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## PATIENT AND SAMPLE INFORMATION

### PATIENT

Name: 嚴言  
Gender: Male  
Date of Birth: Jul 20, 1952  
Patient ID: 47885950  
Diagnosis: Poorly differentiated carcinoma

### SPECIMEN

Type: FFPE tissue  
Date received: Dec 14, 2021  
Collection site: Liver  
Specimen ID: S11062270A  
Lab ID: AA-21-06185  
D/ID: NA

### ORDERING PHYSICIAN

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## VARIANT(S) WITH CLINICAL RELEVANCE

Only variant(s) with clinical significance are listed. See the "DETAILED TEST RESULTS" section for full details.

### SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
SERPINB4	D311Y	221	29.0%	-
TP53	Y236D	752	48.9%	COSM43602

### COPY NUMBER VARIANTS (CNVS)

Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on **54%** tumor purity.

#### Amplification (Copy number ≥ 8)

Chr	Gene	Copy Number
ND	ND	ND

#### Homozygous deletion (Copy number=0)

Chr	Gene
chr17	MAP2K4

#### Heterozygous deletion (Copy number=1)

Chr	Gene
chr4	FBXW7
chr9	CDKN2A
chr10	PTEN
chr11	ATM, CHEK1, MRE11
chr16	TSC2
chr17	FLCN
chr18	SMAD4
chr19	ERCC1

ND, Not Detected

TUMOR MUTATIONAL BURDEN (TMB)

1.9 muts/Mb

Muts/Mb, mutations per megabase

MICROSATELLITE INSTABILITY (MSI)

Microsatellite stable (MSS)

Note:

TMB was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at  $\geq 7.5$  mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is  $< 30\%$ .

**This specimen did not meet acceptance criteria due to low tumor purity. The test was performed with client's consent.**

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  
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## THERAPEUTIC IMPLICATIONS

### TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
<b>Level 3B</b>		
<b>ATM</b> Heterozygous deletion	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<b>CHEK1</b> Heterozygous deletion	Olaparib, Rucaparib	sensitive
<b>PTEN</b> Heterozygous deletion	Olaparib, Everolimus, Temsirolimus	sensitive
<b>CDKN2A</b> Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	sensitive
<b>Level 4</b>		
<b>ERCC1</b> Heterozygous deletion	Olaparib, Rucaparib	sensitive
<b>FBXW7</b> Heterozygous deletion	Everolimus, Temsirolimus	sensitive
<b>FLCN</b> Heterozygous deletion	Everolimus	sensitive
<b>TSC2</b> Heterozygous deletion	Everolimus, Temsirolimus	sensitive
<b>MAP2K4</b> Homozygous deletion	Selumetinib, Trametinib	sensitive
<b>MRE11</b> Heterozygous deletion	Olaparib, Talazoparib	sensitive
<b>PTEN</b> Heterozygous deletion	Cetuximab, Erlotinib, Gefitinib, Panitumumab, Trastuzumab	resistant
<b>FBXW7</b> Heterozygous deletion	Gefitinib, Regorafenib	resistant
<b>SMAD4</b> Heterozygous deletion	Cetuximab	resistant

† Refer to "ONGOING CLINICAL TRIALS" section for detailed trial information.

**Note:** Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence.

Level	Description
1	FDA-recognized biomarker predictive of response to an FDA approved drug in this indication
2	Standard care biomarker (recommended as standard care by the NCCN or other expert panels) predictive of response to an FDA approved drug in this indication
3	A Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor
	B Biomarkers that serve as inclusion criteria for clinical trials
4	Biomarkers that show plausible therapeutic significance based on small studies, few case reports or preclinical studies

## IMMUNE CHECKPOINT INHIBITORS (ICI) THERAPIES

Genomic markers and alterations that are associated with response to ICI therapies

Positive Biomarker	Negative Biomarker
TMB-H: ND	EGFR aberration: ND
MSI-H: ND	MDM2/MDM4 amplification: ND
MMR biallelic inactivation: ND	STK11 biallelic inactivation: ND
PBRM1 biallelic inactivation: ND	PTEN biallelic inactivation: ND
SERPINB3/SERPINB4 mutation: <b>Yes</b>	B2M biallelic inactivation: ND
	JAK1/2 biallelic inactivation: ND

MMR, mismatch repair; ND, 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

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

## OTHERS

Pharmacogenomic implication

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

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

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

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

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

### Note:

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

## VARIANT INTERPRETATION

### **SERPINB4 D311Y**

#### **Biological Impact**

SERPINB4 encodes a protein of the serpin family of serine protease inhibitors. SERPINB4 is a close human homolog of SERPINB3 with which shares 92% protein sequence identity. SERPINB3 and SERPINB4 proteins have overlapping functions and are involved in both oncogenesis and immunity<sup>[1][2]</sup>.

#### **Therapeutic and prognostic relevance**

Results from a clinical study showed that somatic mutations in SERPINB3 and SERPINB4 predicted improved survival from treatment with anti-CTLA4 therapy in two independent cohorts of patients with melanoma (n=174)<sup>[3]</sup>.

### **TP53 Y236D**

#### **Biological Impact**

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis<sup>[4]</sup>. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation<sup>[5]</sup>.

TP53 Y236D lies within the DNA-binding domain of the p53 protein (UniProtKB). This mutation has not been characterized in scientific literature; therefore, its effect on the p53 protein function remains unknown.

#### **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>[6]</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>[7]</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>[8]</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>[9][10][11]</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>[12]</sup>. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary

chemotherapy<sup>[13][14]</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>[15]</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>[16]</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>[17][18][19][20][21]</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>[22]</sup>. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies<sup>[23][24][25][26]</sup> and a broad range of tumors such as prostate cancer<sup>[27]</sup>, head and neck squamous cell carcinoma (HNSCC)<sup>[28]</sup>, pancreatic cancer<sup>[29]</sup>, lung adenocarcinoma<sup>[30]</sup>, breast cancer<sup>[31]</sup>, and ovarian cancer<sup>[18]</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<sup>[32]</sup>.

In addition, ATM has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer<sup>[33]</sup> or prostate cancer<sup>[34]</sup>, niraparib efficacy in pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in advanced or metastatic cancer (NCT02286687), HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

Besides, another randomized, double-blind Phase II trial in patients with metastatic gastric cancer has shown that addition of olaparib to paclitaxel significantly increased the overall survival in both the overall population and patients with low or undetectable ATM protein expression<sup>[35]</sup>. 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>[36]</sup>. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer<sup>[37]</sup>.



A Retrospective study of the VICTOR clinical trial in patients with colorectal cancer showed that loss of expression of ATM is associated with worse prognosis<sup>[38]</sup>.

## **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<sup>[39][40]</sup>, whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53<sup>[41]</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>[42]</sup>. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation<sup>[43][44]</sup>.

### **Therapeutic and prognostic relevance**

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors<sup>[45][46]</sup>. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments<sup>[47][48][49]</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>[50][51][52]</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).

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>[46][53][54]</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>[48]</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>[55]</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>[56]</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>[57]</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>[58][59]</sup>. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors<sup>[60]</sup>, and CHEK1 mutations are extremely rare<sup>[57]</sup>. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer<sup>[61]</sup>, breast cancer<sup>[62]</sup>, colorectal cancer<sup>[63]</sup>, non-small cell lung (NSCLC) cancer<sup>[64]</sup> and nasopharyngeal cancer<sup>[65]</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<sup>[32]</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<sup>[33]</sup> and 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>[66]</sup>.

## **ERCC1 Heterozygous deletion**

### **Biological Impact**

The Excision Repair Cross-Complementation Group 1 (ERCC1) gene encodes a non-catalytic component of a structure-specific DNA repair endonuclease that is responsible for 5' incision. This endonuclease is a heterodimer containing ERCC1 and ERCC4 and is involved in recombinational DNA repair and in the repair of inter-strand crosslinks (ICL). In addition, ERCC1 participates in the processing of anaphase bridge-generating DNA structures. Other genes associated with the nucleotide excision repair pathway includes ERCC1-5, CDK7, DDB1-2, XPA, and XPC<sup>[67]</sup>. ERCC1 haploinsufficiency is associated with tumorigenesis in the mouse model<sup>[68]</sup>.

### **Therapeutic and prognostic relevance**

Loss of expression of ERCC1 has long been implicated in increased sensitivity towards cisplatin in non-small cell lung cancer (NSCLC)<sup>[69]</sup> and ovarian carcinoma<sup>[70][71][72]</sup>. PARP inhibitors demonstrated anti-tumor activity against ERCC1-deficient non-small cell lung cancer (NSCLC) cell line<sup>[73][74][75]</sup>. Preclinical studies also showed that inhibiting

topoisomerase I and PARP1 in combination, as was demonstrated with the combination of ABT-888 and CPT-11, may result in the synergistic decrease in tumor regression for women with triple-negative breast cancer (TNBC)<sup>[76]</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>[77][78]</sup>, c-Jun<sup>[79]</sup>, cyclin E<sup>[80]</sup>, Notch family members<sup>[81][82]</sup>, Aurora-A<sup>[83]</sup>, mTOR<sup>[84]</sup>, KLF5<sup>[85]</sup>, and MCL-1<sup>[86]</sup>. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation<sup>[87]</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>[85][86][88]</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>[89][90]</sup>. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor<sup>[84]</sup>.

Preclinical studies suggested that mutations or loss of FBXW7 were associated with regorafenib and oxaliplatin resistance in CRC cell lines<sup>[91][92]</sup> and gefitinib resistance in lung cancer cells<sup>[93][94]</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>[95][93]</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>[96]</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>[97][98]</sup>. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling<sup>[99][100]</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>[101]</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

survival (PFS) of 15.2 months after receiving everolimus<sup>[102]</sup>. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting<sup>[103]</sup>.

### **MAP2K4 Homozygous deletion**

#### **Biological Impact**

MAP2K4 (mitogen-activated protein kinase kinase 4) gene encodes a dual specificity kinase which phosphorylates and activates JNK (c-Jun N-terminal kinase) and p38 MAP kinase pathways in response to environmental stressors, such as DNA damage, hypoxia, heat shock, ionizing radiation, as well as inflammatory cytokines and growth factors<sup>[104]</sup>. The protein plays essential roles in apoptosis, cell survival, growth, and differentiation<sup>[105][106]</sup>. Inactivating mutations and deletions of MAP2K4 have been reported in a variety of cancers, suggesting that MAP2K4 may function primarily as a tumor suppressor<sup>[105][107][108][109][110][111]</sup>. On the other hand, overexpression of MAP2K4 has been observed in laryngeal squamous cell carcinoma<sup>[112]</sup> and osteosarcoma<sup>[113]</sup>.

#### **Therapeutic and prognostic relevance**

Loss-of-function mutations of MAP2K4 was reported to associate with sensitivity to MEK inhibitors, such as trametinib and selumetinib in vitro<sup>[114]</sup>.

### **MRE11 Heterozygous deletion**

#### **Biological Impact**

The MRE11 gene encodes a protein that forms the MRE11-RAD50-NBS (MRN) complex involved in sensing and repairing DNA double-strand breaks via homologous recombination and non-homologous end joining<sup>[115][116]</sup>. MRE11 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function<sup>[115]</sup>. The carrier of MRE11 mutation may confer elevated risks for numerous types of cancers including breast cancer, ovarian cancer, endometrial cancer, colorectal cancer, and lymphoid cancer<sup>[115][116][117][118][119][120][121]</sup>.

#### **Therapeutic and prognostic relevance**

In a Phase II clinical trial (n=50), one castration-resistant prostate cancer patient harboring an MRE11 inactivating mutation responded to olaparib<sup>[122]</sup>. Preclinically, loss of MRE11 also predicted sensitivity to PARP inhibitor talazoparib and ABT-888 in endometrial cancer<sup>[123]</sup> and microsatellite unstable colorectal cancer (CRC) cell lines<sup>[124]</sup>.

CRC patients with tumor deficient of MRE11 showed initially reduced disease-free survival (DFS) and overall survival (OS) but improved long-term DFS and OS compared with patients with an intact MRE11<sup>[125]</sup>.

### **PTEN Heterozygous deletion**

#### **Biological Impact**

The phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene encodes a lipid/protein phosphatase that is important for the regulation of cell proliferation, survival, homologous recombination and

maintenance of genomic integrity<sup>[126][127]</sup>. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway<sup>[128]</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>[5][129][130]</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>[131][132][133]</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>[134][135][136][137][138]</sup>.

### Therapeutic and prognostic relevance

Somatic loss of PTEN results in aberrant activation of PI3K/AKT/mTOR signaling pathway and provides a mechanistic rationale for PI3K pathway inhibitors treatment<sup>[139][140]</sup>. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes<sup>[141][142][143][144][145][146]</sup>. Moreover, early clinical data also indicated that PTEN loss was associated with improved response and longer PFS in patients with advanced breast cancer<sup>[147]</sup>, advanced pancreatic neuroendocrine tumors<sup>[148]</sup> and metastatic castration-resistant prostate cancer<sup>[149]</sup> treated with mTORC1 inhibitor, everolimus.

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>[150][151][152][153][154]</sup>.

Loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab<sup>[155][156][157][158][159][160]</sup>. However, encouraging anti-tumor activity of the combination of an EGFR antibody and a mTORC1 inhibitor (everolimus or temsirolimus) have been reported in early-phase clinical studies (J Clin Oncol. 2011;29 (suppl): abstr 3587; J Clin Oncol. 2013;31 (suppl): abstr 608). Ongoing phase I/II studies testing combinations of EGFR antibodies and PI3K/AKT/mTOR pathway inhibitors (e.g., NCT01816984, NCT01252628, NCT01719380) will provide larger numbers of patients to assess the role of PTEN status in therapeutic response.

Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib<sup>[161][162]</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>[163]</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>[164][165][166]</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 breast cancer (NCT02401347), and niraparib efficacy in breast cancer (NCT04508803) or any malignancy (except prostate) cancer

(NCT03207347). Clinical data also suggested that PTEN deficient cancers may be sensitive to olaparib<sup>[167]</sup>.

### **SMAD4 Heterozygous deletion**

#### **Biological Impact**

The SMAD family member 4 (SMAD4) gene encodes a transcription factor that acts as a downstream effector in the TGF- $\beta$  signaling pathway. Upon phosphorylated and activated by serine-threonine receptor kinase, Smad4 is the Co-Smad which recruits other activated R-Smad proteins to the Smad transcriptional complex and regulate TGF- $\beta$ -targeted genes<sup>[168]</sup>. Smad4 has been identified as a haploinsufficient gene with one copy loss may lead to a weak protein expression and is insufficient to execute its original physiological function<sup>[169]</sup>. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)<sup>[170][171][172][173]</sup>. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer<sup>[174]</sup>, colorectal cancer (CRC)<sup>[172][175][176]</sup> and less frequently seen in other cancers such as lung adenocarcinoma<sup>[177]</sup>, head and neck cancer<sup>[178][179]</sup> and cutaneous squamous cell carcinoma<sup>[180]</sup>.

#### **Therapeutic and prognostic relevance**

In Chinese patients with metastatic colorectal cancer, SMAD4 or NF1 mutations are suggested as a potential biomarker for poor prognosis to cetuximab-based therapy<sup>[181]</sup>. Preclinical data demonstrated that depletion of SMAD4 by shRNA knockdown increased clonogenic survival and cetuximab resistance in HPV-negative head and neck squamous cell carcinoma cells<sup>[182]</sup>.

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)<sup>[183][184]</sup>. CRC patients with normal SMAD4 diploidy exhibited three-fold higher benefit of 5-FU/mitomycin-based adjuvant therapy when compared with those with SMAD4 deletion<sup>[185]</sup>.

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis<sup>[186][187][188][189][190][191][192][193]</sup>. In cervical cancer patients, weak cytoplasmic SMAD4 expression and absent nuclear SMAD4 expression were shown to be significantly associated with poor disease-free and overall 5-year survival<sup>[194]</sup>.

### **TSC2 Heterozygous deletion**

#### **Biological Impact**

The tuberous sclerosis complex 2 (TSC2) gene encodes a protein called tuberlin, which interact with a protein called hamartin (encoded by the TSC1 gene). This hamartin-tuberlin tumor suppressor complex plays a critical role in growth control as a negative regulator of the mammalian target of rapamycin (mTOR) pathway<sup>[195][196]</sup>. Mutations in TSC1/TSC2 tumor suppressor genes that result in inactivation of the complex are commonly found in patients with tuberous sclerosis complex<sup>[197][198][199]</sup>, while the loss of heterozygosity (LOH) in TSC1/TSC2 has been identified in head and neck squamous cell carcinoma (HNSCC)<sup>[200]</sup> and endometrial cancer<sup>[201]</sup>. TSC2 deletion, splicing-mutant, and inactivating mutations such as A1141T, G305V, S1514X, and R1032X, has been identified in TSC2-null hepatocellular carcinoma (HCC) cell lines, patient-derived xenograft, and primary tumors. Mutations in the TSC1

and TSC2 genes cause the autosomal dominant genetic disorder tuberous sclerosis complex (TSC)<sup>[202]</sup>.

### Therapeutic and prognostic relevance

Genomic alterations with activating effects of the mTOR signaling pathway (including deletion/inactivation of TSC1/TSC2) have been shown to confer sensitivity to everolimus across multiple cancer types, such as bladder cancer, gastric cancer, sarcoma, thyroid cancer, hepatocellular carcinoma (HCC) as well as head and neck squamous cell carcinoma (HNSCC)<sup>[203][204][205]</sup>. Results from one Phase II study of advanced endometrial cancer showed that mutations in AKT1, TSC1, and TSC2 might predict sensitivity to temsirolimus<sup>[206]</sup>. Recent studies indicated that there are mTORC1-independent signaling pathways downstream of hamartin-tuberin, which may represent new therapeutic targets<sup>[207]</sup>.



## 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>monarchE</b> NCT03155997	<b>Breast cancer</b> (Approved on 2021/10/12)
	<b>HR-positive, HER2-negative</b> Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
<b>MONARCH 3<sup>[208]</sup></b> NCT00246621	<b>Breast cancer</b> (Approved on 2018/02/26)
	<b>HR-positive, HER2-negative</b> Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
<b>MONARCH 1<sup>[209]</sup></b> NCT02102490	<b>Breast cancer</b> (Approved on 2017/09/28)
	<b>HR-positive, HER2-negative</b> Abemaciclib [ORR(%): 19.7 vs. 17.4]
<b>MONARCH 2<sup>[54]</sup></b> NCT02107703	<b>Breast cancer</b> (Approved on 2017/09/28)
	<b>HR-positive, HER2-negative</b> Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]

### 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>[210]</sup></b> 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<sup>[211]</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]

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。

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AG4-QP4001-02(05)



<b>RADIANT-3<sup>[148]</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>[212]</sup></b> NCT00789828	<b>Subependymal giant cell astrocytoma</b> (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
<b>RECORD-1<sup>[213]</sup></b> NCT00410124	<b>Renal cell carcinoma</b> (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

### 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>QUADRA<sup>[214]</sup></b> NCT02354586	<b>Ovarian cancer</b> (Approved on 2019/10/23)
	<b>HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)</b>
	Niraparib [ORR(%): 24.0, DOR(M): 8.3]
<b>NOVA<sup>[215]</sup></b> NCT01847274	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2017/03/27)
	<b>gBRCA+ CR/PR to platinum-based chemotherapy</b>
	Niraparib vs. Placebo [PFS(M): 21 vs. 5.5]
<b>NOVA<sup>[215]</sup></b> NCT01847274	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2017/03/27)
	<b>gBRCA- CR/PR to platinum-based chemotherapy</b>
	Niraparib vs. Placebo [PFS(M): 9.3 vs. 3.9]

## 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>PROfound</b> <sup>[32]</sup> NCT02987543	<b>Prostate cancer</b> (Approved on 2020/05/19)
	<b>ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm, RAD54Lm</b> Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
<b>PAOLA-1</b> <sup>[216]</sup> NCT02477644	<b>Ovarian cancer</b> (Approved on 2020/05/08)
	<b>HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)</b> Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
<b>POLO</b> <sup>[217]</sup> NCT02184195	<b>Pancreatic adenocarcinoma</b> (Approved on 2019/12/27)
	<b>Germline BRCA mutation (deleterious/suspected deleterious)</b> Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
<b>SOLO-1</b> <sup>[218]</sup> NCT01844986	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2018/12/19)
	<b>Germline or somatic BRCA-mutated (gBRCAm or sBRCAm)</b> Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
<b>OlympiAD</b> <sup>[219]</sup> NCT02000622	<b>Breast cancer</b> (Approved on 2018/02/06)
	<b>Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative</b> Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
<b>SOLO-2/ENGOT-Ov21</b> <sup>[220]</sup> NCT01874353	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2017/08/17)
	<b>gBRCA+</b> Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]

<b>Study19<sup>[221]</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]
<b>Study 42<sup>[222]</sup></b> NCT01078662	<b>Ovarian cancer</b> (Approved on 2014/12/19)
	<b>Germline BRCA mutation (deleterious/suspected deleterious)</b>
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

### Palbociclib (IBRANCE)

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

### FDA Approval Summary of Palbociclib (IBRANCE)

<b>PALOMA-2<sup>[223]</sup></b> 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<sup>[224]</sup></b> 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]

### 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<sup>[53]</sup></b> NCT01958021	<b>Breast cancer</b> (Approved on 2017/03/13)
	<b>HR+, HER2-</b>
	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)

<b>TRITON2</b> NCT02952534	<b>Prostate cancer</b> (Approved on 2020/05/15)
	<b>gBRCA+, sBRCA</b>
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
<b>ARIEL3<sup>[33]</sup></b> NCT01968213	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2018/04/06)
	<b>All   HRD   tBRCA</b>
	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]
<b>ARIEL2<sup>[225]</sup></b> NCT01482715, NCT01891344	<b>Ovarian cancer</b> (Approved on 2016/12/19)
	<b>Germline and/or somatic BRCA mutation</b>
	Rucaparib [ORR(%): 54.0]

## Selumetinib (KOSELUGO)

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

### FDA Approval Summary of Selumetinib (KOSELUGO)

<b>SPRINT</b> NCT01362803	<b>Plexiform neurofibromas</b> (Approved on 2020/04/10)
	<b>Neurofibromatosis type 1</b>
	Selumetinib [ORR(%): 66.0]

### 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>[226]</sup></b> NCT01945775	<b>Breast cancer</b> (Approved on 2018/10/16)
	<b>Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative</b>
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

### Temsirolimus (TORISEL)

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

#### FDA Approval Summary of Temsirolimus (TORISEL)

<b>[227]</b> NCT00065468	<b>Renal cell carcinoma</b> (Approved on 2007/05/30)
	-
	Temsirolimus vs. Ifn- $\alpha$ [OS(M): 10.9 vs. 7.3]

### Trametinib (MEKINIST)

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

#### FDA Approval Summary of Trametinib (MEKINIST)

<b>BRF117019<sup>[228]</sup></b> NCT02034110	<b>Anaplastic thyroid cancer</b> (Approved on 2018/05/04)
	<b>BRAF V600E</b>
	Dabrafenib + trametinib [ORR(%): 61.0]
<b>BRF113928<sup>[229]</sup></b> NCT01336634	<b>Non-small cell lung cancer</b> (Approved on 2017/06/22)
	<b>BRAF V600E</b>
	Trametinib + dabrafenib vs. Dabrafenib [ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9]

<b>COMBI-d<sup>[230]</sup></b> NCT01584648	<b>Melanoma</b> (Approved on 2014/01/10)
	<b>BRAF V600E/K</b>
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
<b>METRIC<sup>[231]</sup></b> NCT01245062	<b>Melanoma</b> (Approved on 2013/05/29)
	<b>BRAF V600E/K</b>
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

d=day; w=week; m=month

## ONGOING CLINICAL TRIALS

Clinical trials shown below were selected 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.



## DETAILED TEST RESULTS

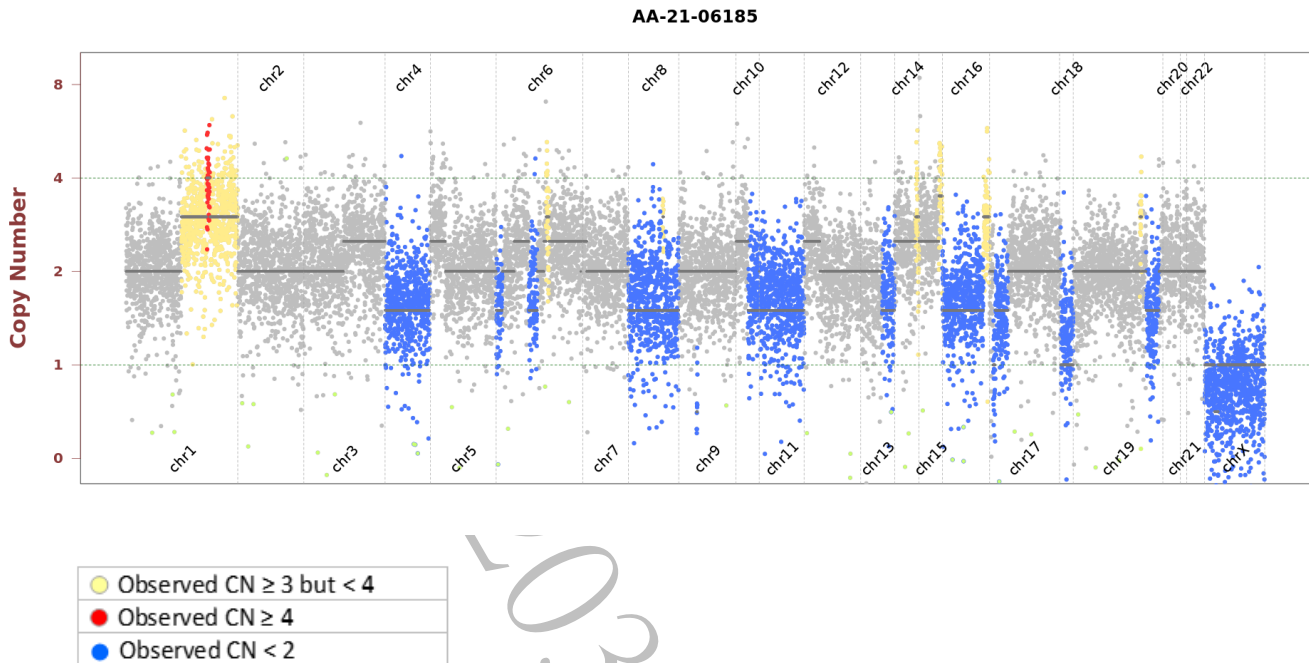
### SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Chr	Exon	Accession Number	cDNA Change	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
ABL1	9	1	NM_005157	c.62C>G	S21C	214	14.0%	-
ADAMTS16	5	13	NM_139056	c.1964A>G	H655R	813	42.1%	-
ADAMTSL1	9	18	NM_001040272	c.2404A>G	T802A	299	80.9%	-
ADAMTSL1	9	28	NM_001040272	c.5156G>A	R1719H	1026	22.7%	COSM8888781
AXIN1	16	6	NM_003502	c.1750G>A	A584T	376	27.9%	COSM6914525
BCL9	1	5	NM_004326	c.316G>A	D106N	556	26.1%	COSM4021824
CD58	1	2	NM_001779	c.241G>A	V81I	750	63.3%	-
EPHA7	6	7	NM_004440	c.1606G>C	E536Q	516	28.5%	-
FGFR4	5	5	NM_213647	c.590T>C	I197T	279	19.0%	-
IRS2	13	1	NM_003749	c.1457C>A	A486D	129	32.6%	-
MUC6	11	-	NM_005961	c.1453+4C>T	Splice region	177	71.2%	COSM2108620
PIK3R2	19	15	NM_005027	c.1923T>A	D641E	907	64.6%	-
<b>SERPINB4</b>	<b>18</b>	<b>8</b>	<b>NM_002974</b>	<b>c.931G&gt;T</b>	<b>D311Y</b>	<b>221</b>	<b>29.0%</b>	<b>-</b>
<b>TP53</b>	<b>17</b>	<b>7</b>	<b>NM_000546</b>	<b>c.706T&gt;G</b>	<b>Y236D</b>	<b>752</b>	<b>48.9%</b>	<b>COSM43602</b>

Mutations with clinical relevance are highlighted in red.

## COPY NUMBER VARIANTS (CNVs)

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.



## HOTSPOT GENOTYPES

Listed variants are biomarkers or hotspots that are recommended as standard care by the NCCN or other expert panels and not necessarily FDA-recognized for a particular indication. The genotypes have been manually checked to ensure sufficient coverage for each hotspot of the target gene.

Gene	Variant	Genotype Detected
<i>BRAF</i>	V600X	Not detected
<i>EGFR</i>	A763_Y764insFQEA, E709K, E709_T710delinsD, Exon 19 deletion, Exon 19 insertion, Exon 20 insertion, G719A/C/D/S, L747P, L833V, L858R, L861Q/R, S768I, T790M	Not detected
<i>IDH2</i>	R140Q, R172G/K/M/S	Not detected
<i>KIT</i>	A502_Y503dup, D419del, D579del, D816F/V/Y, D820A/E/G/Y, E554_I571del, E554_K558del, E554_V559del, Exon 11 mutation, F522C, H697Y, I563_L576del, I653T, K550_W557del, K558N, K558_E562del, K558_V559del, K558delinsNP, K642E, M552_W557del, N505I, N564_Y578del, N822H/I/K/Y, P551_M552del, P573_D579del, P577_D579del, P577_W582delinsPYD, P838L, Q556_K558del, T417_D419delinsI, T417_D419delinsRG, T574_Q575insTQLPYD, V530I, V555_L576del, V555_V559del, V559A/C/D/G, V559_V560del, V559del, V560D/G, V560del, V569_L576del, V654A, W557G/R, W557_K558del, Y553N, Y553_K558del, Y570H, Y578C	Not detected
<i>KRAS</i>	A146T/V/P, G12X, G13X, Q61X	Not detected
<i>MET</i>	D1028H/N/Y	Not detected
<i>NRAS</i>	G12X, G13X, Q61X	Not detected
<i>PDGFRA</i>	A633T, C450_K451insMIEWMI, C456_N468del, C456_R481del, D568N, D842I/V, D842_H845del, D842_M844del, D846Y, E311_K312del, G853D, H650Q, H845Y, H845_N848delinsP, I843del, N659K/R/S, N848K, P577S, Q579R, R560_V561insER, R748G, R841K, S566_E571delinsR, S584L, V469A, V536E, V544_L545insAVLVLLVIVISLI, V561A/D, V561_I562insER, V658A, W559_R560del, Y375_K455del, Y555C, Y849C/S	Not detected
<i>PIK3CA</i>	C420R, E542K/V, E545A/D/G/K, H1047X, Q546E/R	Not detected

V600X= any mutation in the valine (V) at amino acid 600 being replaced by a different amino acid.

G12X= any mutation in the glycine (G) at amino acid 12 being replaced by a different amino acid.

G13X= any mutation in the glycine (G) at amino acid 13 being replaced by a different amino acid.

Q61X= any mutation in the glutamine (Q) at amino acid 61 being replaced by a different amino acid.

H1047X= any mutation in the histidine (H) at amino acid 1047 being replaced by a different amino acid.

Gene	Copy Number Detected
<i>CDK4</i>	2
<i>EGFR</i>	2
<i>ERBB2</i>	2
<i>MET</i>	2

Copy number ≥ 8 is considered amplification

Other known alterations that are associated with sensitivity, resistance, and toxicity to therapies.

Gene	Variant	Genotype Detected
AKT1	E17K	Not detected
ALK	C1156Y, D1203N, G1202R, L1152R, S1206Y, T1151_L1152insT	Not detected
BRAF	K601E, L597V/Q/R/S	Not detected
DPYD	D949V, I560S, splice-site mutation	Not detected
EGFR	A750P, C797S/Y, S492R	Not detected
ERBB2	V659E	Not detected
ESR1	D538G, E380Q, L469V, L536H/P/Q/R, S432L, S463P, V422del, V534E, Y537C/N/S	Not detected
FGFR3	G370C, G380R, K650E/N/R/M/T/Q, R248C, S249C, S371C, Y373C	Not detected
IDH1	R132C/G/H/L/Q/S	Not detected
MAP2K1	D67N, E203K, F53L, K57E/N, P124S, Q56P, Q56_V60del, R47Q, R49L, S222D	Not detected
PTEN	R130*/fs/G/L/P/Q	Not detected
TPMT	A154T, Y240C	Not detected

Gene	Copy Number Detected
FGFR1	2
MDM2	2
MDM4	4

Copy number  $\geq 8$  is considered amplification

## TEST DETAILS

### ABOUT ACTOnco®+

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 variations (CNVs).

See ACTOnco®+ Gene List' Section for details of gene sequenced.

### DATABASE USED

- Reference genome: human genome sequence hg19
- COSMIC v.92
- Genome Aggregation database r2.1.1
- ClinVar (version 20210208)
- ACT Genomics in-house database

### NEXT-GENERATION SEQUENCING (NGS) METHODS

Extracted genomic DNA was amplified using four pools of primer pairs targeting coding exons of analyzed genes. Amplicons were ligated with barcoded adaptors. Quality and quantity of amplified library were determined using the fragment analyzer (AATI) and Qubit (Invitrogen). Barcoded libraries were subsequently conjugated with sequencing beads by emulsion PCR and enriched using Ion Chef system (Thermo Fisher Scientific) according to the Ion PI Hi-Q Chef Kit protocol (Thermo Fisher Scientific) or Ion 540 Kit-Chef protocol (Thermo Fisher Scientific). Sequencing was performed on the Ion Proton or Ion S5 sequencer (Thermo Fisher Scientific).

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite (version 5.10). 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 (version 5.10). The coverage was down-sampled to 4000. VEP (Variant Effect Predictor) (version 100) was used to annotate every variant using databases from Clinvar (version 20210208), COSMIC v.92 and Genome Aggregation database r2.1.1. Variants with coverage  $\geq 25$ , 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  $100x \geq 85\%$  with a mean coverage  $\geq 500x$ .

Variants reported in Genome Aggregation database r2.1.1 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 variations (CNVs) 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 from samples in ACT Genomics in-house database.

Tumor mutational burden (TMB) was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The TMB calculation predicted somatic variants and applied a machine learning model with a cancer hotspot correction. TMB may be reported as "TMB-High", "TMB-Low" or "Cannot Be Determined". TMB-High corresponds to  $\geq 7.5$  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).

## STANDARD OPERATING PROCEDURES (SOPS)

Standard operating procedures (SOPs) are shown below:

- AG2-QP-15 Specimen Management Procedure
- AG3-QP16-03 SOP of Cancer Cell DNA and RNA Extraction
- AG3-QP16-07 SOP of Nucleic Acid Extraction with QIAasympyphony SP
- AG3-QP16-08 SOP of FFPE Nucleic Acid Extraction
- AG3-QP16-10 SOP of HE Staining
- AG3-QP16-13 SOP of Library Construction and Preparation
- AG3-QP16-17 SOP of DNA Quantification with Qubit Fluorometer
- AG3-QP16-20 SOP of CE-Fragment Analysis
- AG3-QP16-22 SOP of Variant Calling
- AG3-QP16-24 SOP of Ion Torrent System Sequencing Reaction
- AG3-QP16-26 SOP of Ion Chef Preparation

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- AG3-QP16-35 SOP of Variant Annotation
- AG3-QP16-96 SOP of Manual Inspection for SNV/Indel Variant
- AG3-QP16-95 SOP of Manual Inspection for Copy Number Variant
- AG3-QP40-08 (02) Standard protocol for variant interpretation, curation and classification
- AG3-QP16-41 SOP of The user manual for clinical report system (CRS)

## LIMITATIONS

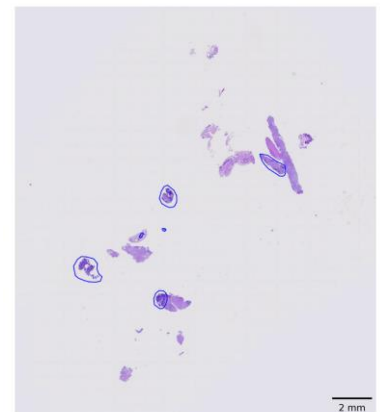
This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject to validation by Sanger or other technologies.

## NOTES

We do not exclude the possibility that pathogenic variants may not be reported by one or more of the tools and the parameters used.

## PATHOLOGY EVALUATION

- H&E-stained section No.: S11062270A
- Collection site: Liver
- Examined by: Dr. Pei-Yi Chu
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 10%  
The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 70%  
The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 45%  
The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 5%  
Additional comment: NA
- Manual macrodissection: Not performed



The outline highlights the area of malignant neoplasm annotated by a pathologist.



## SPECIMEN PHOTO(S)



- Collection date: Dec 2021
- Facility retrieved: 臺北榮總

## RUN QC

- Panel: ACTOnco<sup>®</sup>+
- Mean Depth: 579x
- Target Base Coverage at 100x: 92%

## ACTOnco® + GENE LIST

ABCB1*	AURKB	CBL	CDKN2B	E2F3	FAT1	GRIN2A	JAK2	MED12	NOTCH4	PMS1	RAD51D	SLCO1B3*	TNFRSF14
ABCC2*	AXIN1	CCNA1	CDKN2C	EGFR	FBXW7	GSK3B	JAK3	MEF2B	NPM1	PMS2	RAD52	SMAD2	TNFSF11
ABCG2*	AXIN2	CCNA2	CEBPA*	EP300	FCGR2B	GSTP1*	JUN*	MEN1	NQO1*	POLB	RAD54L	SMAD3	TOP1
ABL1	AXL	CCNB1	CHEK1	EPCAM	FGF1*	GSTT1*	KAT6A	MET	NRAS	POLD1	RAF1	SMAD4	TP53
ABL2	B2M	CCNB2	CHEK2	EPHA2	FGF10	HGF	KDM5A	MITF	NSD1	POLE	RARA	SMARCA4	TPMT*
ADAMTS1	BAP1	CCNB3	CIC	EPHA3	FGF14	HIF1A	KDM5C	MLH1	NTRK1	PPARG	RB1	SMARCB1	TSC1
ADAMTS13	BARD1	CCND1	CREBBP	EPHA5	FGF19*	HIST1H1C*	KDM6A	MPL	NTRK2	PPP2R1A	RBM10	SMO	TSC2
ADAMTS15	BCL10	CCND2	CRKL	EPHA7	FGF23	HIST1H1E*	KDR	MRE11	NTRK3	PRDM1	RECQL4	SOC1*	TSHR
ADAMTS16	BCL2*	CCND3	CRLF2	EPHB1	FGF3	HNF1A	KEAP1	MSH2	PAK3	PRKAR1A	REL	SOX2*	TYMS
ADAMTS18	BCL2L1	CCNE1	CSF1R	ERBB2	FGF4*	HR	KIT	MSH6	PALB2	PRKCA	RET	SOX9	U2AF1
ADAMTS6	BCL2L2*	CCNE2	CTCF	ERBB3	FGF6	HRAS*	KMT2A	MTHFR*	PARP1	PRKCB	RHOA	SPEN	UBE2A*
ADAMTS9	BCL6	CCNH	CTLA4	ERBB4	FGFR1	HSP90AA1	KMT2C	MTOR	PAX5	PRKCG	RICTOR	SPOP	UBE2K
ADAMTSL1	BCL9	CD19	CTNNA1	ERCC1	FGFR2	HSP90AB1	KMT2D	MUC16	PAX8	PRKCI	RNF43	SRC	UBR5
ADGRA2	BCOR	CD274	CTNNB1	ERCC2	FGFR3	HSPA4	KRAS	MUC4	PBRM1	PRKCQ	ROS1	STAG2	UGT1A1*
ADH1C*	BIRC2	CD58	CUL3	ERCC3	FGFR4	HSPA5	LCK	MUC6	PDCD1	PRKDC	RPPH1	STAT3	USH2A
AKT1	BIRC3	CD70*	CYLD	ERCC4	FH	IDH1	LIG1	MUTYH	PDCD1LG2	PRKN	RPTOR	STK11	VDR*
AKT2	BLM	CD79A	CYP1A1*	ERCC5	FLCN	IDH2	LIG3	MYC	PDGFRA	PSMB8	RUNX1	SUFU	VEGFA
AKT3	BMPR1A	CD79B	CYP2B6*	ERG	FLT1	IFNL3*	LMO1	MYCL	PDGFRB	PSMB9	RUNX1T1	SYK	VEGFB
ALDH1A1*	BRAF	CDC73	CYP2C19*	ESR1	FLT3	IGF1	LRP1B	MYCN	PDIA3	PSME1	RXRA	SYNE1	VHL
ALK	BRCA1	CDH1	CYP2C8*	ESR2	FLT4	IGF1R	LYN	MYD88	PGF	PSME2	SDHA	TAF1	WT1
AMER1	BRCA2	CDK1	CYP2D6	ETV1	FOXL2*	IGF2	MALT1	NAT2*	PHOX2B*	PSME3	SDHB	TAP1	XIAP
APC	BRD4	CDK12	CYP2E1*	ETV4	FOXP1	IKBKB	MAP2K1	NBN	PIK3C2B	PTCH1	SDHC	TAP2	XPO1
AR	BRIP1	CDK2	CYP3A4*	EZH2	FRG1	IKBKE	MAP2K2	NEFH	PIK3C2G	PTEN	SDHD	TAPBP	XRCC2
ARAF	BTG1*	CDK4	CYP3A5*	FAM46C	FUBP1	IKZF1	MAP2K4	NF1	PIK3C3	PTGS2	SERPINB3	TBX3	ZNF217
ARID1A	BTG2*	CDK5	DAXX	FANCA	GATA1	IL6	MAP3K1	NF2	PIK3CA	PTPN11	SERPINB4	TEK	
ARID1B	BTK	CDK6	DCUN1D1	FANCC	GATA2	IL7R	MAP3K7	NFE2L2	PIK3CB	PTPRD	SETD2	TERT	
ARID2	BUB1B	CDK7	DDR2	FANCD2	GATA3	INPP4B	MAPK1	NFKB1	PIK3CD	PTPRT	SF3B1	TET1	
ASXL1	CALR	CDK8	DICER1	FANCE	GNA11	INSR	MAPK3	NFKBIA	PIK3CG	RAC1	SGK1	TET2	
ATM	CANX	CDK9	DNMT3A	FANCF	GNA13	IRF4	MAX	NKX2-1*	PIK3R1	RAD50	SH2D1A*	TGFBR2	
ATR	CARD11	CDKN1A	DOT1L	FANCG	GNAQ	IRS1	MCL1	NOTCH1	PIK3R2	RAD51	SLC19A1*	TMSB4X*	
ATRX	CASP8	CDKN1B	DPYD	FANCL	GNAS	IRS2*	MDM2	NOTCH2	PIK3R3	RAD51B	SLC22A2*	TNF	
AURKA	CBFB	CDKN2A	DTX1	FAS	GREM1	JAK1	MDM4	NOTCH3	PIM1	RAD51C	SLCO1B1*	TNFAIP3	

\*Analysis of copy number alteration not available.

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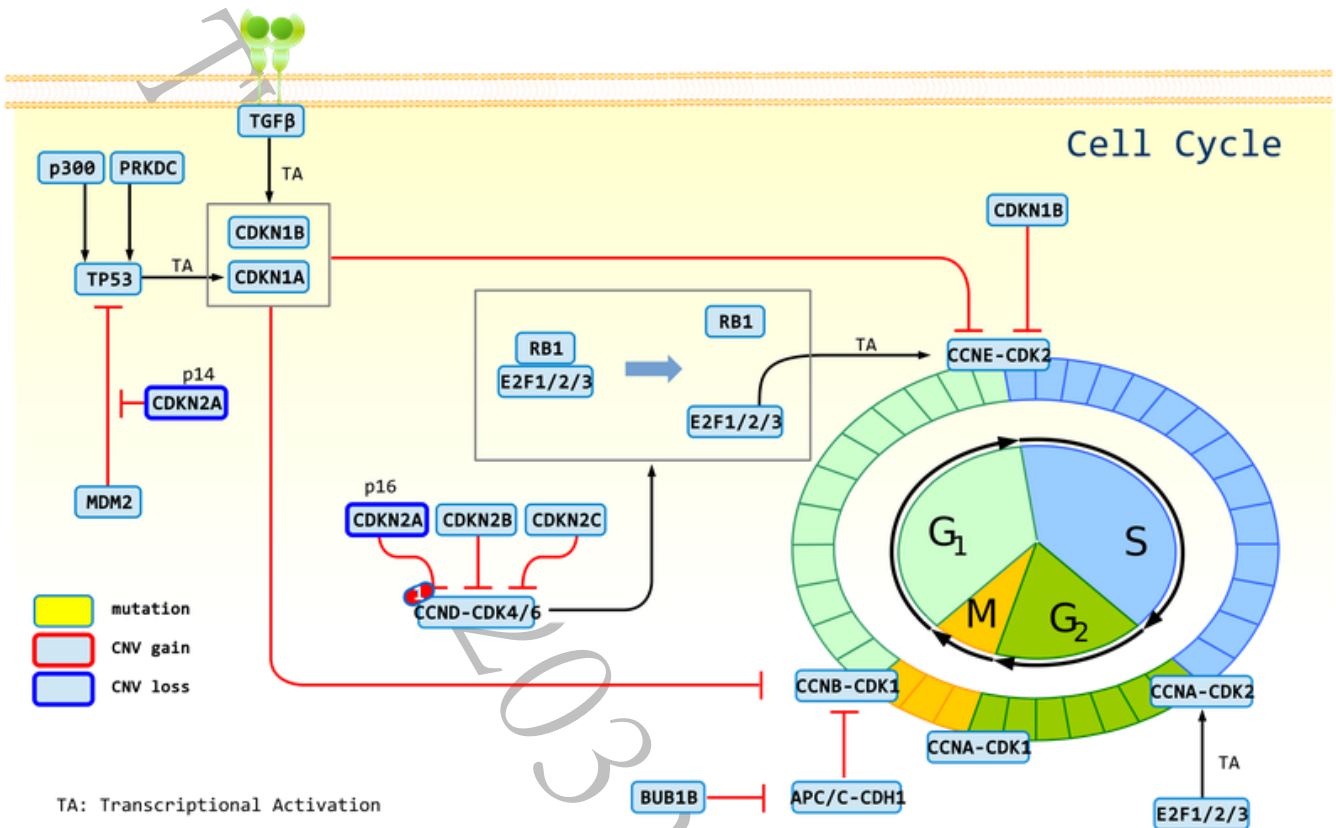
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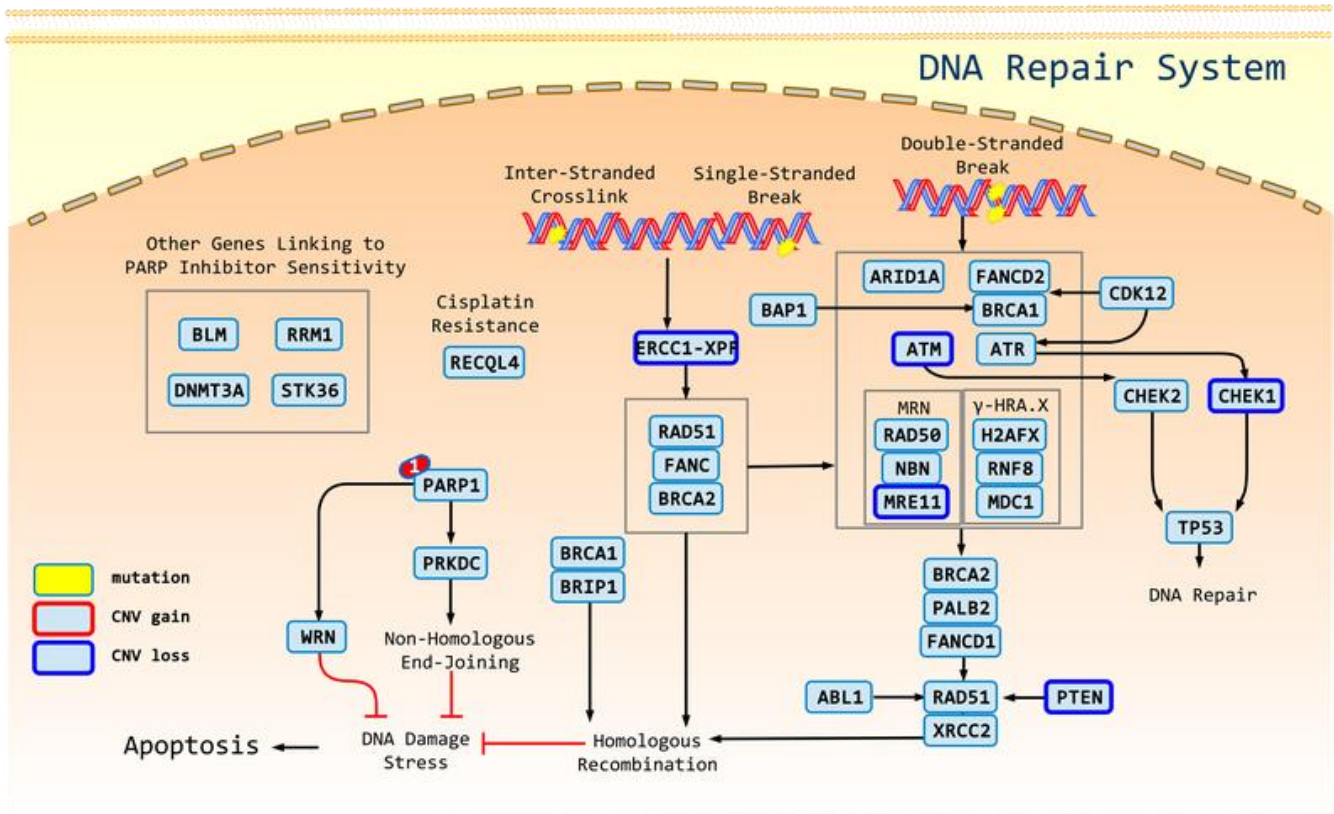
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## SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

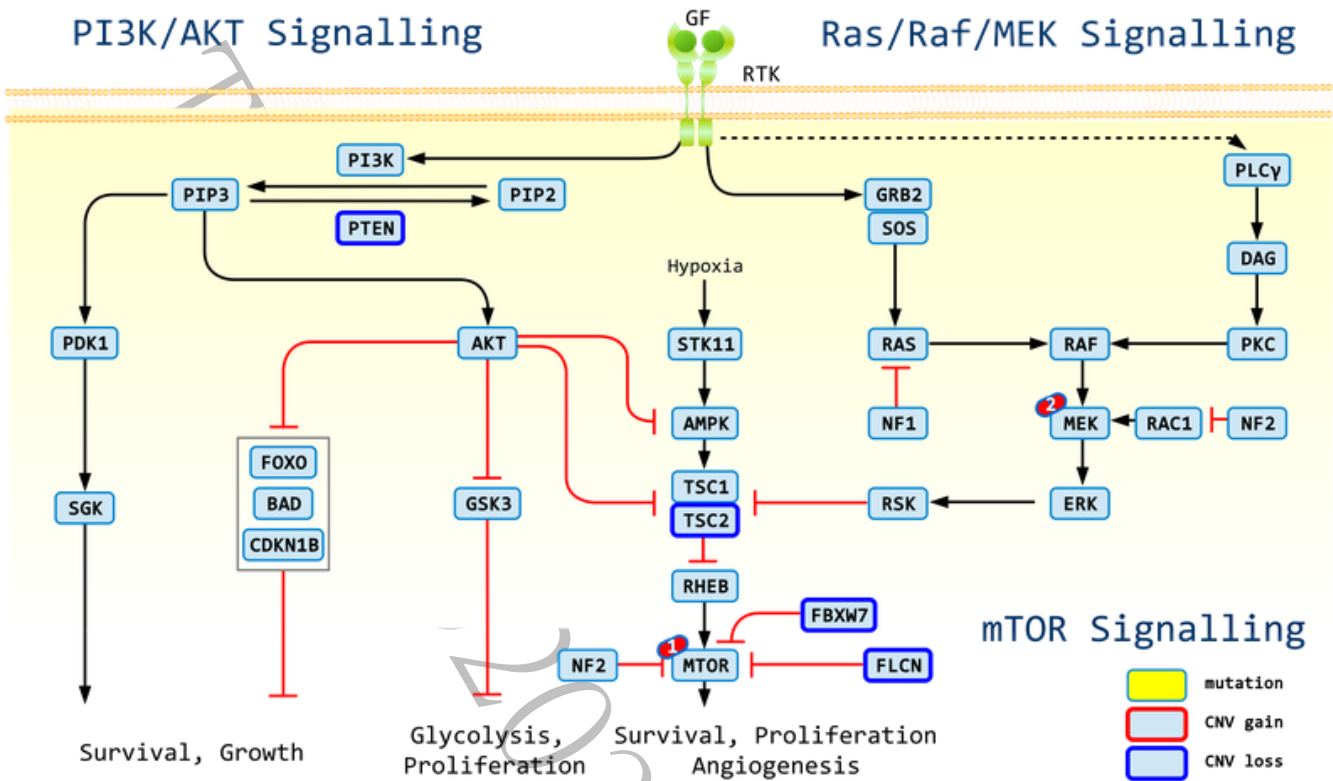


1: Abemaciclib, Palbociclib, Ribociclib



1: Olaparib, Niraparib, Rucaparib, Talazoparib





1: Everolimus, Temsirolimus; 2: Trametinib, Selumetinib



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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。

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# ACTFusion™ Report

PATIENT		
Name: 嚴言		Patient ID: 47885950
Date of Birth: Jul 20, 1952		Gender: Male
Diagnosis: Poorly differentiated carcinoma		
ORDERING PHYSICIAN		
Name: 陳明晃醫師		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: S11062270A		Date received: Dec 14, 2021
Lab ID: AA-21-06185		D/ID: NA
Collection site: Liver		
Type: FFPE tissue		

## ABOUT ACTFusion™

The test is a next-generation sequencing (NGS) based in vitro diagnostic assay to detect fusion transcripts of 13 genes, including *ALK*, *BRAF*, *EGFR*, *FGFR1*, *FGFR2*, *FGFR3*, *MET*, *NRG1*, *NTRK1*, *NTRK2*, *NTRK3*, *RET*, and *ROS1*.

## TESTING RESULTS

### VARIANT(S) WITH CLINICAL RELEVANCE

#### - Fusions

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

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## THERAPEUTIC IMPLICATION

Not Applicable.

## VARIANT INTERPRETATION

Not Applicable.

## US FDA-APPROVED DRUG(S)

Not Applicable.

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## ONGOING CLINICAL TRIALS

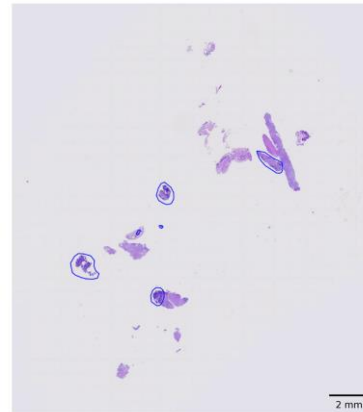
Trials were searched by applying filters: study status, patient's diagnosis, intervention, location and/or biomarker(s). Please visit <https://clinicaltrials.gov> to search and view for a complete list of open available and updated matched trials.

No trial has been found.

# ACTFusion™ Report

## TEST DETAILS

### SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Dec 2021
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11062270A
- Collection site: Liver
- Examined by: Dr. Pei-Yi Chu
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 10%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 70%
  3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 45%
  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: ACTFusion™
- Total reads: 590764
- Average unique RNA Start Sites per control GSP2: 166

## LIMITATIONS

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.

# ACTFusion™ Report

## NEXT-GENERATION SEQUENCING (NGS) METHODS

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.

## STANDARD OPERATING PROCEDURES (SOPs)

- AG2-QP-15 Specimen Management Procedure
- AG3-QP16-08 SOP of FFPE Nucleic Acid Extraction
- AG3-QP16-10 SOP of HE Staining
- AG3-QP16-17 SOP of DNA Quantification with Qubit Fluorometer
- AG3-QP16-20 SOP of CE-Fragment Analysis
- AG3-QP16-24 SOP of Ion Torrent System Sequencing Reaction
- AG3-QP16-26 SOP of Ion Chef Preparation
- AG3-QP40-08 (02) Standard protocol for variant interpretation, curation and classification
- AG3-QP16-94 (01) SOP of ACTFusion v3 Library Construction and Preparation
- AG3-QP16-36(02) SOP of Fusion Gene Detection
- AG3-QP16-41 SOP of The user manual for clinical report system (CRS)

## DATABASES USED

- Quiver Gene Fusion Database version 5.1.18

## GENE LIST

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

This specimen did not meet acceptance criteria due to low tumor purity. The test was performed with client's consent.

### 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



# ACTFusion™ Report

## 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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## REFERENCE

Not Applicable.