

# ACT Onco<sup>®</sup> + Report

PATIENT		
Identifier: 謝*賦		Patient ID: ***46325
Date of Birth: Apr **, 1963		Gender: Male
Diagnosis: Hepatocellular carcinoma		
ORDERING PHYSICIAN		
Name: 黃怡翔醫師		Tel: 886-228712121
Facility: 臺北榮總		
Address: 臺北市北投區石牌路二段 201 號		
SPECIMEN		
Specimen ID: S11302373	Collection site: Liver	Type: FFPE tissue
Date received: Jan 18, 2024	Lab ID: AA-24-00393	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	
PTEN Homozygous deletion	-	-	Capivasertib

### VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
CCND1 Amplification	Abemaciclib, Palbociclib, Ribociclib	-
CDKN2A Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	-
PTEN Homozygous deletion	Olaparib, Rucaparib	Erlotinib, Gefitinib, Panitumumab, Cetuximab, Trastuzumab

#### 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 criterion for clinical trials (FDA level 3/AMP tier 2).
- The therapeutic agents and possible effects to a given drug are based on mapping the variants/biomarkers with ACT Genomics clinical knowledge database. The mapping results only provide information for reference, but not medical recommendation.
- Please refer to corresponding sections for more detailed information about genomic alteration and clinical relevance listed above.

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## TESTING RESULTS

### VARIANT(S) WITH CLINICAL RELEVANCE

#### - Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
Not detected		

#### - Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr10	<i>PTEN</i>	Homozygous deletion	0
Chr9	<i>CDKN2A</i>	Homozygous deletion	0
Chr17	<i>FLCN</i>	Heterozygous deletion	1
Chr11	<i>CCND1, FGF19</i>	Amplification	72

#### - Fusions

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

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

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

#### Note:

- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 51% 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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## SUPPLEMENTARY INFORMATION FOR THERAPEUTIC IMPLICATIONS TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
<b>Level 3A</b>		
<b>PTEN</b> Homozygous deletion	Capivasertib	<b>sensitive</b>
<b>Level 3B</b>		
<b>CCND1</b> Amplification	Abemaciclib, Palbociclib, Ribociclib	<b>sensitive</b>
<b>CDKN2A</b> Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	<b>sensitive</b>
<b>PTEN</b> Homozygous deletion	Olaparib, Rucaparib	<b>sensitive</b>
<b>Level 4</b>		
<b>PTEN</b> Homozygous deletion	Erlotinib, Gefitinib, Panitumumab, Cetuximab, Trastuzumab	<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

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

## HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
CCND1 Amplification	Anastrozole	Less sensitive	Clinical	Breast cancer
	Tamoxifen	Less sensitive	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

### CCND1 Amplification

#### Biological Impact

The cyclin D1 (CCND1) gene encodes a protein involved in the control of cell growth, proliferation, transcription, and DNA repair<sup>[1]</sup>. CCND1 forms a complex with CDK4 and CDK6, leading to G1-S cell-cycle transition by inhibiting the retinoblastoma (RB) protein<sup>[1]</sup>. Amplification or overexpression of CCND1 could be oncogenic and is associated with carcinogenesis of various cancer types<sup>[2]</sup>.

#### Therapeutic and prognostic relevance

Several CDK4 inhibitors, including palbociclib (PD0332991), LEE011, and LY2835219 have entered clinical trials for tumors with CCND1 amplification<sup>[3][4]</sup>. In the Phase II study of palbociclib and letrozole in patients with ER-positive HER2-negative metastatic breast cancer, patient selection based on CCND1 amplification or p16 loss did not further improve patient outcome<sup>[5]</sup>. Preclinical studies also demonstrated conflicting results regarding the correlation between high-level CCND1 and palbociclib sensitivity<sup>[6][7][8]</sup>.

CCND1 amplification has been implicated in predicting poor clinical outcomes in postmenopausal breast cancer patients treated with either anastrozole or tamoxifen<sup>[9]</sup>. In lung cancer patients, the increased CCND1 copy number is associated with poorer overall survival<sup>[10]</sup>. A retrospective study showed that melanoma patients whose tumor harboring CCND1, cRAF or KRAS gene copy number gain had better treatment response with CPS (carboplatin, paclitaxel, and sorafenib)<sup>[11]</sup>. Of note, 3 of 4 patients treated with ribociclib for the longest duration had CCND1 amplification in a phase I trial<sup>[12]</sup>.

Amplification of CCND1 are frequent and contributes to dedifferentiation and cellular proliferative activity of intrahepatic cholangiocarcinoma (ICC), and also indicates a poor prognosis for ICC patients<sup>[13]</sup>. Of note, CCND1 amplification has been selected as an inclusion criterion for the trial examining CDK4/6 inhibitors in different types of malignant solid tumors (NCT02187783, NCT02896335, NCT03526250, NCT02693535, NCT01037790, NCT03454919, NCT03310879, and NCT03356223).

### CDKN2A Homozygous deletion

#### Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53<sup>[14][15][16]</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>[17]</sup>. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation<sup>[18][19]</sup>.

#### Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors<sup>[20][5]</sup>. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments<sup>[21][22][23]</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>[24][12][25]</sup>. 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

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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>[26][27]</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>[5][28][29]</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>[22]</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>[30]</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>[31]</sup>.

## FGF19 Amplification

### **Biological Impact**

The fibroblast growth factor 19 (FGF19) gene encodes a member of the fibroblast growth factor (FGF) family that plays critical roles in neuronal functions, development, and metabolism<sup>[32]</sup>. Amplification of the chromosome locus 11q13, a region harbors several genes with known or suspected oncogenic potential such as CCND1, FGF19, FGF23 and ANO1, is commonly observed in breast, ovarian, head and neck, oral, liver and esophageal cancer<sup>[33]</sup>. FGF19 is also a biomarker of renal failure, coronary artery disease, intestinal failure-associated liver disease, diabetes and Crohn's disease<sup>[34][35][36][37][38][39][40][41][42]</sup>.

### **Therapeutic and prognostic relevance**

In a retrospective study of hepatocellular carcinoma, the frequency of FGF19 amplification among the CR cases (2/6, 33.3%) was significantly higher than that among the other cases (PR + SD + PD) (2/39, 5.1%) after sorafenib treatment<sup>[43]</sup>. However, results from a preclinical study suggested that FGF19/FGFR4 signaling is associated with sorafenib resistance in hepatocellular carcinoma cell lines<sup>[44]</sup>. FGF19 protein expression is associated with early recurrence and poor prognosis of hepatocellular carcinoma after curative hepatectomy<sup>[45]</sup>. Breast cancer patients with high FGF19 expression exhibited a significantly shorter disease-specific 5-year survival<sup>[46]</sup>. In prostate cancer patients, the 5-year biochemical recurrence-free survival rate after radical prostatectomy was 46.4% in the FGF19-positive group and 70.0% in the FGF19-negative group<sup>[42]</sup>.

## FLCN Heterozygous deletion

### **Biological Impact**

The FLCN gene encodes the tumor suppressor, Folliculin, a GTPase activating protein (GAP) for RagC/D GTPase proteins involved in amino acid sensing and signaling to mTORC1<sup>[47]</sup>. FLCN has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions<sup>[48][49]</sup>. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling<sup>[50][51]</sup>. Germline mutation of the FLCN gene causes the Birt-Hogg-Dubé syndrome, a rare disorder that is characterized by benign hamartomatous skin lesions and an increased risk of pneumothorax and renal tumors<sup>[52]</sup>.

### **Therapeutic and prognostic relevance**

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTC) patients who had PI3K/mTOR/AKT alterations, including TSC2, FLCN or NF1, showed impressive progression-free



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survival (PFS) of 15.2 months after receiving everolimus<sup>[53]</sup>. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting<sup>[54]</sup>.

## PTEN Homozygous deletion

### Biological Impact

The phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene encodes a lipid/protein phosphatase that is important for the regulation of cell proliferation, survival, homologous recombination and maintenance of genomic integrity<sup>[55][56]</sup>. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway<sup>[57]</sup>. PTEN is a haploinsufficient tumor suppressor gene, in which having only one copy of the wild-type allele does not produce enough protein product to execute wild-type functions<sup>[58][59][60]</sup>. Germline loss-of-function PTEN mutations are found in approximately 80% of patients with Cowden syndrome, a disorder that is associated with high-penetrance breast and thyroid cancer<sup>[61][62][63]</sup>. Somatic mutations or monoallelic loss of PTEN is regularly observed in a significant fraction of human cancers, including sporadic breast cancer, colon cancer, endometrial cancer, prostate cancer, and glioblastoma<sup>[64][65][66][67][68]</sup>.

### Therapeutic and prognostic relevance

FDA 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.

Somatic loss of PTEN results in aberrant activation of PI3K/AKT/mTOR signaling pathway and provides a mechanistic rationale for PI3K pathway inhibitors treatment<sup>[69][70]</sup>. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes<sup>[71][72][73][74][75][76]</sup>. Although early clinical data indicated that PTEN loss was associated with improved response and survival in solid tumor patients treated with mTORC1 inhibitor, everolimus<sup>[77][78][79]</sup>, several phase II trials showed no clinical benefit of everolimus or temsirolimus treatment in patients with advanced solid tumors harboring PTEN loss<sup>[80][81][82]</sup>.

Several groups found that PTEN loss was generally associated with poor response to trastuzumab therapy, whether this agent was administered in the neoadjuvant, adjuvant, or metastatic settings<sup>[83][84][85][86][87]</sup>. Also, loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab<sup>[88][89][90][91][92][93]</sup>. Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib<sup>[94][95]</sup>. Inhibition of the PI3K/AKT/mTOR signal pathway has been shown to be an effective strategy to radiosensitize NSCLC cells harboring the EGFR activating mutation that acquires resistance to both TKIs due to PTEN loss or inactivation mutations<sup>[96]</sup>. Loss or biallelic inactivation of PTEN is associated with resistance to anti-PD-1 checkpoint blockade therapies, including pembrolizumab and nivolumab in melanoma and leiomyosarcoma patients<sup>[97][98][99]</sup>.

PTEN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in metastatic biliary tract cancer (NCT04042831); talazoparib efficacy in HER2-negative solid tumors (NCT02401347); rucaparib efficacy in prostate cancer (NCT02952534, NCT03533946), and niraparib efficacy in breast cancer (NCT04508803) or any malignancy (except prostate) cancer (NCT03207347). Clinical data also suggested that PTEN deficient cancers may be sensitive to olaparib<sup>[100]</sup>. However, in a phase II trial (NCT02286687), 13 patients with advanced solid tumors harboring PTEN mutation or loss (by IHC) had limited response to talazoparib treatment; only one patient with PTEN mutation had prolonged SD (Mol Cancer Ther 2018;17(1 Suppl):Abstract nr A096; NCT02286687). Besides, in a phase I trial (NCT00749502), no association between loss of PTEN expression and the efficacy of niraparib was identified in patients with castration-resistant prostate cancer<sup>[101]</sup>.

In a preclinical study, PTEN null cancer cells were sensitive to rucaparib treatment in vitro<sup>[102]</sup>.



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

Email: service@actgenomics.com T: +886-2-2795-3660 F: +886-2-2795-5016

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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<sup>[103]</sup></b> 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<sup>[29]</sup></b> 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<sup>[104]</sup></b> NCT02102490	<b>Breast cancer</b> (Approved on 2017/09/28)
	<b>HR+/HER2-</b> Abemaciclib [ORR(%): 19.7 vs. 17.4]

### 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]

### 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<sup>[105]</sup></b> NCT01524783	<b>Lung or gastrointestinal neuroendocrine tumor</b> (Approved on 2016/02/26)
	<b>-</b> Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
<b>BOLERO-2<sup>[106]</sup></b> 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]



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<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<sup>[78]</sup></b> NCT00510068	<b>Pancreatic neuroendocrine tumor</b> (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
<b>EXIST-1<sup>[107]</sup></b> NCT00789828	<b>Subependymal giant cell astrocytoma</b> (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
<b>RECORD-1<sup>[108]</sup></b> NCT00410124	<b>Renal cell carcinoma</b> (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

## 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]
<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>[109]</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>[110]</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>[111]</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>[112]</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>[113]</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>[114]</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]

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Study19 <sup>[116]</sup> NCT00753545	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

## Palbociclib (IBRANCE)

Palbociclib is an oral, cyclin-dependent kinase (CDK) inhibitor specifically targeting CDK4 and CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Palbociclib is developed and marketed by Pfizer under the trade name IBRANCE.

### - FDA Approval Summary of Palbociclib (IBRANCE)

PALOMA-2 <sup>[116]</sup> NCT01740427	Breast cancer (Approved on 2017/03/31)
	ER+/HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3 <sup>[117]</sup> NCT01942135	Breast cancer (Approved on 2016/02/19)
	ER+/HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

## Ribociclib (KISQALI)

Ribociclib is a cyclin-dependent kinase (CDK) inhibitor specifically targeting cyclin D1/CDK4 and cyclin D3/CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Ribociclib is developed by Novartis and Astex Pharmaceuticals and marketed by Novartis under the trade name KISQALI.

### - FDA Approval Summary of Ribociclib (KISQALI)

MONALEESA-2 <sup>[28]</sup> NCT01958021	Breast cancer (Approved on 2017/03/13)
	HR+/HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

## Rucaparib (RUBRACA)

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

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

TRITON2 NCT02952534	Prostate cancer (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3 <sup>[118]</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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## 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)

[119] 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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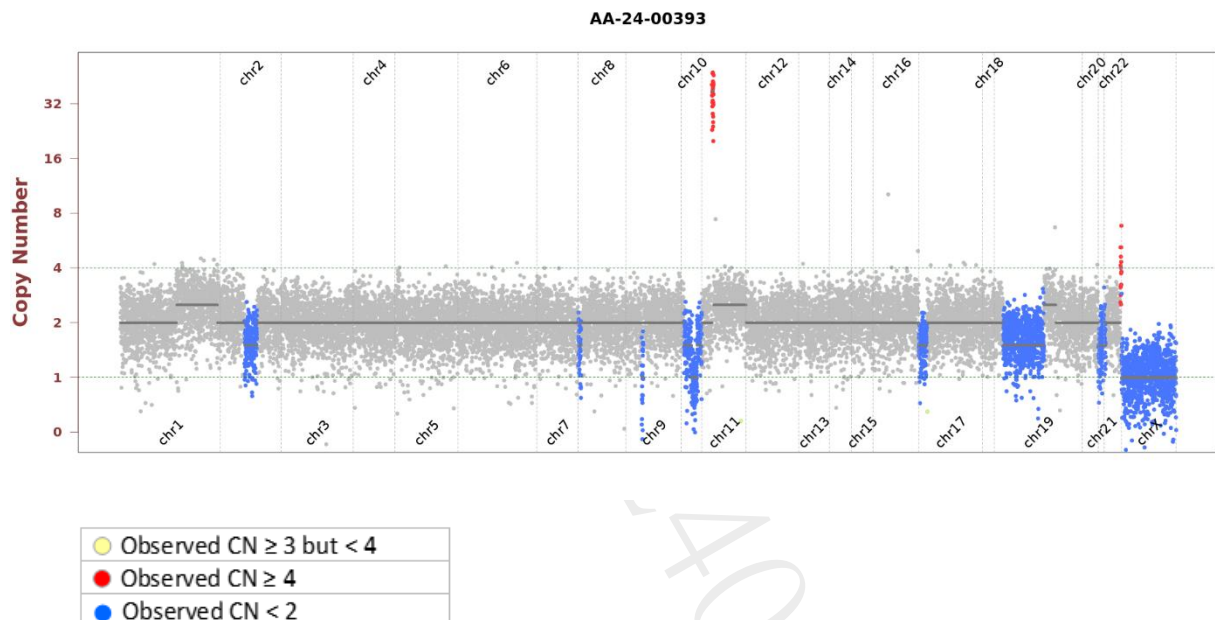
## SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

### - Single Nucleotide and Small InDel Variants

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

### - Copy Number Alterations

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



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## OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
BRCA2	K2729N	18	c.8187G>T	NM_000059	COSM5021109	47.4%	835
EPHA5	G963A	17	c.2888G>C	NM_001281765	-	48.4%	634
ERBB2	L1197*	27	c.3590T>A	NM_004448	-	23.3%	780
FGFR3	V329I	8	c.985G>A	NM_000142	COSM6928248	56.1%	488
HNF1A	P291T	4	c.871C>A	NM_000545	-	57.0%	858
MET	A1381T	21	c.4141G>A	NM_001127500	-	46.1%	1671
MYD88	C205G	3	c.613T>G	NM_002468	-	26.5%	925
NTRK3	Y376N	9	c.1126T>A	NM_001012338	-	26.9%	2405
PTPRD	R1650G	38	c.4948C>G	NM_002839	-	42.2%	519
SDHD	A9S	1	c.25G>T	NM_003002	-	18.6%	403
TSC2	E1344del	34	c.4030_4032del	NM_000548	COSM6968158	48.0%	1226

### Note:

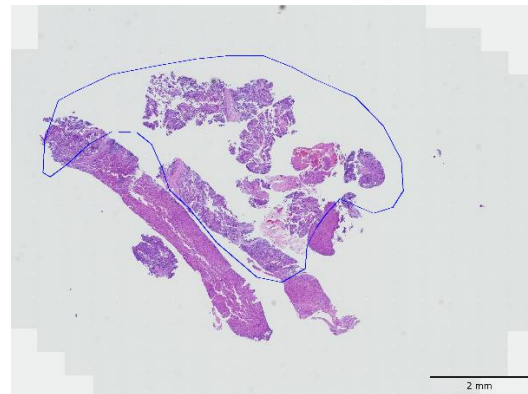
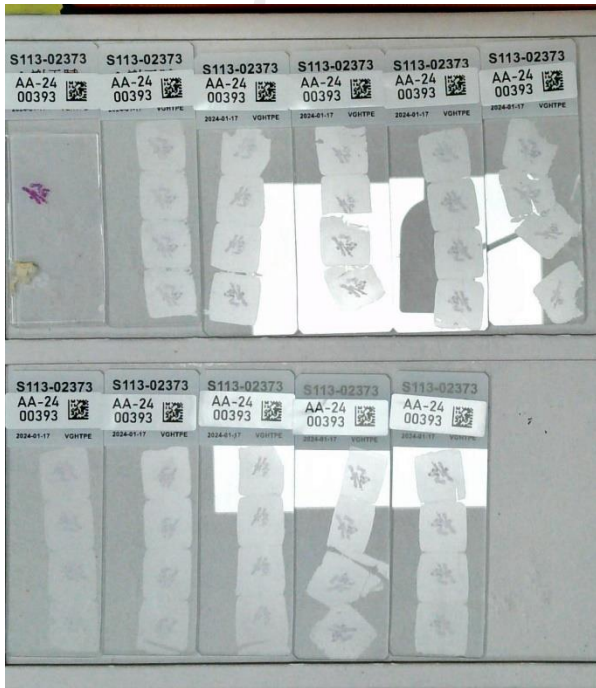
- This table enlists variants detected by the panel other than those with clinical relevance (reported in Testing Result section). The clinical impact of a genetic variant is determined according to ACT Genomics in-house clinical knowledge database. A negative result does not necessarily indicate absence 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 12, 2024
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11302373
- Collection site: Liver
- Examined by: Dr. Yeh-Han Wang
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 40%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 80%
  3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
  4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
  5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

## RUN QC

- Panel: ACTOnco<sup>®</sup>+

### DNA test

- Mean Depth: 1024x
- Target Base Coverage at 100x: 96%

### RNA test

- Average unique RNA Start Sites per control GSP2: 151

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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).

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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:

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



## Sign Off

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



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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

Email: service@actgenomics.com T: +886-2-2795-3660 F: +886-2-2795-5016

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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	IKBK	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*	SLC18A1*
SLC18A1*	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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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

Email: service@actgenomics.com T: +886-2-2795-3660 F: +886-2-2795-5016

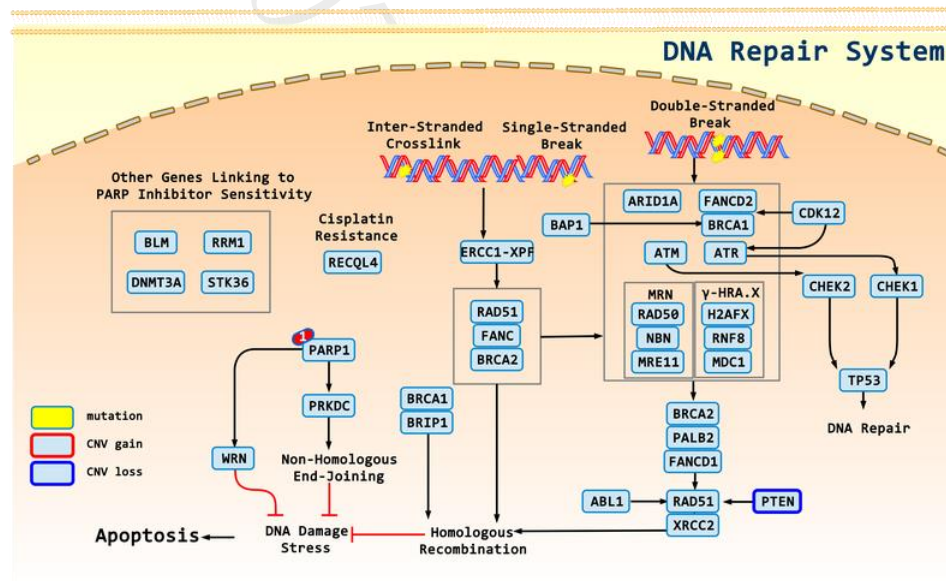
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## APPENDIX

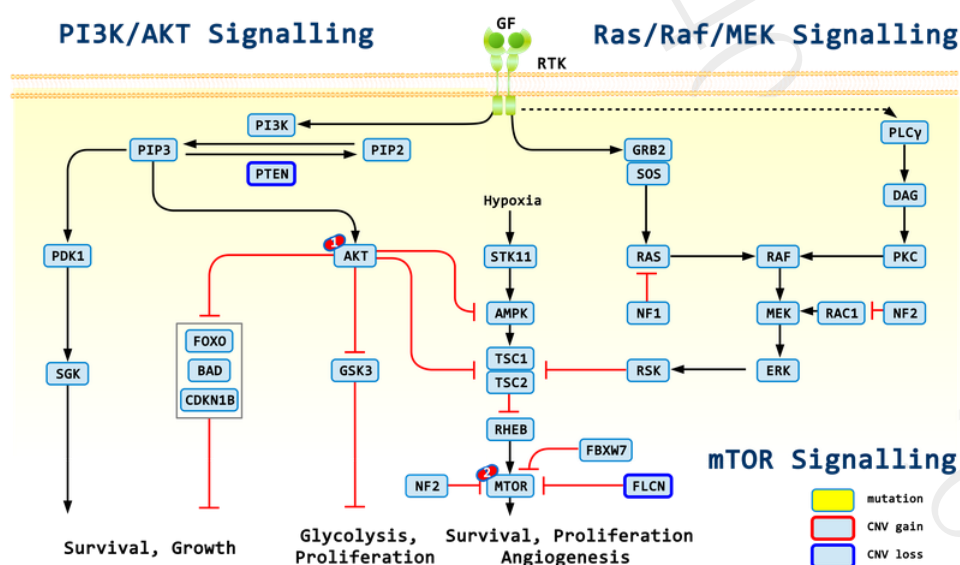
### POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
FLCN	Everolimus, Temsirolimus	sensitive

### SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



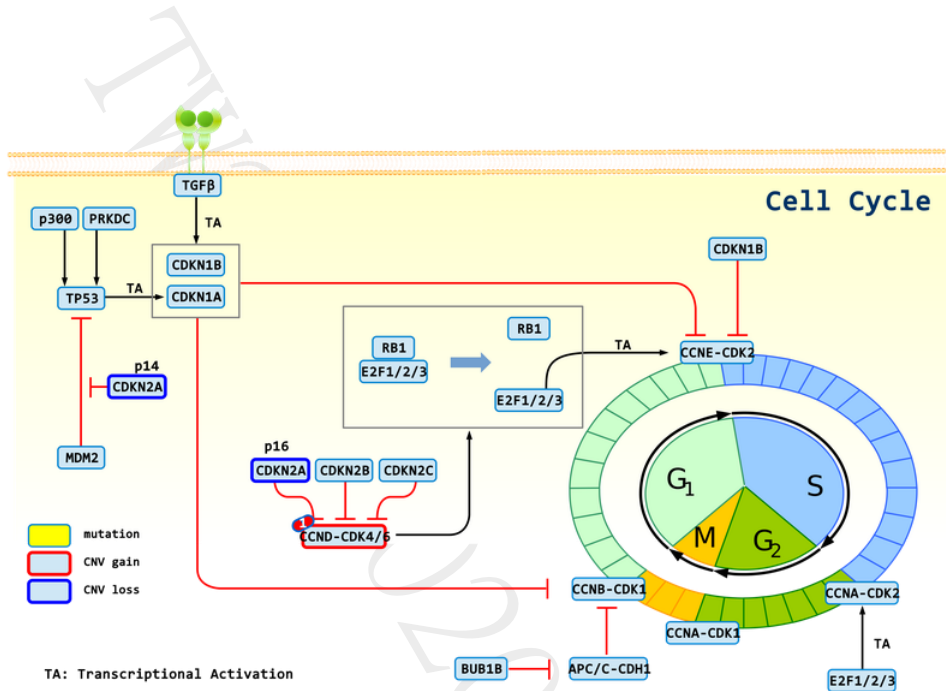
1: Olaparib, Rucaparib



1: Capivasertib; 2: Everolimus, Temsirolimus



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## 1: Abemaciclib, Palbociclib, Ribociclib



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## DISCLAIMER

### 法律聲明

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

本檢驗報告非經本公司許可，不得私自變造、塗改，或以任何方式作為廣告及其他宣傳之用途。

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

### 醫療決策需由醫師決定

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

### 基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

### 證據等級

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

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行動基因是美國病理學會認證實驗室，認證實驗室號碼: 9028096。

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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

Email: service@actgenomics.com T: +886-2-2795-3660 F: +886-2-2795-5016

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