21.7%	681
FBXW7	R479Q	10	c.1436G>A	NM_033632	COSM22974	17.0%	1699
KRAS	G13C	2	c.37G>T	NM_004985	COSM527	18.2%	2798
PIK3CA	C420R	8	c.1258T>C	NM_006218	COSM757	25.9%	645
POLD1	Splice acceptor	-	c.3121-1G>T	NM_001256849	-	17.5%	114
PRKDC	Splice donor	-	c.966+2T>C	NM_006904	-	6.7%	1301
SDHB	R90*	3	c.268C>T	NM_003000	-	17.6%	1452

### - 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
ADAMTSL1	G915D	19	c.2744G>A	NM_001040272	-	21.6%	722
AR	A278T	1	c.832G>A	NM_000044	COSM6939198	17.7%	1112
ARAF	Splice region	-	c.1420-3T>C	NM_001654	-	18.9%	625
ATR	A1363V	22	c.4088C>T	NM_001184	COSM7283020	18.3%	1774
BCL10	P195H	3	c.584C>A	NM_003921	-	18.9%	1569
CDK1	E196D	6	c.588A>C	NM_001786	-	18.1%	2011
CDK4	F214S	6	c.641T>C	NM_000075	-	19.2%	1187
CIC	P74H	3	c.221C>A	NM_015125	-	16.1%	977
CREBBP	S1761L	31	c.5282C>T	NM_004380	-	17.9%	173
DICER1	Q1135R	21	c.3404A>G	NM_177438	COSM6959699	19.0%	1396
DNMT3A	A910V	23	c.2729C>T	NM_175629	COSM133138	18.8%	559
DNMT3A	R596Q	15	c.1787G>A	NM_175629	-	16.2%	142
DNMT3A	D531del	14	c.1592_1594del	NM_175629	COSM1583078	15.5%	477
EGFR	R677C	17	c.2029C>T	NM_005228	COSM3266626	25.8%	561
EP300	Q491R	6	c.1472A>G	NM_001429	-	18.5%	788
EPHA3	S906fs	16	c.2717del	NM_005233	-	55.4%	605
FANCA	A797V	26	c.2390C>T	NM_000135	-	22.4%	994
FANCE	A329T	5	c.985G>A	NM_021922	-	20.1%	2416
FAT1	L3144P	13	c.9431T>C	NM_005245	-	20.7%	1467
FAT1	Y497H	2	c.1489T>C	NM_005245	-	22.8%	2195
FGFR2	R61C	3	c.181C>T	NM_000141	COSM7429185	18.5%	130
FLCN	A27T	4	c.79G>A	NM_144997	COSM4617732	18.9%	541
FLT4	R1041Q	23	c.3122G>A	NM_182925	COSM3697185	26.1%	234
FLT4	R1354H	30	c.4061G>A	NM_182925	COSM9359782	54.2%	332
GSTP1	Y104H	5	c.310T>C	NM_000852	-	17.6%	131
HNF1A	A326V	5	c.977C>T	NM_000545	COSM5988501	50.7%	229
HR	R245H	3	c.734G>A	NM_005144	COSM7264008	14.6%	568
INSR	R1201Q	20	c.3602G>A	NM_000208	COSM6971144	16.4%	1611
IRS1	P591S	1	c.1771C>T	NM_005544	-	16.9%	254
JAK2	A140V	5	c.419C>T	NM_004972	COSM6502940	18.0%	1207
KDM6A	R1111C	23	c.3331C>T	NM_021140	COSM2965441	8.6%	1261
KDM6A	T940A	18	c.2818A>G	NM_021140	-	6.8%	1939
KMT2C	S4042G	47	c.12124A>G	NM_170606	-	17.2%	854
KMT2D	N5051_L5052del	48	c.15151_15156del	NM_003482	COSM9113951	18.6%	478
LRP1B	Q928P	18	c.2783A>C	NM_018557	-	53.4%	1210
MEN1	Y324H	7	c.970T>C	NM_130802	-	17.7%	989
MET	I161T	2	c.482T>C	NM_001127500	-	19.4%	1675
MRE11	L493I	13	c.1477C>A	NM_005591	-	17.9%	955
MTOR	R1132P	22	c.3395G>C	NM_004958	-	17.5%	907
MUC16	R13554C	56	c.40660C>T	NM_024690	-	60.3%	554
MUC16	P10056T	3	c.30166C>A	NM_024690	-	34.1%	2209
MUC4	A4981V	17	c.14942C>T	NM_018406	-	17.6%	951
MUC4	P4826L	14	c.14477C>T	NM_018406	COSM5864161	20.1%	219
NEFH	A380T	3	c.1138G>A	NM_021076	COSM2936486	39.9%	514



行動基因是美國病理學會認證實驗室，認證實驗室號碼: 9028096。

行動基因僅提供技術檢測服務及檢測報告，檢測結果之臨床解釋及相關醫療處置，請諮詢專業醫師。報告結果僅對此試驗件有效。

行動基因臨床分子醫學實驗室 台北市內湖區新湖二路345號3F

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NOTCH1	R902S	17	c.2704C>A	NM_017617	-	25.4%	287
NOTCH2	E297D	6	c.891G>T	NM_024408	-	18.2%	1874
PAX8	H231R	7	c.692A>G	NM_003466	-	27.7%	455
PIK3C2B	C691W	14	c.2073C>G	NM_002646	COSM5749128	52.1%	534
PIK3CD	Y936H	22	c.2806T>C	NM_005026	-	16.0%	425
PMS2	C515Y	11	c.1544G>A	NM_000535	-	16.9%	656
PMS2	S516C	11	c.1546A>T	NM_000535	-	16.4%	651
POLD1	A152V	4	c.455C>T	NM_001256849	-	55.3%	465
POLE	V2108M	45	c.6322G>A	NM_006231	-	20.8%	754
PTEN	G132V	5	c.395G>T	NM_000314	COSM5229	16.8%	3087
RUNX1T1	S3Y	2	c.8C>A	NM_175634	-	9.0%	664
SETD2	V892M	3	c.2674G>A	NM_014159	-	18.7%	855
SPOP	D140Y	6	c.418G>T	NM_001007229	COSM8975409	20.5%	1083
SYNE1	I6651T	108	c.19952T>C	NM_182961	-	21.2%	605
TAP2	S287N	5	c.860G>A	NM_018833	COSM6383416	19.6%	759
TAPBP	Q76*	3	c.226C>T	NM_172208	-	49.2%	248
TET2	A211T	3	c.631G>A	NM_001127208	-	20.1%	993
TET2	G105V	3	c.314G>T	NM_001127208	-	17.0%	1512
TET2	M1729V	11	c.5185A>G	NM_001127208	-	18.3%	618
TSC2	Splice region	-	c.849-8A>G	NM_000548	-	51.6%	254
WT1	R369L	7	c.1106_1107delinsTG	NM_024426	-	22.9%	1835

Note:

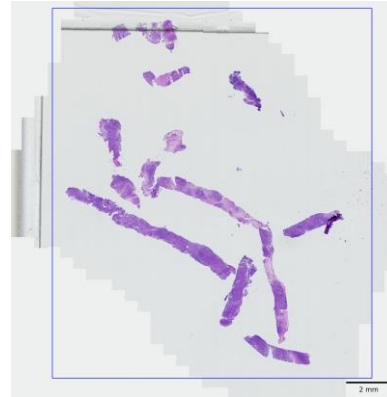
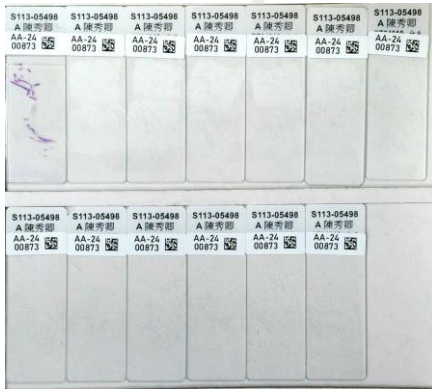
- This table enlists variants detected by the panel other than those with clinical relevance (reported in Testing Result section). The clinical impact of a genetic variant is determined according to ACT Genomics in-house clinical knowledge database. A negative result does not necessarily indicate absence of biological effect on the tumor. Some variants listed here may possibly have preclinical data or may show potential clinical relevance in the future.



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## TEST DETAILS

### SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Jan 29, 2024
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11305498A
- Collection site: Retroperitoneal
- Examined by: Dr. Yeh-Han Wang
  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 (%): 10%
  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: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

## RUN QC

- Panel: ACTOnco<sup>®</sup>+

### DNA test

- Mean Depth: 898x
- Target Base Coverage at 100x: 94%

### RNA test

- Average unique RNA Start Sites per control GSP2: 162

## LIMITATIONS

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



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## NEXT-GENERATION SEQUENCING (NGS) METHODS

### DNA test

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

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite. Coverage depth was calculated using Torrent Coverage Analysis plug-in. Single nucleotide variants (SNVs) and short insertions/deletions (InDels) were identified using the Torrent Variant Caller plug-in. VEP (Variant Effect Predictor) was used to annotate every variant using databases from Clinvar, COSMIC and Genome Aggregation database. Variants with coverage  $\geq 20$ , 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  $\geq 0.3$  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<sup>®</sup> 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  $\geq 7.5$  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  $\geq 10$ .

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  $\geq 3$ ; (2) Number of supporting reads spanning the fusion junction  $\geq 5$ ; (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:

醫檢師蘇柏安 碩士  
Po An Su, M.S.  
檢字第 018036 號

Po An Su

## Sign Off

醫檢師陳韻仔 博士  
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Yun Yu Chen



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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*	SLCO1B1*
SLCO1B3*	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1*	SOX2*	SOX9	SPEN	SPOP
SRC	STAG2	STAT3	STK11	SUFU	SYK	SYNE1	TAF1	TAP1	TAP2	TAPBP	TBX3
TEK	TERT	TET1	TET2	TGFBR2	TMSB4X*	TNF	TNFAIP3	TNFRSF14	TNFSF11	TOP1	TP53
TPMT*	TSC1	TSC2	TSHR	TYMS	U2AF1	UBE2A*	UBE2K	UBR5	UGT1A1*	USH2A	VDR*
VEGFA	VEGFB	VHL	WT1	XIAP	XPO1	XRCC2	ZNF217				

\*Analysis of copy number alterations NOT available.

## FUSION

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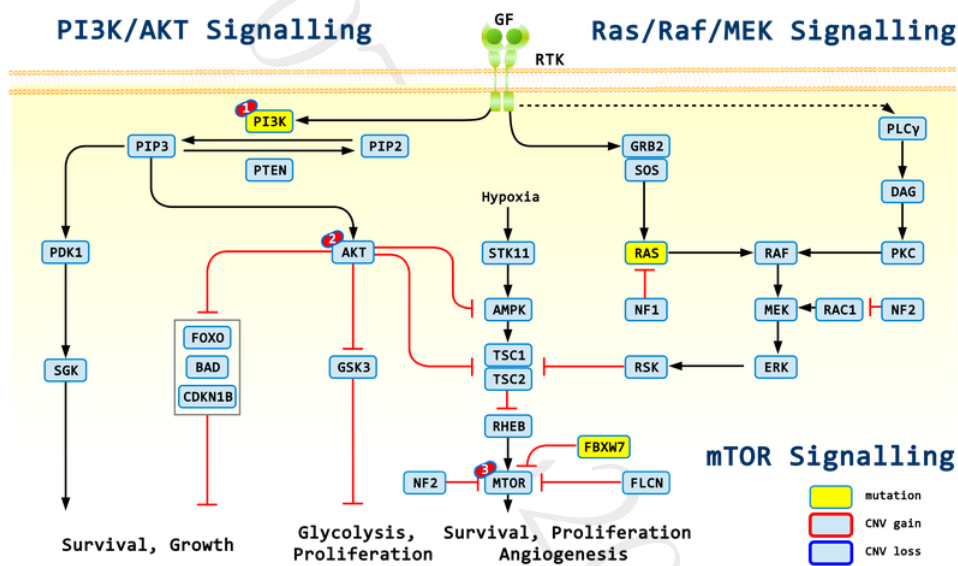
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## APPENDIX

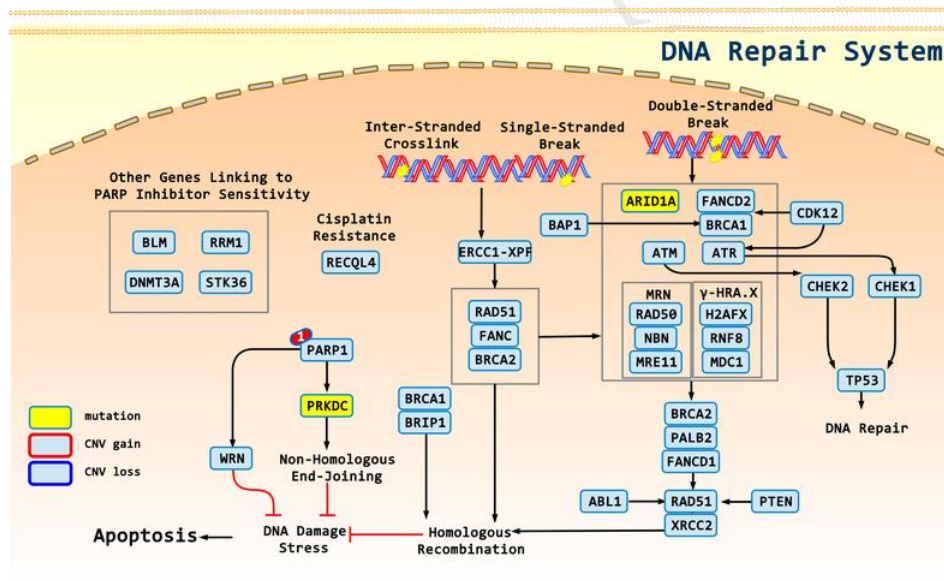
### POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Not Applicable.

### SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Alpelisib; 2: Capivasertib; 3: Everolimus, Temsirolimus



1: Olaparib, Rucaparib, Talazoparib



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## DISCLAIMER

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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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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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