ACT Onco® + Report

PATIENT	
Name: 張美	Patient ID: 13550931
Date of Birth: Aug 25, 1958	Gender: Female
Diagnosis: Myxoid sarcoma ,recurrent	

ORDERING PHYSICIAN	
Name: 顏厥全醫師	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: S11127040D	Collection site: Soft tissue	Type: FFPE tissue
Date received: Aug 04, 2022	Lab ID: AA-22-04544	D/ID: NA

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) (≤ 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
ATRX Homozygous deletion	Olaparib, Talazoparib	-
RECQL4 Homozygous deletion	Olaparib	-
RB1 Homozygous deletion	-	Abemaciclib, Palbociclib, Ribociclib

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 criterial 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
SPEN	G46fs	23.7%
TP53	D281V	58.1%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr13	*RB1*	Homozygous deletion	0
Chr8	*RECQL4*	Homozygous deletion	0
Chrx	*ATRX*	Homozygous deletion	0
Chr11	*CHEK1*	Heterozygous deletion	1
Chr22	*CHEK2, NF2*	Heterozygous deletion	1
Chr18	*TYMS*	Amplification	11

- Fusions

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

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	< 1 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:
- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 90% 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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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3B		
ATRX Homozygous deletion	Olaparib	**sensitive**
RECQL4 Homozygous deletion	Olaparib	**sensitive**
Level 4		
ATRX Homozygous deletion	Talazoparib	**sensitive**
RB1 Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	**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
RB1 Homozygous deletion	Cisplatin	**Sensitive**	Clinical	Bladder carcinoma
	FAC T/FAC taxane/doxorubicin	**Sensitive**	Clinical	Breast cancer
TYMS Amplification	Fluorouracil	**Less sensitive**	Clinical	Colorectal cancer
	Pemetrexed	**Less sensitive**	Clinical	Lung cancer

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
RB1 Homozygous deletion	Tamoxifen	**Resistant**	Clinical	Breast cancer

OTHERS

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

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

VARIANT INTERPRETATION

SPEN G46fs

Biological Impact

SPEN (Spen Family Transcriptional Repressor, also called Split end) encodes a hormone-inducible transcriptional repressor, SMRT/HDAC1-associated repressor protein (SHARP), which involves in regulation of embryogenesis and development through modulating output from the Notch and EGFR signaling pathways[1][2]. Notably, SPEN has been associated with tumor growth inhibition. Somatic mutations and loss of heterozygosity of SPEN have been recurrently identified in prostate cancer[3], breast cancer[4], and chronic lymphocytic leukemia (CLL)[5].

G46fs mutation results in a change in the amino acid sequence beginning at 46, likely to cause premature truncation of the functional SPEN protein (UniProtKB). This mutation is predicted to lead to a loss of SPEN protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

Given that the expression of SPEN is hormone-inducible[6], studies have revealed nonsense mutations and loss-of-heterozygosity in SPEN which lead to low expression may predict shorter progression-free survival in patients with hormone receptor-positive, HER2-negative breast cancer when treated with tamoxifen[4].

TP53 D281V

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[7]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[8].

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)[9].

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[10]. 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[11].

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[12][13][14]. 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)[15]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[16][17]. 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[18].

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ATRX Homozygous deletion

Biological Impact

The alpha thalassemia/mental retardation syndrome X-linked (ATRX) gene encodes a tumor suppressor and member of the SWI1/SNF2 family of helicase/adenosine triphosphatase (ATPase) involved in chromatin remodeling[19][20]. ATRX mutations are associated with chromosomal instability and are hence implicated in oncogenesis[21]. Mutations in the ATRX gene cause alpha thalassemia/ mental retardation X-linked syndrome[22].

Therapeutic and prognostic relevance

ATRX has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in metastatic/advanced urothelial carcinoma (NCT03375307) and ovarian cancer[23], niraparib efficacy in melanoma (NCT03925350), and rucaparib efficacy in ovarian cancer[24]. In a preclinical study, immortalized astrocytes with loss of ATRX were sensitive to olaparib and talazoparib treatment in vitro[25].

A retrospective study of patients with glioma showed that those with loss of ATRX expression showed increased overall survival compared to those with retained ATRX expression ($p < 0.0001$)[26]. However, loss of ATRX or DAXX expression in uterine leiomyosarcoma and mutations in the DAXX/ATRX genes in Chinese patients with pancreatic neuroendocrine tumors are correlated with poor overall survival[27][28], and progression-free survival[28].

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[29]. 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[30][31]. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors[32], and CHEK1 mutations are extremely rare[29]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer[33], breast cancer[34], colorectal cancer[35], non-small cell lung (NSCLC) cancer[36], and nasopharyngeal cancer[37].

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[38].

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[24], 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[39].

CHEK2 Heterozygous deletion

Biological Impact

The checkpoint kinase 2 (CHEK2 or CHK2) gene encodes a serine/threonine protein kinase involved in transducing DNA damage signals that are required for both the intra-S phase and G2/M checkpoints[40]. CHEK2 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[30][31]. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers[41][42][43][44][45].

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[38].

In addition, CHEK2 has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer(NCT03533946)[24][46], niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

In a phase 2 trial, two prostate cancer patients harboring CHEK2 homozygous deletion was enrolled. One of the two patients had a response to olaparib[47].

NF2 Heterozygous deletion

Biological Impact

The neurofibromin (NF2) gene encodes the protein Merlin, a tumor suppressor that functions as a negative regulator of the PI3K/AKT/mTOR pathway[48][49][50]. NF2 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[51]. Inactivation germline mutations in the NF2 are associated with the hereditary neurofibromatosis type 2, a disorder characterized by the growth of noncancerous tumors in the nervous system[48][52]. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas[53], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers[54].

Therapeutic and prognostic relevance

Genomic alterations with activating effects on the mTOR signaling pathway have been identified to confer sensitivity to everolimus across multiple cancer types[55][56][57][58]. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer and urothelial carcinoma[59][60], both harboring NF2 truncating mutations. Preclinical evidence has shown the efficacy of MEK1/2 inhibitor selumetinib in KRAS-mutant thyroid cancer model with NF2 loss[61].

Analysis of afatinib-plus-cetuximab-resistant biopsy specimens revealed a loss-of-function alteration in genes that modulate mTOR signaling pathway, including NF2 and TSC1[62].

RB1 Homozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[63]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[64]. RB1 has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[65][66][67]. Deletion or inactivating mutation of RB1 is found in a number of tumors, including lung, prostate, bladder, breast cancers and sarcomas. RB1 mutations are found in approximately half of all retinoblastoma cases[68].

Therapeutic and prognostic relevance

A deleterious mutation in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response and better overall survival to cisplatin-based chemotherapy for muscle-invasive bladder cancer patients[69]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytoxan (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy[70].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[71][72].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[73]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[74].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[75][76]. Analyses of repeat biopsy samples from patients with EGFR-mutant adenocarcinoma that had transformed to the SCLC subtype have revealed that 100% of these patients have loss of RB1 and may be the alteration that induces this non-small-cell to small-cell transformation[72][77].

RECQL4 Homozygous deletion

Biological Impact

The RECQL4 gene encodes a member of the RECQ helicase family that plays an important role in DNA replication and various types of DNA repair, including double-strand break repair, nucleotide excision repair, base excision repair, and single-strand repair[78][79][80][81].

Therapeutic and prognostic relevance

There are currently no therapies targeting RECQL4 mutations. Expression of RECQL4 has been shown to drive cisplatin resistance in gastric cancer cell lines[82]. In contrast, RECQL4-deficient breast cancer cell lines were sensitive to cisplatin and PARP inhibitions but demonstrated resistance to taxane[83]. RECQL4 mutations have been selected as an inclusion criteria for the trials examining olaparib efficacy in metastatic urothelial cancer (NCT03448718) and relapsed small cell lung cancer (NCT03009682).

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TYMS Amplification

Biological Impact

TYMS (Thymidylate Synthetase) gene encodes the thymidylate synthase that catalyzes the methylation of deoxyuridylate to deoxythymidylate. The enzyme is critical for DNA replication and repair[84][85][86]. TYMS polymorphisms may be associated with etiology of neoplasia, including acute lymphoblastic leukemia[87], breast cancer, and response to chemotherapy[88].

Therapeutic and prognostic relevance

Thymidylate synthase gene amplification was associated with pemetrexed resistance in patients with advanced non-small cell lung cancer[89][90][91][92], and 5-FU resistance in CRC patients[93]

US FDA-APPROVED DRUG(S)

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)

RADIANT-4[94] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[95] NCT00863655	**Breast cancer** (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
EXIST-2 NCT00790400	**Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma** (Approved on 2012/04/26)
	-
	Everolimus vs. Placebo [ORR(%): 41.8 vs. 0]
RADIANT-3[96] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[97] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[98] NCT00410124	**Renal cell carcinoma** (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)

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]
QUADRA[99] NCT02354586	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2019/10/23)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Niraparib [ORR(%): 24.0, DOR(M): 8.3]
NOVA[100] 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)

OlympiA NCT02032823	**Her2-negative high-risk early breast cancer** (Approved on 2022/03/11)
	gBRCA
	Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound[38] NCT02987543	**Prostate cancer** (Approved on 2020/05/19)
	ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm, RAD54Lm
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1[101] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[102] NCT02184195	**Pancreatic adenocarcinoma** (Approved on 2019/12/27)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1[103] NCT01844986	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19)
	Germline or somatic BRCA-mutated (gBRCAm or sBRCAm)
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD[104] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[105] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA+
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19[106] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]
Study 42[107] NCT01078662	**Ovarian cancer** (Approved on 2014/12/19)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

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Rucaparib (RUBRACA)

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

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA+, sBRCA
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[24] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	All|HRD|tBRCA
	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]
ARIEL2[108] NCT01482715, NCT01891344	**Ovarian cancer** (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation
	Rucaparib [ORR(%): 54.0]

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)

EMBRACA[109] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	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)

[110] NCT00065468	**Renal cell carcinoma** (Approved on 2007/05/30)
	-
	Temsirolimus vs. Ifn-α [OS(M): 10.9 vs. 7.3]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

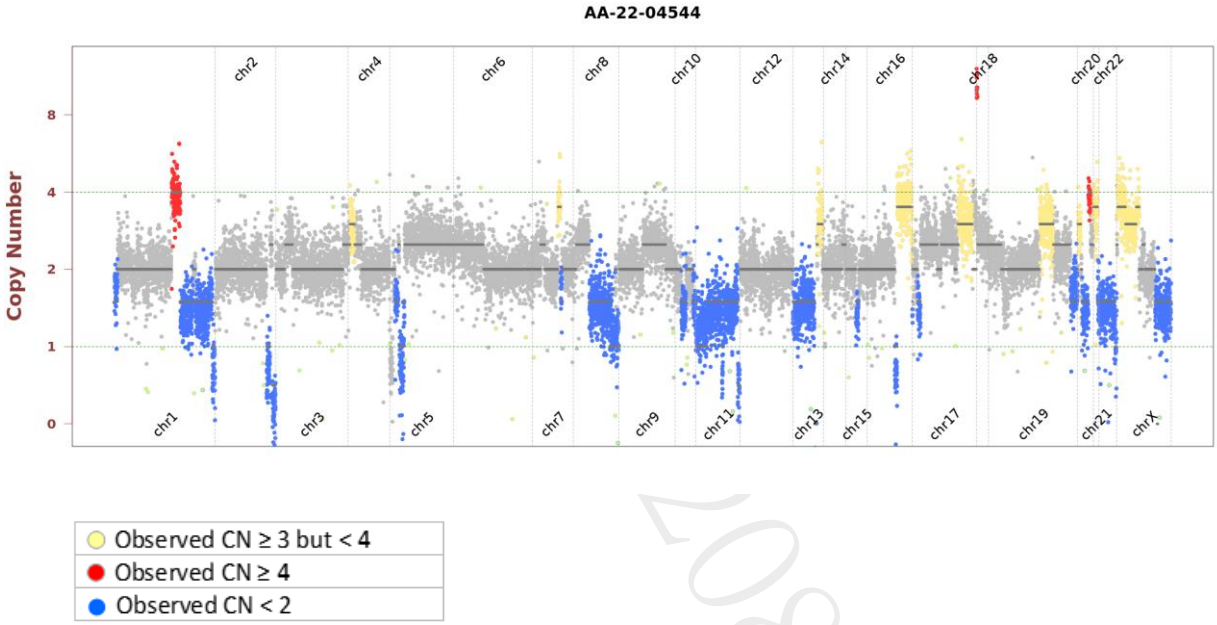
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
SPEN	G46fs	2	c.135_153del	NM_015001	-	23.7%	695
TP53	D281V	8	c.842A>T	NM_000546	COSM45729	58.1%	866

- Copy Number Alterations

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



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OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ADH1C	R364H	8	c.1091G>A	NM_000669	-	31.4%	287
BRIP1	N775S	16	c.2324A>G	NM_032043	-	49.9%	999
CIC	R863H	10	c.2588G>A	NM_015125	-	48.0%	892
EP300	I1366T	25	c.4097T>C	NM_001429	-	94.6%	811
IL7R	S105N	3	c.314G>A	NM_002185	-	47.2%	1304
NTRK1	V13A	2	c.38T>C	NM_001007792	-	53.2%	1746
RECQL4	E711K	13	c.2131G>A	NM_004260	COSM3670381	50.9%	844
RNF43	R454C	9	c.1360C>T	NM_017763	COSM1224016	53.6%	987

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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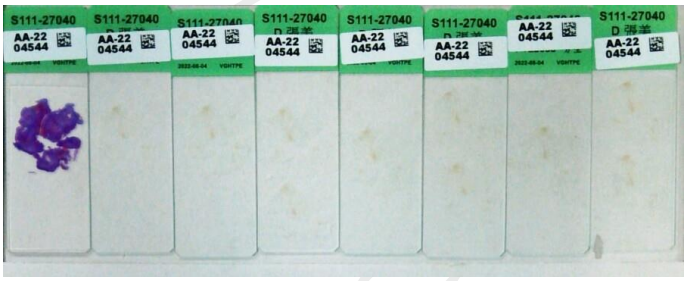
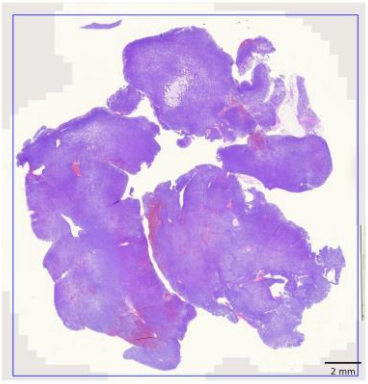
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: Jul 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11127040D
- Collection site: Soft tissue
- Examined by: Dr. Yeh-Han Wang
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 90%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 90%
  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: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 870x
- Target Base Coverage at 100x: 93%

RNA test

- Average unique RNA Start Sites per control GSP2: 108

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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 ≥ 5% and actionable variants with allele frequency ≥ 2% were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at 100x ≥ 85% with a mean coverage ≥ 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 ≥ 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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Chu-Yuan Chang Ph.D.
檢字第 020115 號

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

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**	*BTK*	*BUB1B*	*CALR*
CANX	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCNA1*	*CCNA*	*CCNB1*	*CCNB2*	*CCNB3*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CCNE2*	*CCNH*	*CD19*	*CD274*	*CD58*	*CD70**	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK1	*CDK12*	*CDK2*	*CDK4*	*CDK5*	*CDK6*	*CDK7*	*CDK8*	*CDK9*	*CDKN1A*	*CDKN1B*	*CDKN2A*
CDKN2B	*CDKN2C*	*CEBPA**	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CTCF*	*CTLA4*
CTNNA1	*CTNNB1*	*CUL3*	*CYLD*	*CYP1A1**	*CYP2B6**	*CYP2C19**	*CYP2C8**	*CYP2D6*	*CYP2E1**	*CYP3A4**	*CYP3A5**
DAXX	*DCUN1D1*	*DDR2*	*DICER1*	*DNMT3A*	*DOT1L*	*DPYD*	*DTX1*	*E2F3*	*EGFR*	*EP300*	*EPCAM*
EPHA2	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC1*	*ERCC2*	*ERCC3*	*ERCC4*
ERCC5	*ERG*	*ESR1*	*ESR2*	*ETV1*	*ETV4*	*EZH2*	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*
FANCF	*FANCG*	*FANCL*	*FAS*	*FAT1*	*FBXW7*	*FCGR2B*	*FGF1**	*FGF10*	*FGF14*	*FGF19**	*FGF23*
FGF3	*FGF4**	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*	*FH*	*FLCN*	*FLT1*	*FLT3*	*FLT4*
*FOXL2**	*FOXP1*	*FRG1*	*FUBP1*	*GATA1*	*GATA2*	*GATA3*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GREM1*
GRIN2A	*GSK3B*	*GSTP1**	*GSTT1**	*HGF*	*HIF1A*	*HIST1H1C**	*HIST1H1E**	*HNF1A*	*HR*	*HRAS**	*HSP90AA1*
HSP90AB1	*HSPA4*	*HSPA5*	*IDH1*	*IDH2*	*IFNL3**	*IGF1*	*IGF1R*	*IGF2*	*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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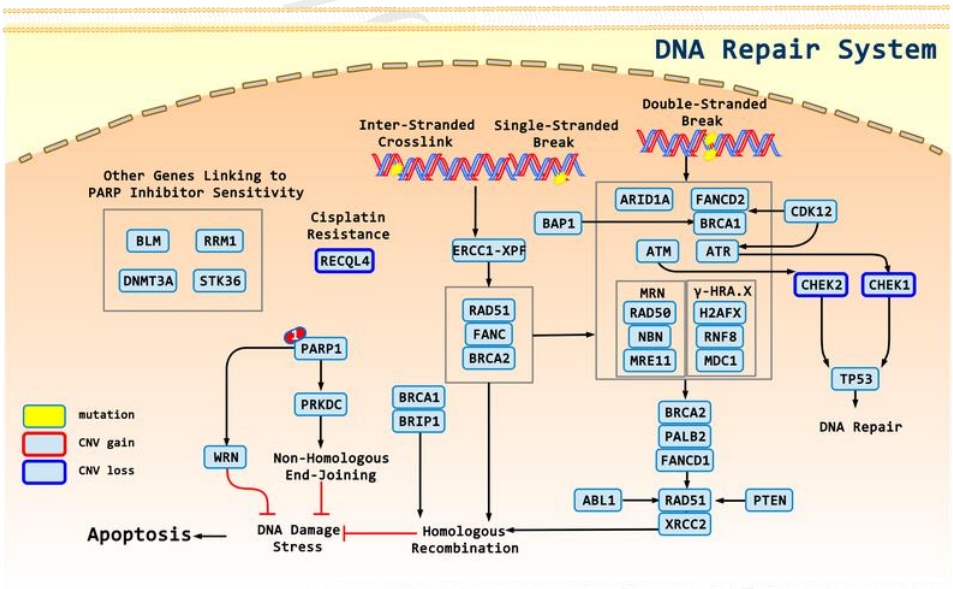
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
NF2	Everolimus, Temsirolimus	**sensitive**
CHEK1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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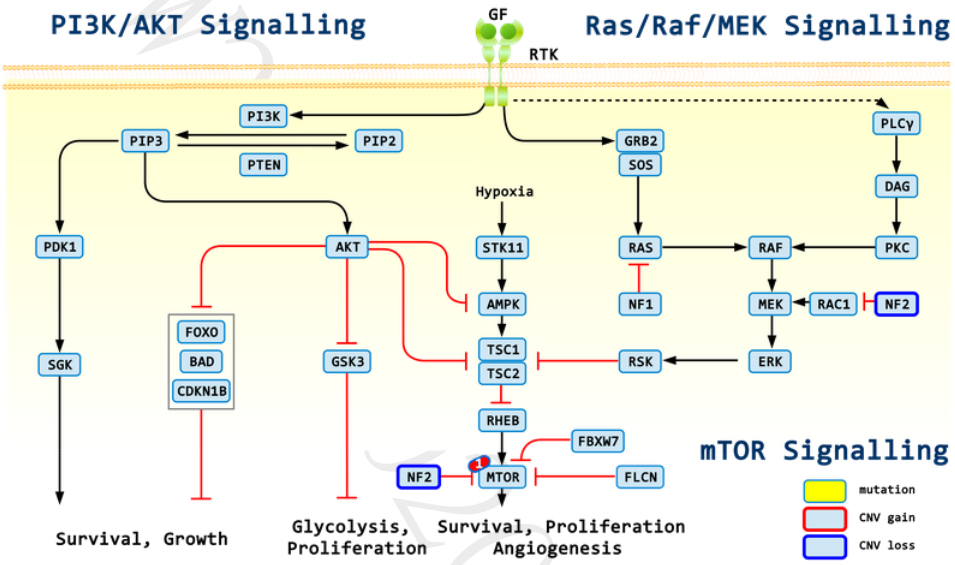

1: Everolimus, Temsirolimus

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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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