

ACT Onco[®] + Report

PATIENT		
Identifier: 邱*換		Patient ID: ***99699
Date of Birth: Mar **, 1959		Gender: Male
Diagnosis: Ampulla of Vater adenocarcinoma		
ORDERING PHYSICIAN		
Name: 洪逸平醫師		Tel: 886-228712121
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SPECIMEN		
Specimen ID: S11390067H	Collection site: Ampulla of Vater	Type: FFPE tissue
Date received: Feb 06, 2024	Lab ID: AA-24-00782	D/ID: NA

ABOUT ACT Onco[®]+

The test is a next-generation sequencing (NGS)-based assay developed for efficient and comprehensive genomic profiling of cancers. This test interrogates coding regions of 440 genes associated with cancer treatment, prognosis and diagnosis. Genetic mutations detected by this test include small-scale mutations like single nucleotide variants (SNVs), small insertions and deletions (InDels) (≤ 15 nucleotides) and large-scale genomic alterations like copy number alterations (CNAs). The test also includes an RNA test, detecting fusion transcripts of 13 genes.

SUMMARY FOR ACTIONABLE VARIANTS

VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Probable Effects in Patient's Cancer Type		Probable Sensitive in Other Cancer Types
	Sensitive	Resistant	
Not detected			

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
KRAS Q61H	-	Cetuximab, Panitumumab
CDKN2A A85fs	Abemaciclib, Palbociclib, Ribociclib	-
CDKN2A Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	-
CRKL Amplification	-	Gefitinib
MAPK1 Amplification	-	Erlotinib

Note:

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



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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
<i>CDKN2A</i>	A85fs	30.7%
<i>KRAS</i>	Q61H	23.7%
<i>TP53</i>	R248W	27.4%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr5	<i>NSD1</i>	Homozygous deletion	0
Chr1	<i>CDKN2C</i>	Heterozygous deletion	1
Chr10	<i>PTEN</i>	Heterozygous deletion	1
Chr9	<i>CDKN2A</i>	Heterozygous deletion	1
Chr22	<i>CRKL, MAPK1</i>	Amplification	7

- Fusions

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

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	0.1 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 33% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco[®] to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is $< 30\%$.

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SUPPLEMENTARY INFORMATION FOR THERAPEUTIC IMPLICATIONS TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3A		
KRAS Q61H	Cetuximab, Panitumumab	resistant
Level 3B		
CDKN2A A85fs	Abemaciclib, Palbociclib, Ribociclib	sensitive
CDKN2A Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	sensitive
Level 4		
CRKL Amplification	Gefitinib	resistant
MAPK1 Amplification	Erlotinib	resistant

Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence in professional guidelines or peer-reviewed journals.

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

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

No genomic alterations detected to confer sensitivity or lack of benefit to immune checkpoint therapies.

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
Not detected	

Note: Tumor non-genomic factors, such as patient germline genetics, PDL1 expression, tumor microenvironment, epigenetic alterations or other factors not provided by this test may affect ICI response.

CHEMOTHERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
TP53 R248W	Platinum- and taxane-based regimens	Less sensitive	Clinical	Ovarian cancer

HORMONAL THERAPIES

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

OTHERS

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

Note:

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

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VARIANT INTERPRETATION

CDKN2A A85fs, Heterozygous deletion

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53^{[1][2][3]}. 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^[4]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation^{[5][6]}.

A85fs mutation results in a change in the amino acid sequence beginning at 85, likely to cause premature truncation of the functional CDKN2A protein (UniProtKB). This mutation is predicted to lead to a loss of CDKN2A protein function, despite not being characterized in the literature. Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors^{[7][8]}. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments^{[9][10][11]}. 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^{[12][13][14]}. CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

The phase II TAPUR trial demonstrated clinical benefits to palbociclib monotherapy in advanced NSCLC or head and neck cancer harboring a CDKN2A mutation or copy number loss. However, pancreatic and biliary cancer patients harboring a CDKN2A mutation or copy number loss did not demonstrate an objective response or stable disease when treated with palbociclib monotherapy for 16 weeks (DOI: 10.1200/JCO.2021.39.15_suppl.6043)^{[15][16]}.

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^{[8][17][18]}.

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^[10]. 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^[19].

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^[20].

KRAS Q61H

Biological Impact

The V-Ki-Ras2 Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (KRAS) gene encodes a small GTPase protein, a member of the RAS family of small GTPases, which catalyze the hydrolysis of GTP to GDP. RAS proteins cycle between an active (GTP-bound) and an inactive (GDP-bound) state, to activate the downstream oncogenic pathways, including the PI3K/AKT/mTOR and MAPK pathways^[21].



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

KRAS Q61H is a missense mutation, which interferes with Ras GTPase activity and results in downstream pathway activation^{[30][31][32]}.

Therapeutic and prognostic relevance

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

KRAS mutation has been determined as an inclusion criterion for the trials evaluating MEK inhibitors efficacies in various types of solid tumors (NCT03704688, NCT02399943, NCT02285439, NCT03637491, NCT04214418).

KRAS mutations are associated with a lack of efficacy of EGFR TKIs^{[33][34][35]}. Some case reports suggest that MEK inhibitors may benefit patients with KRAS mutations, as shown in cervical and ovarian cancer cases (Am J Clin Exp Obstet Gynecol 2015;2(3):140-143)^{[36][37]}. However, a randomized Phase II study did not find trametinib to be superior to docetaxel in KRAS-mutant non-small cell lung cancer patients^[38]. MEK inhibitors as a monotherapy have limited response^[39].

Combining MEK and mTOR inhibitors is being evaluated as a potential strategy in RAS-mutant CRC^{[40][41]}. The combination of trametinib and palbociclib has resulted in objective responses in KRAS mutant models^[42].

Sorafenib has been shown to be beneficial in KRAS-mutant CRC/NSCLC, and KRAS-amplified melanoma^{[43][44][45]}. KRAS mutations in exon 2 (codon 12 or 13) and codon 61 have been associated with poor prognosis in CRC^[46].

Patients with KRAS or BRAF mutations in low-grade serous carcinoma of the ovary or peritoneum had better overall survival than those with wild-type genes^[47]. In ovarian serous borderline tumor, KRAS G12V mutation was linked to shorter survival time^[48].

TP53 R248W

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[49]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[50].

R248W is a missense mutation located in the DNA-binding domain (DBD) of the p53 protein^[51]. This mutation results in abrogation of the p53 tumor suppressor activity and a gain-of-function in ATM inactivation, resulting in increased genetic instability and increased tumorigenesis in mouse models^[52].

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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)^[53].

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^[54]. 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^[55].

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^{[56][57][58]}. 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)^[59]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[60][61]}. 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^[62].

TP53 oncomorphic mutations, including P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L, and R282W have been shown to predict resistance to platinum- and taxane-based chemotherapy in advanced serous ovarian carcinoma patients^[63].

CDKN2C Heterozygous deletion

Biological Impact

CDKN2C gene encodes for cyclin-dependent kinase inhibitor 2C (CDKN2C) or p18 or INK4C, a member of the INK4 family of cyclin-dependent kinase inhibitors. CDKN2C binds to CDK4 or CDK6 and inhibits the activation of cyclin-dependent kinases (CDK) to prevent cell cycle progression at the G1 phase^[64]. CDKN2C has been implicated as a haploinsufficient tumor suppressor gene^[65] with one copy loss may promote cell cycle progression and induce proliferation in a variety of cancers^{[66][67][68]}. Loss of CDKN2C by gene deletion or inactivating mutation has been reported in multiple cancer types, including myeloma, lymphoma, glioblastoma, meningioma, testicular cancers, melanoma, hepatocellular carcinomas, thyroid, and parathyroid cancer^{[69][70][71][72][73][74][75][76][77]}.

Therapeutic and prognostic relevance

CDKN2C loss has been determined as an inclusion criterion for the trial evaluating abemaciclib and ribociclib efficacies in patients with glioblastoma and myeloma (NCT02981940, NCT04118036, NCT03834740, NCT02933736).

An in vitro study demonstrated that cells expressing CDKN2A/B/C triple deletions activates cyclin-dependent kinases (CDK) and improves the sensitivity to palbociclib in glioblastoma multiforme (GBM) tumor cells^[78]. Deletion of CDKN2C was associated with poorer prognosis in myeloma, acute lymphoblastic leukemia, hepatocellular carcinomas, and diffuse large B cell lymphoma (DLBCL)^{[79][80][76][81]}.

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CRKL Amplification

Biological Impact

The CRKL gene encodes an oncogenic protein that facilitates signal transduction from multiple different kinases to downstream targets, including the BCR-ABL translocation kinase that enhances transformation in chronic myelogenous leukemia (CML)^{[82][83]}. Amplification of CRKL has been implicated in lung and gastric cancer^{[84][85]}.

Therapeutic and prognostic relevance

Preclinical data suggest that amplification of the CRKL gene is associated with acquired resistance to EGFR tyrosine kinase inhibitor, gefitinib, in lung cancer^[84].

MAPK1 Amplification

Biological Impact

The MAPK1 gene (mitogen-activated protein kinase 1, also known as ERK2) encodes for a serine/threonine kinase, a member of the MAP kinase family (also known as extracellular signal-regulated kinases (ERKs)), involved in the RAS-RAF-MEK-ERK signal transduction pathway. Upon triggering by mitosis and differentiation factors as well as cytokines, MAPK1 is phosphorylated by its upstream kinases, resulting in its homodimerization and translocation to the nucleus where it phosphorylates its target proteins^{[86][87][88]}. MAPK1 and MAPK3 are two homologs that show functional redundancy for cell proliferation^{[89][90][88]}. Although MAPK1 mutations are rarely found in human tumors, the recurrent mutation, E322K, is found in cervical and head and neck cancers and amplification is observed in ovarian cancer^{[91][92][93]}.

Therapeutic and prognostic relevance

A few Inhibitors of MAPK1/3 (ERK2 and ERK1) are being explored as complementary and alternative options to RAF and MEK inhibition in cases of resistance or partial response^{[94][95][96]}. More recently, a characterization of the 'dual-mechanism' ERK inhibitor SCH727294 (Merck/Schering Plough) was reported^[97].

MAPK1 amplification has been reported in an erlotinib resistant EGFR mutant non-small cell lung cancer (NSCLC) patient and MAPK1-amplified cells demonstrated a decrease in sensitivity to cytotoxic chemotherapy and EGFR therapy^[98].

Patients with type II ovarian carcinoma harboring MAPK1 amplification had poorer progression-free survival than patients without MAPK1 amplification^[93].

NSD1 Homozygous deletion

Biological Impact

Nuclear receptor binding SET domain protein 1 (NSD1) is a SET domain histone methyltransferase that demethylates nucleosomal histone H3 lysine 36 (H3K36)^[99]. NSD1 mutations have been identified in developmental syndrome (Sotos syndrome, Beckwith-Wiedemann syndrome) and are frequently detected in head and neck cancer, endometrial carcinoma, and melanoma^[100].

Therapeutic and prognostic relevance

In laryngeal cancer, patients with tumor carrying highly damaging impact (mostly are nonsense or frameshift) NSD1 mutations had better overall survival by comparing with those harboring low damaging impact (missense) mutation or wild-type NSD1^[101].

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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^{[102][103]}. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway^[104]. 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^{[50][105][106]}. 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^{[107][108][109]}. 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^{[110][111][112][113][114]}.

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^{[115][116]}. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes^{[117][118][119][120][121][122]}. Although early clinical data indicated that PTEN loss was associated with improved response and survival in solid tumor patients treated with mTORC1 inhibitor, everolimus^{[123][124][125]}, several phase II trials showed no clinical benefit of everolimus or temsirolimus treatment in patients with advanced solid tumors harboring PTEN loss^{[126][127][128]}.

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^{[129][130][131][132][133]}. Also, loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab^{[134][135][136][137][138][139]}. Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib^{[140][141]}. 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^[142]. 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^{[143][144][145]}.

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^[146]. 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^[147].

In a preclinical study, PTEN null cancer cells were sensitive to rucaparib treatment in vitro^[148].

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US FDA-APPROVED DRUG(S)

Abemaciclib (VERZENIO)

Abemaciclib is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. Abemaciclib is developed and marketed by Eli Lilly under the trade name VERZENIO.

- FDA Approval Summary of Abemaciclib (VERZENIO)

MONARCH E NCT03155997	Breast cancer (Approved on 2021/10/12)
	HR+/HER2- Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3 ^[149] NCT02246621	Breast cancer (Approved on 2018/02/26)
	HR+/HER2- Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 2 ^[18] NCT02107703	Breast cancer (Approved on 2017/09/28)
	HR+/HER2- Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1 ^[150] NCT02102490	Breast cancer (Approved on 2017/09/28)
	HR+/HER2- 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)

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

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)

MAGNITUDE NCT03748641	Prostate cancer (Approved on 2023/08/11)
	BRCA mutation Niraparib and abiraterone acetate plus prednisone vs. placebo and abiraterone acetate plus prednisone [rPFS(M): 16.6 vs. 10.9]
PRIMA NCT02655016	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2020/04/29)
	- Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
NOVA ^[151] NCT01847274	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/03/27)
	- Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

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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)

PROpel NCT03732820	Prostate cancer (Approved on 2023/05/31)
	BRCA mutation Olaparib + abiraterone + prednisone vs. Placebo + abiraterone + prednisone [rPFS(M): not reached vs. 8]
OlympiA NCT02032823	HER2-negative high-risk early breast cancer (Approved on 2022/03/11)
	HER2-/gBRCA mutation Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound ^[152] NCT02987543	Prostate cancer (Approved on 2020/05/19)
	HRR genes mutation Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1 ^[153] NCT02477644	Ovarian cancer (Approved on 2020/05/08)
	HRD+ Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO ^[154] NCT02184195	Pancreatic adenocarcinoma (Approved on 2019/12/27)
	gBRCA mutation Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1 ^[155] NCT01844986	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2018/12/19)
	gBRCA mutation or sBRCA mutation Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD ^[156] NCT02000622	Breast cancer (Approved on 2018/02/06)
	HER2-/gBRCA mutation Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21 ^[157] NCT01874353	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	gBRCA mutation Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19 ^[158] 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 ^[159] NCT01740427	Breast cancer (Approved on 2017/03/31)
	ER+/HER2- Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]

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PALOMA-3 ^[160] 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 ^[17] 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 ^[161] 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]

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)

TALAPRO-2 NCT03395197	Prostate cancer (Approved on 2023/06/20)
	HRR genes mutation
	Talazoparib + enzalutamide vs. Placebo + enzalutamide [rPFS(M): Not reached vs. 13.8]
EMBRACA ^[162] NCT01945775	Breast cancer (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

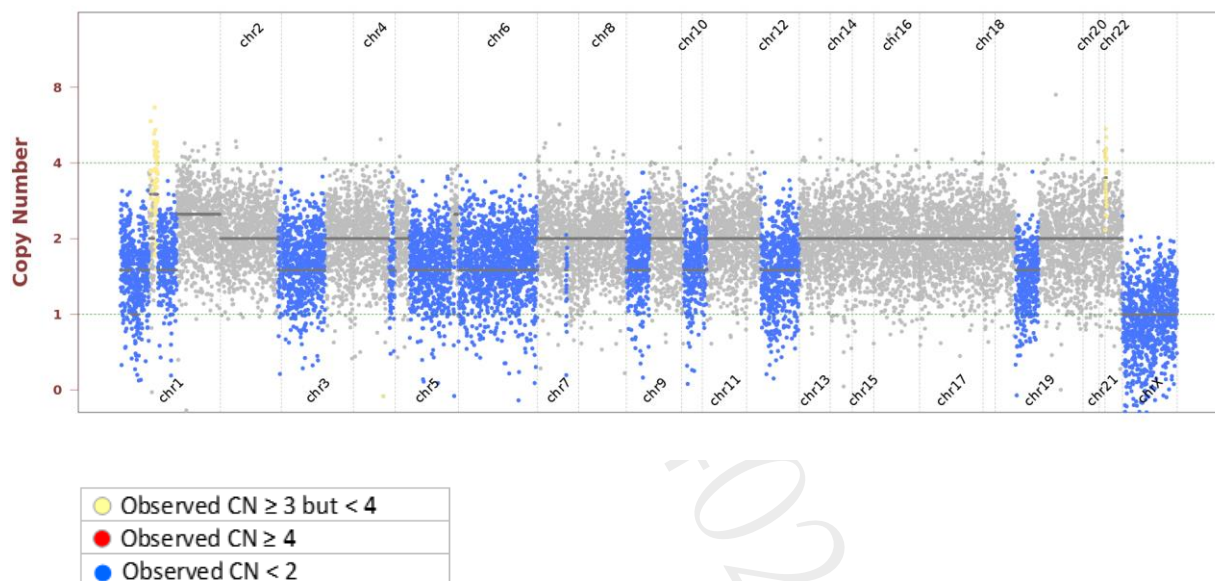
Trials were searched by applying filters: study status, patient's diagnosis, intervention, location and/or biomarker(s). Please visit <https://clinicaltrials.gov> to search and view for a complete list of open available and updated matched trials.

No trial has been found.

- Single Nucleotide and Small InDel Variants

- Copy Number Alterations

AA-24-00782



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OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ADGRA2	R255H	7	c.764G>A	NM_032777	-	34.8%	313
BLM	R132W	3	c.394C>T	NM_000057	COSM3887787	49.9%	945
EPCAM	N31K	2	c.93C>G	NM_002354	-	49.8%	528
HSP90AA1	Splice region	-	c.1487-5C>A	NM_005348	-	46.8%	1351
KMT2C	N4686S	54	c.14057A>G	NM_170606	-	49.7%	1323
MSH2	V78I	2	c.232G>A	NM_000251	COSM6019377	39.8%	600
MUC16	R13647W	59	c.40939C>T	NM_024690	-	56.8%	1151
MUC4	T113_A114ins VMQET	2	c.338_339insTGTTATG CAGGAGAC	NM_018406	-	47.2%	1214
RET	R886Q	15	c.2657G>A	NM_020975	COSM5414810	67.5%	1055

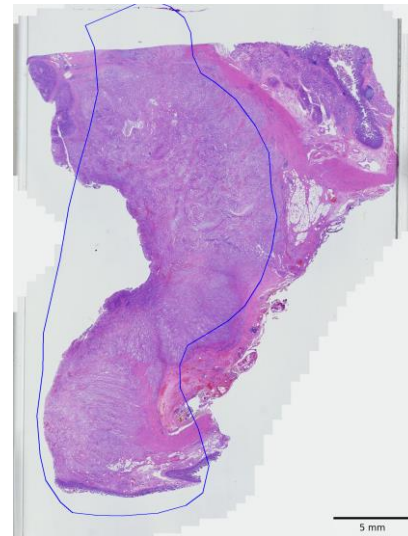
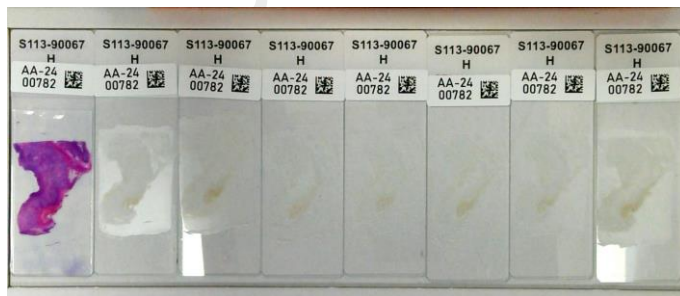
Note:

- 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 09, 2024
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11390067H
- Collection site: Ampulla of Vater
- 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 (%): 60%
- 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[®]+

DNA test

- Mean Depth: 943x
- Target Base Coverage at 100x: 96%

RNA test

- Average unique RNA Start Sites per control GSP2: 160

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LIMITATIONS

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite. Coverage depth was calculated using Torrent Coverage Analysis plug-in. Single nucleotide variants (SNVs) and short insertions/deletions (InDels) were identified using the Torrent Variant Caller plug-in. VEP (Variant Effect Predictor) was used to annotate every variant using databases from Clinvar, COSMIC and Genome Aggregation database. Variants with coverage ≥ 20 , allele frequency $\geq 5\%$ and actionable variants with allele frequency $\geq 2\%$ were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at $100x \geq 85\%$ with a mean coverage $\geq 500x$.

Variants reported in Genome Aggregation database with $> 1\%$ minor allele frequency (MAF) were considered as polymorphisms. ACT Genomics in-house database was used to determine technical errors. Clinically actionable and biologically significant variants were determined based on the published medical literature.

The copy number alterations (CNAs) were predicted as described below:

Amplicons with read counts in the lowest 5th percentile of all detectable amplicons and amplicons with a coefficient of variation ≥ 0.3 were removed. The remaining amplicons were normalized to correct the pool design bias. ONCOCNV (an established method for calculating copy number aberrations in amplicon sequencing data by Boeva et al., 2014) was applied for the normalization of total amplicon number, amplicon GC content, amplicon length, and technology-related biases, followed by segmenting the sample with a gene-aware model. The method was used as well for establishing the baseline of copy number variations.

Tumor mutational burden (TMB) was calculated by using the sequenced regions of ACTOnco[®] to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The TMB calculation predicted somatic variants and applied a machine learning model with a cancer hotspot correction. TMB may be reported as "TMB-High", "TMB-Low" or "Cannot Be Determined". TMB-High corresponds to ≥ 7.5 mutations per megabase (Muts/Mb); TMB-Low corresponds to < 7.5 Muts/Mb. TMB is reported as "Cannot Be Determined" if the tumor purity of the sample is $< 30\%$.

Classification of microsatellite instability (MSI) status is determined by a machine learning prediction algorithm. The change of a number of repeats of different lengths from a pooled microsatellite stable (MSS) baseline in > 400 genomic loci are used as the features for the algorithm. The final output of the results is either microsatellite Stable (MSS) or microsatellite instability high (MSI-H).

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RNA test

Extracted RNA was reverse-transcribed and subjected to library construction. Sequencing was performed according to Ion Proton or Ion S5 sequencer protocol (Thermo Fisher Scientific). To ensure sequencing quality for fusion variant analysis, the average unique RNA Start Sites (SS) per control Gene Specific Primer 2 (GSP 2) should be ≥ 10 .

The fusion analysis pipeline aligned sequenced reads to the human reference genome, identified regions that map to noncontiguous regions of the genome, applied filters to exclude probable false-positive events and, annotated previously characterized fusion events according to Quiver Gene Fusion Database, a curated database owned and maintained by ArcherDX. In general, samples with detectable fusions need to meet the following criteria: (1) Number of unique start sites (SS) for the GSP2 ≥ 3 ; (2) Number of supporting reads spanning the fusion junction ≥ 5 ; (3) Percentage of supporting reads spanning the fusion junction $\geq 10\%$; (4) Fusions annotated in Quiver Gene Fusion Database.

DATABASE USED

- Reference genome: Human genome sequence hg19
- COSMIC v.92
- Genome Aggregation database r2.1.1
- ClinVar (version 20210404)
- ACT Genomics in-house database
- Quiver Gene Fusion Database version 5.1.18

Variant Analysis:

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Ching-Ting Huang Ph.D.
檢字第 016511 號

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Sign Off

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GENE LIST SNV & CNV

ABCB1*	ABCC2*	ABCG2*	ABL1	ABL2	ADAMTS1	ADAMTS13	ADAMTS15	ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9
ADAMTSL1	ADGRA2	ADH1C*	AKT1	AKT2	AKT3	ALDH1A1*	ALK	AMER1	APC	AR	ARAF
ARID1A	ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2	AXL
B2M	BAP1	BARD1	BCL10	BCL2*	BCL2L1	BCL2L2*	BCL6	BCL9	BCOR	BIRC2	BIRC3
BLM	BMPR1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2*	BTB	BUB1B	CALR
CANX	CARD11	CASP8	CBFB	CBL	CCNA1	CCNA	CCNB1	CCNB2	CCNB3	CCND1	CCND2
CCND3	CCNE1	CCNE2	CCNH	CD19	CD274	CD58	CD70*	CD79A	CD79B	CDC73	CDH1
CDK1	CDK12	CDK2	CDK4	CDK5	CDK6	CDK7	CDK8	CDK9	CDKN1A	CDKN1B	CDKN2A
CDKN2B	CDKN2C	CEBPA*	CHEK1	CHEK2	CIC	CREBBP	CRKL	CRLF2	CSF1R	CTCF	CTLA4
CTNNA1	CTNNB1	CUL3	CYLD	CYP1A1*	CYP2B6*	CYP2C19*	CYP2C8*	CYP2D6	CYP2E1*	CYP3A4*	CYP3A5*
DAXX	DCUN1D1	DDR2	DICER1	DNMT3A	DOT1L	DPYD	DTX1	E2F3	EGFR	EP300	EPCAM
EPHA2	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2	ERBB3	ERBB4	ERCC1	ERCC2	ERCC3	ERCC4
ERCC5	ERG	ESR1	ESR2	ETV1	ETV4	EZH2	FAM46C	FANCA	FANCC	FANCD2	FANCE
FANCF	FANCG	FANCL	FAS	FAT1	FBXW7	FCGR2B	FGF1*	FGF10	FGF14	FGF19*	FGF23
FGF3	FGF4*	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLT1	FLT3	FLT4
FOXL2*	FOXP1	FRG1	FUBP1	GATA1	GATA2	GATA3	GNA11	GNA13	GNAQ	GNAS	GREM1
GRIN2A	GSK3B	GSTP1*	GSTT1*	HGF	HIF1A	HIST1H1C*	HIST1H1E*	HNF1A	HR	HRAS*	HSP90AA1
HSP90AB1	HSPA4	HSPA5	IDH1	IDH2	IFNL3*	IGF1	IGF1R	IGF2	IKBKB	IKBKE	IKZF1
IL6	IL7R	INPP4B	INSR	IRF4	IRS1	IRS2*	JAK1	JAK2	JAK3	JUN*	KAT6A
KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT	KMT2A	KMT2C	KMT2D	KRAS	LCK	LIG1
LIG3	LMO1	LRP1B	LYN	MALT1	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAP3K7	MAPK1	MAPK3
MAX	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MPL	MRE11
MSH2	MSH6	MTHFR*	MTOR	MUC16	MUC4	MUC6	MUTYH	MYC	MYCL	MYCN	MYD88
NAT2*	NBN	NEFH	NF1	NF2	NFE2L2	NFKB1	NFKBIA	NKX2-1*	NOTCH1	NOTCH2	NOTCH3
NOTCH4	NPM1	NQO1*	NRAS	NSD1	NTRK1	NTRK2	NTRK3	PAK3	PALB2	PARP1	PAX5
PAX8	PBRM1	PDCD1	PDCD1LG2	PDGFRA	PDGFRB	PDIA3	PGF	PHOX2B*	PIK3C2B	PIK3C2G	PIK3C3
PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1	PIK3R2	PIK3R3	PIM1	PMS1	PMS2	POLB	POLD1
POLE	PPARG	PPP2R1A	PRDM1	PRKAR1A	PRKCA	PRKCB	PRKCG	PRKCI	PRKCQ	PRKDC	PRKN
PSMB8	PSMB9	PSME1	PSME2	PSME3	PTCH1	PTEN	PTGS2	PTPN11	PTPRD	PTPRT	RAC1
RAD50	RAD51	RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10	RECQL4
REL	RET	RHOA	RICTOR	RNF43	ROS1	RPPH1	RPTOR	RUNX1	RUNX1T1	RXRA	SDHA
SDHB	SDHC	SDHD	SERPINB3	SERPINB4	SETD2	SF3B1	SGK1	SH2D1A*	SLC19A1*	SLC22A2*	SLCO1B1*
SLCO1B3*	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1*	SOX2*	SOX9	SPEN	SPOP
SRC	STAG2	STAT3	STK11	SUFU	SYK	SYNE1	TAF1	TAP1	TAP2	TAPBP	TBX3
TEK	TERT	TET1	TET2	TGFBR2	TMSB4X*	TNF	TNFAIP3	TNFRSF14	TNFSF11	TOP1	TP53
TPMT*	TSC1	TSC2	TSHR	TYMS	U2AF1	UBE2A*	UBE2K	UBR5	UGT1A1*	USH2A	VDR*
VEGFA	VEGFB	VHL	WT1	XIAP	XPO1	XRCC2	ZNF217				

*Analysis of copy number alterations NOT available.

FUSION

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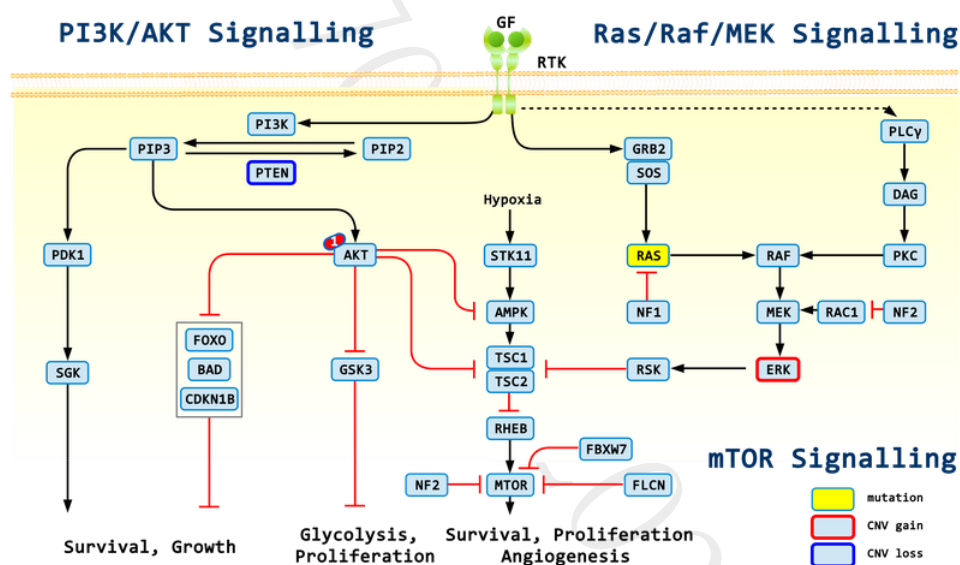
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
<i>PTEN</i>	Capivasertib, Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<i>PTEN</i>	Erlotinib, Gefitinib, Cetuximab, Panitumumab, Trastuzumab	resistant

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Capivasertib



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DISCLAIMER

法律聲明

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

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

醫療決策需由醫師決定

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

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

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