

# ACT Onco<sup>®</sup> + Report

PATIENT		
Identifier: 袁志成		Patient ID: 24044539
Date of Birth: Mar 15, 1961		Gender: Male
Diagnosis: Undifferentiated spindle cell sarcoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11145261A	Collection site: Retroperitoneum	Type: FFPE tissue
Date received: Nov 10, 2022	Lab ID: AA-22-06836	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	
Not detected			

### VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
RB1 Splice donor	-	Abemaciclib, Palbociclib, Ribociclib
RB1 Heterozygous deletion	-	Abemaciclib, Palbociclib, Ribociclib
MCL1 Amplification	Regorafenib, Sorafenib	-

#### 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
<i>PBRM1</i>	F1045fs	55.5%
<i>RB1</i>	Splice donor	54.4%

#### - Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr17	<i>TP53</i>	Homozygous deletion	0
Chr11	<i>ATM, CHEK1</i>	Heterozygous deletion	1
Chr13	<i>BRCA2, RB1</i>	Heterozygous deletion	1
Chr4	<i>FBXW7</i>	Heterozygous deletion	1
Chr9	<i>CDKN2A</i>	Heterozygous deletion	1
Chr1	<i>MCL1, NTRK1</i>	Amplification	7
Chr8	<i>NBN</i>	Amplification	7

#### - Fusions

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

#### - Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	1.3 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 67% 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<sup>®</sup>+ 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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## THERAPEUTIC IMPLICATIONS TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
<b>Level 4</b>		
<b>MCL1</b> Amplification	Regorafenib, Sorafenib	<b>sensitive</b>
<b>RB1</b> Splice donor	Abemaciclib, Palbociclib, Ribociclib	<b>resistant</b>
<b>RB1</b> Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	<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)

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
<b>RB1</b> Splice donor Heterozygous deletion	Cisplatin	<b>Sensitive</b>	Clinical	Bladder carcinoma
	FAC T/FAC taxane/doxorubicin	<b>Sensitive</b>	Clinical	Breast cancer

## HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
<b>RB1</b> Splice donor Heterozygous deletion	Tamoxifen	<b>Resistant</b>	Clinical	Breast cancer

## OTHERS

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

### Note:

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

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## VARIANT INTERPRETATION

### PBRM1 F1045fs

#### Biological Impact

The PBRM1 gene encodes the protein BAF180 tumor suppressor, which is a component of the nucleosome-remodeling complex switching defective/sucrose non-fermenting (SWI/SNF)<sup>[1]</sup>. Loss of PBRM1 activity is associated with chromosomal instability<sup>[2]</sup>. PBRM1, BAP1 and SETD2 are three frequently altered tumor suppressor genes on chromosome 3p in a region that is deleted in over 90% of clear cell renal cell carcinoma (ccRCC)<sup>[3][4]</sup>.

F1045fs mutation results in a change in the amino acid sequence beginning at 1045, likely to cause premature truncation of the functional PBRM1 protein (UniProtKB). This mutation is predicted to lead to a loss of PBRM1 protein function, despite not being characterized in the literature.

#### Therapeutic and prognostic relevance

Biallelic loss or loss-of-function mutation of PBRM1 has been shown to correlate with clinical benefit in clear cell renal cell carcinoma (ccRCC), melanoma, lung cancer, bladder cancer, and head and neck squamous carcinoma (HNSCC) patients treated with immune checkpoint inhibitors<sup>[5][6]</sup>.

Decreased expression of PBRM1 has been shown to predict unfavorable clinical outcome in patients with ccRCC<sup>[7]</sup>.

### RB1 Splice donor, Heterozygous deletion

#### Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication<sup>[8]</sup>. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis<sup>[9]</sup>. 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<sup>[10][11][12]</sup>. 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<sup>[13]</sup>.

RB1 c.380+1G>C is a variant located at the splice donor 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

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<sup>[14]</sup>. 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<sup>[15]</sup>.

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer<sup>[16][17]</sup>.

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment<sup>[18]</sup>. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib<sup>[19]</sup>.

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)<sup>[20][21]</sup>. 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

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the alteration that induces this non-small-cell to small-cell transformation<sup>[17][22]</sup>.

## 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<sup>[23]</sup>. 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<sup>[24][25][26][27][28]</sup>. 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<sup>[29]</sup>. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies<sup>[30][31][32][33]</sup> and a broad range of tumors such as prostate cancer<sup>[34]</sup>, head and neck squamous cell carcinoma (HNSCC)<sup>[35]</sup>, pancreatic cancer<sup>[36]</sup>, lung adenocarcinoma<sup>[37]</sup>, breast cancer<sup>[38]</sup>, and ovarian cancer<sup>[25]</sup>.

### 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)<sup>[39]</sup>.

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<sup>[40]</sup>. 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<sup>[41]</sup>. 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)<sup>[42]</sup>. 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<sup>[43]</sup>. 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)<sup>[44]</sup>. 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)<sup>[45]</sup>.

In preclinical studies, cells with ATM alternation were sensitive to olaparib, niraparib, and talazoparib treatment in vitro and in vivo<sup>[46][47][48][49]</sup>.

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)<sup>[50]</sup> and prostate cancer (NCT02952534, NCT03533946)<sup>[45]</sup>, 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<sup>[14]</sup>. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with



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resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer<sup>[51]</sup>.

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer<sup>[52]</sup>.

## **BRCA2 Heterozygous deletion**

### **Biological Impact**

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair<sup>[53]</sup>. BRCA2 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions<sup>[54]</sup>. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia<sup>[55]</sup>. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers<sup>[56]</sup>.

### **Therapeutic and prognostic relevance**

The U.S. FDA has approved olaparib in advanced ovarian cancer under several settings including (1) first-line maintenance treatment for patients with deleterious or suspected deleterious germline or somatic BRCA mutation who are in complete or partial response to first-line platinum-based chemotherapy<sup>[57]</sup>; (2) in combination with bevacizumab as first-line maintenance treatment for patients who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status<sup>[58]</sup>; (3) maintenance treatment for patients with recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy<sup>[59][60]</sup>. In addition, olaparib has also been approved in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative breast cancer who have been treated with chemotherapy in either neoadjuvant, adjuvant, or metastatic setting<sup>[61]</sup> and germline BRCA-mutated metastatic pancreatic cancer<sup>[62]</sup>. Of note, in May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate(NCT02987543)<sup>[39]</sup>.

Rucaparib has been approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy<sup>[50]</sup>. NCCN guidelines recommend rucaparib as recurrence therapy for patients with BRCA-mutated ovarian cancer, who have been treated with two or more lines of chemotherapies<sup>[63]</sup>. In May 2020, the U.S. FDA also approved rucaparib to treat adult patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy (TRITON2, NCT02952534). Moreover, NCCN guidelines recommend rucaparib as maintenance therapy following prior platinum-based therapy for patients with metastatic pancreatic cancer harboring germline or somatic BRCA mutation.

The U.S. FDA has approved niraparib for the maintenance treatment of patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to first-line platinum-based chemotherapy and patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy<sup>[64][65]</sup>. Besides, NCCN guidelines recommend niraparib as maintenance therapy for ovarian cancer patients with BRCA mutations. The U.S. FDA also approved talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer<sup>[66]</sup>.

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## CDKN2A Heterozygous deletion

### Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53<sup>[67][68][69]</sup>. 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<sup>[70]</sup>. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation<sup>[71][72]</sup>.

### Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors<sup>[73][74]</sup>. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments<sup>[75][76][77]</sup>. 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<sup>[78][79][80]</sup>. However, CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

The phase II TAPUR trial demonstrated clinical benefits to palbociclib monotherapy in advanced NSCLC or head and neck cancer harboring a CDKN2A mutation or copy number loss. However, pancreatic and biliary cancer patients harboring a CDKN2A mutation or copy number loss did not demonstrate an objective response or stable disease when treated with palbociclib monotherapy for 16 weeks (DOI: 10.1200/JCO.2021.39.15\_suppl.6043)<sup>[81][82]</sup>.

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<sup>[74][83][84]</sup>.

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<sup>[76]</sup>. 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<sup>[85]</sup>.

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<sup>[86]</sup>.

## 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<sup>[87]</sup>. 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<sup>[88][89]</sup>. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors<sup>[90]</sup>, and CHEK1 mutations are extremely rare<sup>[87]</sup>. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer<sup>[91]</sup>, breast cancer<sup>[92]</sup>, colorectal cancer<sup>[93]</sup>, non-small cell lung (NSCLC) cancer<sup>[94]</sup>, and nasopharyngeal cancer<sup>[95]</sup>.



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## 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)<sup>[39]</sup>.

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)<sup>[50]</sup>, 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<sup>[96]</sup>.

## FBXW7 Heterozygous deletion

### Biological Impact

The F-box/WD repeat-containing protein 7 (FBXW7) gene encodes a protein that belongs to the SCF (SKP1-CUL1-F-box protein) E3 ligase complex. FBXW7 is recognized as a tumor suppressor which is involved in the negative regulation of oncogenes such as c-Myc<sup>[97][98]</sup>, c-Jun<sup>[99]</sup>, cyclin E<sup>[100]</sup>, Notch family members<sup>[101][102]</sup>, Aurora-A<sup>[103]</sup>, mTOR<sup>[104]</sup>, KLF5<sup>[105]</sup>, and MCL-1<sup>[106]</sup>. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation<sup>[107]</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>[105][106][108]</sup>.

## 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>[109][110]</sup>. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor<sup>[104]</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>[111][112][113][114]</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>[115][113]</sup>.

## MCL1 Amplification

### Biological Impact

The myeloid cell leukemia 1 (MCL1) gene encodes a member of the BCL2 pro-survival family<sup>[116]</sup>. MCL1 is highly regulated by various oncogenic signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway<sup>[117]</sup>, the mTOR pathway<sup>[118]</sup>, and the phosphatidylinositol-3 kinase (PI3K) pathway<sup>[119]</sup>. Oncogenic roles for MCL1 have been previously suggested by the report of increased rates of lymphoma in transgenic mice<sup>[120]</sup>. Somatic amplification of MCL1 may be a common mechanism in cancer cells to increase cell survival<sup>[121]</sup>. MCL1 overexpression was observed from a retrospective analysis of parotid gland carcinomas, including adenoid cystic carcinoma<sup>[122]</sup>.

## Therapeutic and prognostic relevance

Therapies targeting MCL1 and other BCL2 family members with the pan-BCL2 family inhibitors are currently under investigation<sup>[123]</sup>. A case report has demonstrated clinical efficacy of sorafenib, when combined with vorinostat, in a

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metastatic triple-negative breast cancer (TNBC) patient with MCL1-amplified tumor<sup>[124]</sup>. Several in vitro studies also showed that sorafenib induces cell death via inhibition of MCL1 expression in multiple cancer types including, hepatocellular carcinoma (HCC), lung cancer, breast cancer, cholangiocarcinoma, endometrial cancer and chronic lymphocytic leukemia<sup>[125][126][127][128][129][130]</sup>. Preclinical studies have also demonstrated the efficacy of regorafenib in reducing MCL1 expression in human colorectal cancer (CRC) cell lines<sup>[131][132]</sup>. In vivo models of colon cancer showed that MCL-1 expression is inhibited by targeting of the mTOR pathway using everolimus, promoting increased tumor cell killing of cancers with KRAS or BRAF mutations<sup>[133]</sup>.

## **NBN Amplification**

### **Biological Impact**

The NBN gene encodes a component of the MRE11-RAD50-NBN (MRN) complex, which involves in DNA double-strand break sensing and repair<sup>[134]</sup>. NBN mutation is related to Nijmegen breakage syndrome, increased cancer incidence and ionizing radiation sensitivity<sup>[134][135]</sup>. NBN mutations have been found in various cancers, including cholangiocarcinoma, hepatocellular carcinoma<sup>[136]</sup>, prostate cancer<sup>[137]</sup>, leukemia, lymphoma<sup>[138]</sup>, and triple-negative breast cancer<sup>[139]</sup>.

### **Therapeutic and prognostic relevance**

In a phase II trial (ARIEL2), an ovarian cancer patient harboring a NBN germline mutation showed responses to rucaparib treatment<sup>[140]</sup>. NBN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer<sup>[141]</sup>; the trials evaluating rucaparib efficacy in ovarian cancer<sup>[50]</sup> or prostate cancer<sup>[45]</sup>; the trials evaluating talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556), and the trials evaluating niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate) cancer (NCT03207347).

Germline and somatic mutations in homologous recombination genes, including NBN, have been suggested to be prognostic biomarkers for platinum-based treatment response and superior survival in patients with ovarian, fallopian tube, peritoneal carcinomas and pancreatic cancer<sup>[142][143]</sup>.

In a retrospective study of localized prostate cancer, NBN gene amplification has been demonstrated to associate with overall tumor genomic instability and lower biochemical relapse-free rate following image-guided radiotherapy (IGRT)<sup>[144]</sup>.

Another retrospective study showed that amplification of the NBN gene is associated with protein overexpression and mostly correlated with poor prognosis in several cancer types, including ovarian cancer, breast invasive carcinoma, uterine corpus endometrial carcinoma, and sarcoma. Besides, in vivo and in vitro assays demonstrated that amplification of the NBN gene could induce cisplatin and PARP inhibitor resistance in breast and ovarian cancer cells<sup>[145]</sup>.

## **NTRK1 Amplification**

### **Biological Impact**

The NTRK1 gene encodes the TRKA (tropomyosin receptor kinase) receptor which plays an important role in the development and function of the nervous system. Gene fusions of NTRK1 lead to constitutive activation of MAP-kinase, PI3-kinase, and PLC-γ pathways, and represent the main molecular alterations with known oncogenic and transforming potential in various malignancies, including soft tissue sarcoma, non-small cell lung cancer (NSCLC), glioblastoma multiforme (GBM), thyroid carcinoma, and pilocytic astrocytomas<sup>[146][147]</sup>. A pan-cancer study (n=1250) demonstrated that 2.2% of the metastatic cancer patients harbored NTRK amplification and NTRK protein overexpression was observed in 14.8% of NTRK-amplified tumors (doi.org/10.23838/pfm.2017.00142).

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## Therapeutic and prognostic relevance

Patients with NTRK1 amplification had only limited benefit from larotrectinib treatment according to the few clinical studies. One of them had a partial response with larotrectinib of short duration (3.7 months)<sup>[148]</sup>, and the other one with metastatic NTRK1-amplified (copy number=8) esophageal carcinoma showed clinical efficacy for six weeks, and then a progressive disease of new lesions were observed<sup>[149]</sup>.

## TP53 Homozygous deletion

### Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis<sup>[150]</sup>. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation<sup>[151]</sup>.

### 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)<sup>[152]</sup>.

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<sup>[153]</sup>. 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<sup>[154]</sup>.

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<sup>[155][156][157]</sup>. 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)<sup>[158]</sup>. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy<sup>[159][160]</sup>. 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<sup>[161]</sup>.

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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)

<b>MONARCH E</b> NCT03155997	<b>Breast cancer</b> (Approved on 2021/10/12)
	<b>HR+/HER2-</b> Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
<b>MONARCH 3</b> <sup>[162]</sup> NCT02246621	<b>Breast cancer</b> (Approved on 2018/02/26)
	<b>HR+/HER2-</b> Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
<b>MONARCH 2</b> <sup>[84]</sup> NCT02107703	<b>Breast cancer</b> (Approved on 2017/09/28)
	<b>HR+/HER2-</b> Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
<b>MONARCH 1</b> <sup>[163]</sup> NCT02102490	<b>Breast cancer</b> (Approved on 2017/09/28)
	<b>HR+/HER2-</b> Abemaciclib [ORR(%): 19.7 vs. 17.4]

### 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>[164]</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>[165]</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>[166]</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>[167]</sup> NCT00789828	<b>Subependymal giant cell astrocytoma</b> (Approved on 2010/10/29)
	- Everolimus vs. Placebo [ORR(%): 35.0]
<b>RECORD-1</b> <sup>[168]</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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## 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)

<b>PRIMA</b> NCT02655016	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2020/04/29)
	- Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
<b>NOVA<sup>[65]</sup></b> NCT01847274	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (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)

<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<sup>[39]</sup></b> 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<sup>[58]</sup></b> 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<sup>[62]</sup></b> 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<sup>[57]</sup></b> 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<sup>[61]</sup></b> 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<sup>[169]</sup></b> 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<sup>[170]</sup></b> 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]



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## 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)

<b>PALOMA-2</b> <sup>[171]</sup> NCT01740427	<b>Breast cancer</b> (Approved on 2017/03/31)
	<b>ER+/HER2-</b> Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
<b>PALOMA-3</b> <sup>[172]</sup> NCT01942135	<b>Breast cancer</b> (Approved on 2016/02/19)
	<b>ER+/HER2-</b> Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

## 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)

<b>RESORCE</b> <sup>[173]</sup> NCT01774344	<b>Hepatocellular carcinoma, Hepatocellular carcinoma</b> (Approved on 2017/04/27)
	- Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]
<b>GRID</b> <sup>[174]</sup> NCT01271712	<b>Gastrointestinal stromal tumor</b> (Approved on 2013/02/25)
	- Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]
<b>CORRECT</b> <sup>[175]</sup> NCT01103323	<b>Colorectal cancer</b> (Approved on 2012/09/27)
	- Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

## 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)

<b>MONALEESA-2</b> <sup>[83]</sup> NCT01958021	<b>Breast cancer</b> (Approved on 2017/03/13)
	<b>HR+/HER2-</b> Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

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## 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)

<b>TRITON2</b> NCT02952534	<b>Prostate cancer</b> (Approved on 2020/05/15)
	<b>gBRCA mutation or sBRCA mutation</b>
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
<b>ARIEL3<sup>[50]</sup></b> NCT01968213	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2018/04/06)
	-
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]

## Sorafenib (NEXAVAR)

Sorafenib is a small molecule multi-kinase inhibitor that targets multiple kinase families including VEGFR, PDGFRB, and the RAF family kinases. Sorafenib is co-developed and co-marketed by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals under the trade name NEXAVAR.

### - FDA Approval Summary of Sorafenib (NEXAVAR)

<b>DECISION<sup>[176]</sup></b> NCT00984282	<b>Differentiated thyroid carcinoma</b> (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
<b>SHARP<sup>[177]</sup></b> NCT00105443	<b>Hepatocellular carcinoma</b> (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]
<b>TARGET<sup>[178]</sup></b> NCT00073307	<b>Renal cell carcinoma</b> (Approved on 2005/12/20)
	-
	Sorafenib vs. Placebo [PFS(D): 167 vs. 84]

## 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>EMBRACA<sup>[66]</sup></b> 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)

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

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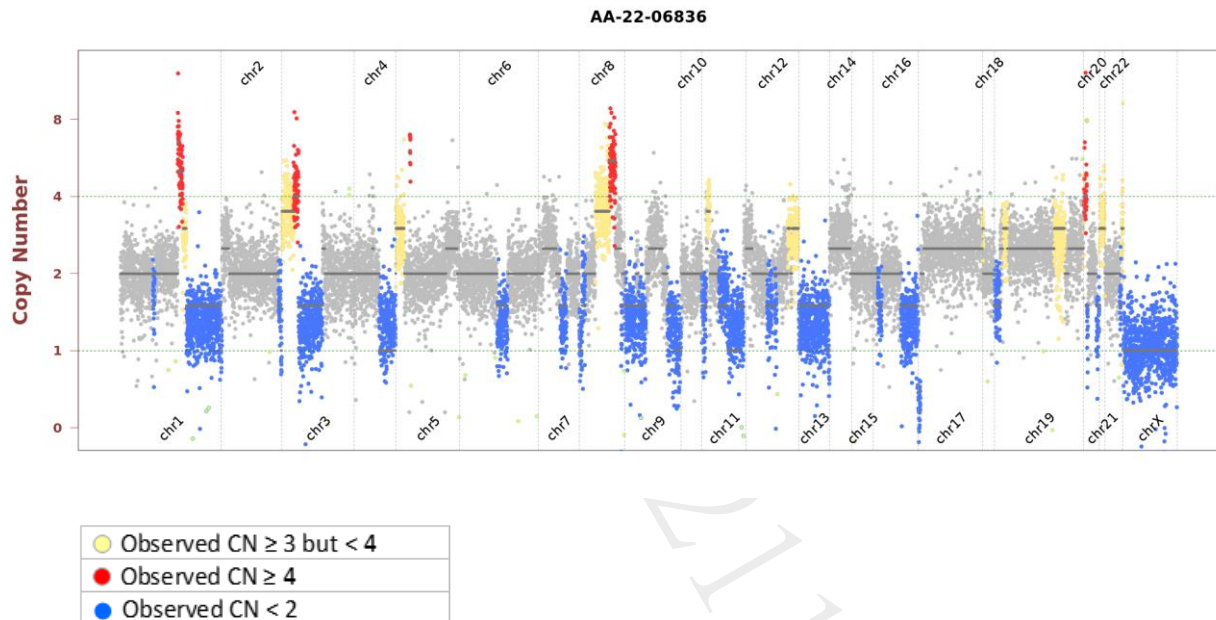
## SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

### - Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
PBRM1	F1045fs	21	c.3132_3145del	NM_018313	-	55.5%	393
RB1	Splice donor	-	c.380+1G>C	NM_000321	-	54.4%	526

### - 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
ALK	L550F	9	c.1648C>T	NM_004304	-	38.2%	1785
ARID1B	Q129_Q131del	1	c.378_386del	NM_017519	COSM6203018	45.3%	492
ATM	N1650S	33	c.4949A>G	NM_000051	-	83.4%	1052
CUL3	S304G	7	c.910A>G	NM_003590	-	49.5%	1077
ETV4	P463R	13	c.1388C>G	NM_001079675	-	39.4%	751
KDM5C	P1365L	24	c.4094C>T	NM_004187	-	98.8%	331
MAP3K1	V889L	14	c.2665G>C	NM_005921	-	50.6%	2540
PDIA3	M434V	11	c.1300A>G	NM_005313	-	33.0%	566
SPEN	R3136C	11	c.9406C>T	NM_015001	-	44.8%	837
SYNE1	T8414M	139	c.25241C>T	NM_182961	COSM206477	49.4%	1306

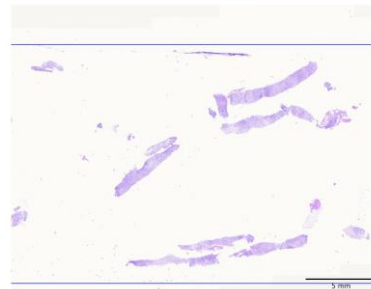
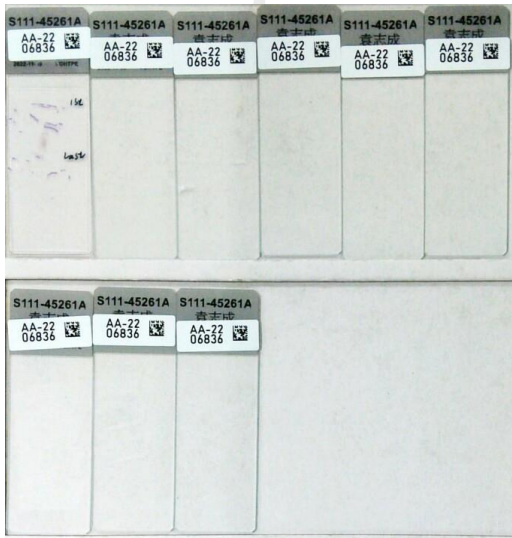
### Note:

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

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## TEST DETAILS

### SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Nov 03, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11145261A
- Collection site: Retroperitoneum
- Examined by: Dr. Chien-Ta Chiang
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 55%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 55%
  3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 5%
  4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 5%
  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: 966x
- Target Base Coverage at 100x: 95%

### RNA test

- Average unique RNA Start Sites per control GSP2: 120

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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  $\geq 20$ , 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).

### 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  $\geq 10$ .

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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:

醫藥資訊研究員  
楊杭哲 博士  
Hang-Che Yang Ph.D.



## Sign Off

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



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## GENE LIST SNV & CNV

ABCB1*	ABCC2*	ABCG2*	ABL1	ABL2	ADAMTS1	ADAMTS13	ADAMTS15	ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9
ADAMTS11	ADGRA2	ADH1C*	AKT1	AKT2	AKT3	ALDH1A1*	ALK	AMER1	APC	AR	ARAF
ARID1A	ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2	AXL
B2M	BAP1	BARD1	BCL10	BCL2*	BCL2L1	BCL2L2*	BCL6	BCL9	BCOR	BIRC2	BIRC3
BLM	BMP1R1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2*	BTK	BUB1B	CALR
CANX	CARD11	CASP8	CBFB	CBL	CCNA1	CCNA	CCNB1	CCNB2	CCNB3	CCND1	CCND2
CCND3	CCNE1	CCNE2	CCNH	CD19	CD274	CD58	CD70*	CD79A	CD79B	CDC73	CDH1
CDK1	CDK12	CDK2	CDK4	CDK5	CDK6	CDK7	CDK8	CDK9	CDKN1A	CDKN1B	CDKN2A
CDKN2B	CDKN2C	CEBPA*	CHEK1	CHEK2	CIC	CREBBP	CRKL	CRLF2	CSF1R	CTCF	CTLA4
CTNNA1	CTNNB1	CUL3	CYLD	CYP1A1*	CYP2B6*	CYP2C19*	CYP2C8*	CYP2D6	CYP2E1*	CYP3A4*	CYP3A5*
DAXX	DCUN1D1	DDR2	DICER1	DNMT3A	DOT1L	DPYD	DTX1	E2F3	EGFR	EP300	EPCAM
EPHA2	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2	ERBB3	ERBB4	ERCC1	ERCC2	ERCC3	ERCC4
ERCC5	ERG	ESR1	ESR2	ETV1	ETV4	EZH2	FAM46C	FANCA	FANCC	FANCD2	FANCE
FANCF	FANCG	FANCL	FAS	FAT1	FBXW7	FCGR2B	FGF1*	FGF10	FGF14	FGF19*	FGF23
FGF3	FGF4*	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLT1	FLT3	FLT4
FOXL2*	FOXP1	FRG1	FUBP1	GATA1	GATA2	GATA3	GNA11	GNA13	GNAQ	GNAS	GREM1
GRIN2A	GSK3B	GSTP1*	GSTT1*	HGF	HIF1A	HIST1H1C*	HIST1H1E*	HNF1A	HR	HRAS*	HSP90AA1
HSP90AB1	HSPA4	HSPA5	IDH1	IDH2	IFNL3*	IGF1	IGF1R	IGF2	IKBK	IKBE	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*	SLC18A1*
SLC18B3*	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
-----	------	------	-------	-------	-------	-----	------	-------	-------	-------	-----	------



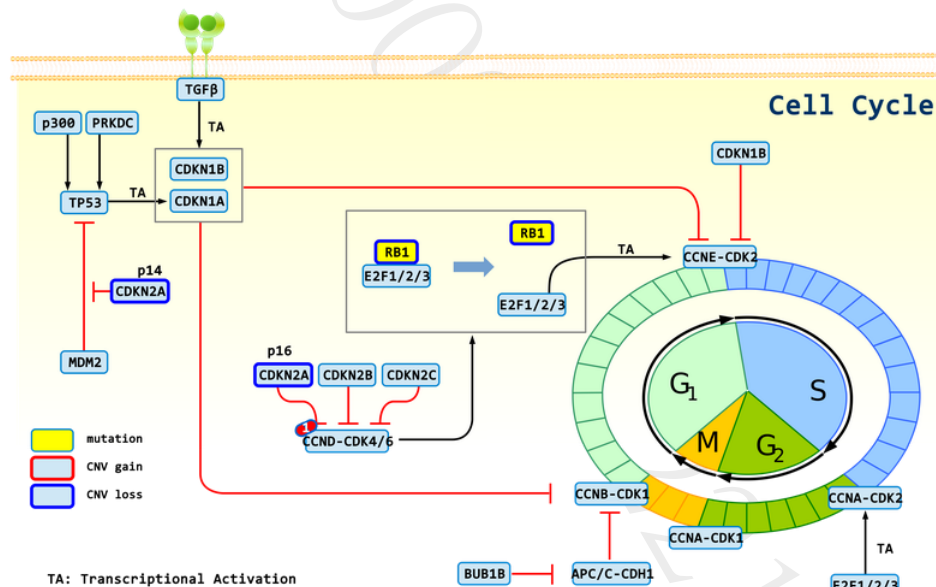
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## APPENDIX

### POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

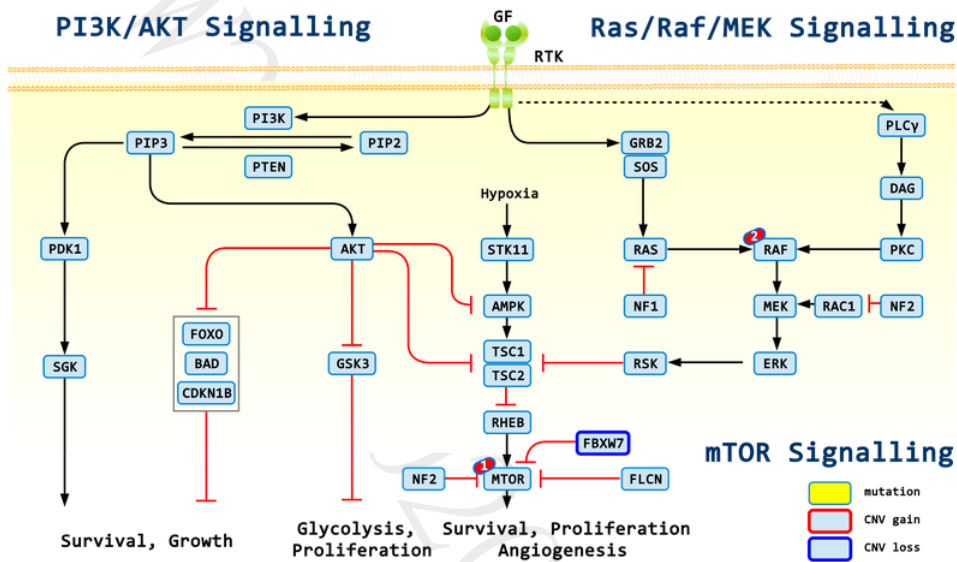
Gene	Therapies	Possible effect
<i>CDKN2A</i>	Abemaciclib, Palbociclib, Ribociclib	<b>sensitive</b>
<i>FBXW7</i>	Everolimus, Temsirolimus	<b>sensitive</b>
<i>ATM</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	<b>sensitive</b>
<i>BRCA2</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	<b>sensitive</b>
<i>CHEK1</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	<b>sensitive</b>
<i>FBXW7</i>	Gefitinib, Regorafenib	<b>resistant</b>

### SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

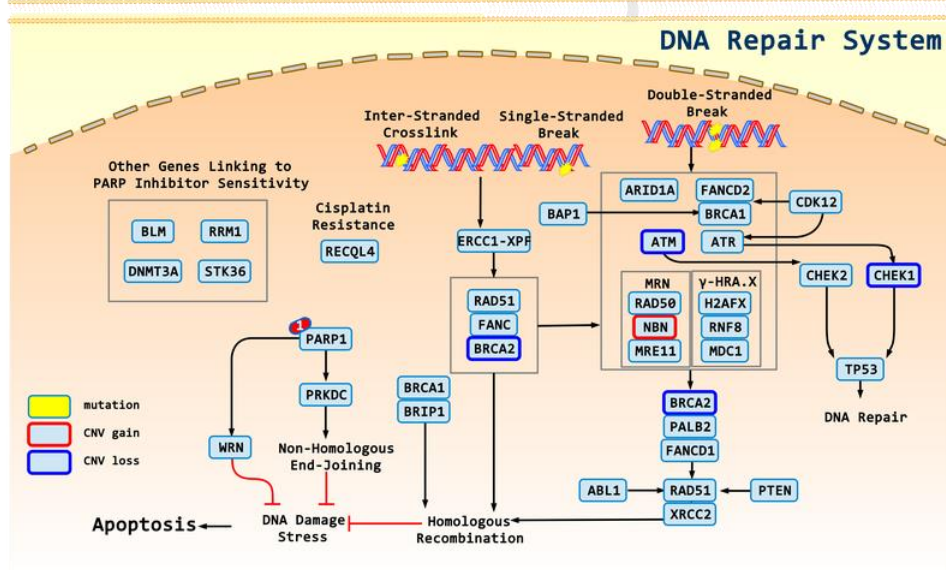


#### 1: Palbociclib, Ribociclib, Abemaciclib

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1: Everolimus, Temsirolimus; 2: Sorafenib



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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## DISCLAIMER

### 法律聲明

本檢驗報告僅提供專業醫療參考，結果需經專業醫師解釋及判讀。基因突變資訊非必具備藥物或治療有效性指標，反之亦然。本檢驗報告提供之用藥指引不聲明或保證其臨床有效性，反之亦然。本基因檢測方法係由本公司研究開發，已經過有效性測試。

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本公司於提供檢驗報告後，即已完成本次契約義務，後續之報告解釋、判讀及用藥、治療，應自行尋求相關專業醫師協助，若需將報告移件其他醫師，本人應取得該醫師同意並填寫移件申請書，主動告知行動基因，行動基因僅能配合該醫師意願與時間提供醫師解說。

### 醫療決策需由醫師決定

任何治療與用藥需經由醫師在考慮病患所有健康狀況相關資訊包含健檢、其他檢測報告和病患意願後，依照該地區醫療照護標準由醫師獨立判斷。醫師不應僅依據單一報告結果(例如本檢測或本報告書內容)做決策。

### 基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

### 證據等級

藥物潛在臨床效益(或缺乏潛在臨床效益)的實證證據是依據至少一篇臨床療效個案報告或臨床前試驗做為評估。本公司盡力提供適時及準確之資料，但由於醫學科技之發展日新月異，本公司不就本報告提供的資料是否為準確、適宜或最新作保證。

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