

# ACT Onco<sup>®</sup> + Report

PATIENT		
Name: 鍾偉銘		Patient ID: 32677397
Date of Birth: Sep 13, 1964		Gender: Male
Diagnosis: Prostate adenocarcinoma metastatic		
ORDERING PHYSICIAN		
Name: 林子平醫師		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: S11127271C	Collection site: Lung	Type: FFPE tissue
Date received: Jul 26, 2022	Lab ID: AA-22-04298	D/ID: NA

## ABOUT ACT Onco<sup>®</sup>+

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

## SUMMARY FOR ACTIONABLE VARIANTS

### VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

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

### VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
Not detected		

#### 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
Not detected		

#### - Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr11	ATM, CHEK1	Heterozygous deletion	1
Chr8	LYN, NBN	Amplification	7*
Chr8	MYC	Amplification	10
Chrx	AR	Amplification	10

\* Increased gene copy number was observed.

#### - 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:

- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 32% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco<sup>®</sup> to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at  $\geq 7.5$  mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is < 30%.

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## THERAPEUTIC IMPLICATIONS

### TARGETED THERAPIES

Not Applicable.

### IMMUNE CHECKPOINT INHIBITORS (ICIs)

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

#### - Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
Not detected	

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

### CHEMOTHERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
<b>MYC</b> Amplification	FAC CMF and P-FEC regimens	<b>Sensitive</b>	Clinical	Breast cancer
	Platinum-based regimens	<b>Sensitive</b>	Clinical	Ovarian cancer

### HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
<b>AR</b> Amplification	Abiraterone	<b>Resistant</b>	Clinical	Prostate cancer
	Enzalutamide	<b>Resistant</b>	Clinical	Prostate cancer
	Tamoxifen	<b>Resistant</b>	Clinical	Breast cancer

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## OTHERS

### Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AG	Irinotecan-based regimens	Level 1B

#### Clinical Interpretation:

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.

\* 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.

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## VARIANT INTERPRETATION

### AR Amplification

#### Biological Impact

The AR gene encodes for the androgen receptor, a steroid-hormone activated transcription factor which expresses in a wide range of adult tissue<sup>[1][2]</sup>. In breast cancer, the AR signaling axis activates the HER3 signaling through the Wnt/ $\beta$ -Catenin pathway<sup>[3]</sup> and followed by c-Myc mediated amplification of AR signaling<sup>[4]</sup>. But in the ER-negative subtype, AR expression was predominantly observed in HER2-positive class<sup>[5][6]</sup>. The amplification of HER2 coupled with AR activation enhances PI3K signaling and the oncogenic function of MYC<sup>[4]</sup>. AR-positive breast cancer tumors have been associated with a high rate of PIK3CA mutations, but the clinical significance of this correlation remains unknown<sup>[7]</sup>. Genetic alterations of AR are frequently identified in castration-resistant prostate cancer (CRPCs)<sup>[8]</sup>, particularly in the drug-resistant form of CRPC<sup>[9][10][11]</sup>.

#### Therapeutic and prognostic relevance

Androgen receptor therapy, such as leuprolide and bicalutamide, is included in NCCN guideline for AR-positive salivary gland tumors<sup>[12][13]</sup>.

In CRPCs, amplification of the AR gene was associated with decreased response to enzalutamide<sup>[14]</sup> and lack of response to abiraterone<sup>[11]</sup>.

In ER-positive breast cancer, high ratio of AR:ER has been shown to be associated with resistance to tamoxifen<sup>[15]</sup>. Clinical reports demonstrated that patients with AR-positive metastatic breast cancer experienced clinical benefit with the bicalutamide<sup>[16][17]</sup>.

Pre-clinical studies on the effect of bicalutamide and enzalutamide, both anti-androgens, has demonstrated inhibitory activities against ER-positive and -negative breast cancer cells<sup>[3][15]</sup>. Several classes of AR-directed therapies for breast cancer are currently under clinical evaluations<sup>[18]</sup>.

Several studies suggested high expression levels of AR predicts better prognosis in patients with breast cancer<sup>[19][20][21][22]</sup>, while the low expression level of AR was associated with increased risk of cancer-related death in ER-positive breast cancer<sup>[23]</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>[24]</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>[25][26][27][28][29]</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>[30]</sup>. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies<sup>[31][32][33][34]</sup> and a board range of tumors such as prostate cancer<sup>[35]</sup>, head and neck squamous cell carcinoma (HNSCC)<sup>[36]</sup>, pancreatic cancer<sup>[37]</sup>, lung adenocarcinoma<sup>[38]</sup>, breast cancer<sup>[39]</sup>, and ovarian cancer<sup>[26]</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

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progressed following prior treatment with enzalutamide or abiraterone acetate<sup>[40]</sup>.

In addition, ATM has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer<sup>[41][42]</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>[43]</sup>. Also, a prospective study in muscle-invasive bladder cancer patients suggested that genomic alterations in the DNA repair genes ATMs, RB1 and FANCC could be recognized as biomarkers predictive of response to cisplatin-based neoadjuvant chemotherapy<sup>[44]</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>[45]</sup>.

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer<sup>[46]</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>[47]</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>[48][49]</sup>. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors<sup>[50]</sup>, and CHEK1 mutations are extremely rare<sup>[47]</sup>. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer<sup>[51]</sup>, breast cancer<sup>[52]</sup>, colorectal cancer<sup>[53]</sup>, non-small cell lung (NSCLC) cancer<sup>[54]</sup>, and nasopharyngeal cancer<sup>[55]</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>[40]</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>[41]</sup>, prostate cancer (NCT03533946), niraparib efficacy in pancreatic cancer (NCT03553004), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in lung cancer (NCT03377556), respectively.

Selective inhibitors for CHEK1 and CHEK2 alone or in combination with other agents are currently being investigated in clinical trials<sup>[56]</sup>.



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## LYN Amplification

### Biological Impact

The LYN Proto-Oncogene, Src Family Tyrosine Kinase (LYN) gene encodes a non-receptor tyrosine protein kinase of the Src family (SFK)<sup>[57]</sup>. LYN plays an important role in the regulation of immune responses, hematopoiesis, signal transduction of growth factors and cytokines and is activated in the cellular response to DNA damage and genotoxic agents<sup>[58][59][60][61]</sup>. LYN has been described to promote tumor growth, invasion, epithelial to mesenchymal transition (EMT) and ERK signaling in different cancer types<sup>[62][63][64]</sup>. Amplification of LYN has been identified in prostate cancer, breast cancer and ovarian cancer (cBioPortal).

### Therapeutic and prognostic relevance

LYN could be pharmacologically targeted with Src-kinase inhibitors. Results of preclinical studies showed that dasatinib, a dual-specificity tyrosine kinase inhibitor of ABL and the Src-family tyrosine kinases, exerted antitumor activity in LYN-expressing breast cancer cells<sup>[62]</sup>.

## MYC Amplification

### Biological Impact

The v-myc avian myelocytomatosis viral oncogene homolog, also known as c-myc (MYC) gene encodes a transcription factor involved in cellular proliferation, inhibiting exit from the cell cycle, stimulating vascularization and enhancing genomic instability<sup>[65][66][67]</sup>. Dysregulated MYC expression is implicated in a wide range of human cancers<sup>[68]</sup>.

### Therapeutic and prognostic relevance

MYC amplification was associated with better clinical outcome in breast cancer patients treated with FAC (5-fluorouracil, doxorubicin, and cyclophosphamide), CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and P-FEC (paclitaxel followed by 5-fluorouracil, epirubicin and cyclophosphamide) and higher expression of MYC was also associated with a better response rate in platinum-treated ovarian cancer patients<sup>[69][70][71]</sup>.

CDK inhibition using the dinaciclib, a CDK1, 2, 5 and 9 inhibitors, exerted antitumor activity in triple-negative breast cancer (TNBC) tumor xenograft and cell lines with increased activity of the MYC pathway<sup>[72][73]</sup>.

Overexpression of MYC has been reported as a favorable prognostic biomarker in colorectal carcinoma (CRC)<sup>[74][75]</sup>. However, the favorable prognostic value of MYC in CRC is abrogated by the TP53 mutation<sup>[75]</sup>.

MYC amplification with the loss of tumor suppressor pathways such as p53 and RB has been shown to be associated with poor outcomes and was correlated with shortened disease-free survival in breast cancer with BRCA1 deficiency in TNBC<sup>[72][76]</sup>.

## NBN Amplification

### Biological Impact

The NBN gene encodes a component of the MRE11-RAD50-NBN (MRN) complex, which involves in DNA double-strand break sensing and repair<sup>[77]</sup>. NBN mutation is related to Nijmegen breakage syndrome, increased cancer incidence and ionizing radiation sensitivity<sup>[77][78]</sup>. NBN mutations have been found in various cancers, including cholangiocarcinoma, hepatocellular carcinoma<sup>[79]</sup>, prostate cancer<sup>[80]</sup>, leukemia, lymphoma<sup>[81]</sup>, and triple-negative breast cancer<sup>[82]</sup>.

### Therapeutic and prognostic relevance

NBN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer<sup>[83]</sup>; the trials evaluating rucaparib efficacy in ovarian cancer<sup>[41]</sup> or prostate cancer<sup>[42]</sup>; the trials evaluating

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talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556), and the trials evaluating niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate) cancer (NCT03207347).

Germline and somatic mutations in homologous recombination genes, including NBN, have been suggested to be prognostic biomarkers for platinum-based treatment response and superior survival in patients with ovarian, fallopian tube, peritoneal carcinomas and pancreatic cancer<sup>[84][85]</sup>.

In a retrospective study of localized prostate cancer, NBN gene amplification has been demonstrated to associate with overall tumor genomic instability and lower biochemical relapse-free rate following image-guided radiotherapy (IGRT)<sup>[86]</sup>.

Another retrospective study showed that amplification of the NBN gene is associated with protein overexpression and mostly correlated with poor prognosis in several cancer types, including ovarian cancer, breast invasive carcinoma, uterine corpus endometrial carcinoma, and sarcoma. Besides, in vivo and in vitro assays demonstrated that amplification of the NBN gene could induce cisplatin and PARP inhibitor resistance in breast and ovarian cancer cells<sup>[87]</sup>.



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## US FDA-APPROVED DRUG(S)

### Niraparib (ZEJULA)

Niraparib is an oral, small molecule inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1 and -2 (PARP-1, -2). Niraparib is developed and marketed by Tesaro under the trade name ZEJULA.

### - FDA Approval Summary of Niraparib (ZEJULA)

<b>PRIMA</b> NCT02655016	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2020/04/29)
	- Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
<b>QUADRA</b> <sup>[88]</sup> NCT02354586	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</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</b> <sup>[89]</sup> NCT01847274	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2017/03/27)
	- Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

### Olaparib (LYNPARZA)

Olaparib is an oral, small molecule inhibitor of poly (ADP-ribose) polymerase-1, -2, and -3 (PARP-1, -2, -3). Olaparib is developed by KuDOS Pharmaceuticals and marketed by AstraZeneca under the trade name LYNPARZA.

### - FDA Approval Summary of Olaparib (LYNPARZA)

<b>OlympiA</b> NCT02032823	<b>Her2-negative high-risk early breast cancer</b> (Approved on 2022/03/11)
	<b>gBRCA</b> Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M): ]
<b>PROfound</b> <sup>[40]</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>[90]</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>[91]</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>[92]</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>[93]</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>[94]</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]

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<b>Study19<sup>[95]</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>[96]</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]

## 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>[41]</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>[97]</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]

## 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>[98]</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]

D=day; W=week; M=month

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## ONGOING CLINICAL TRIALS

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

No trial has been found.

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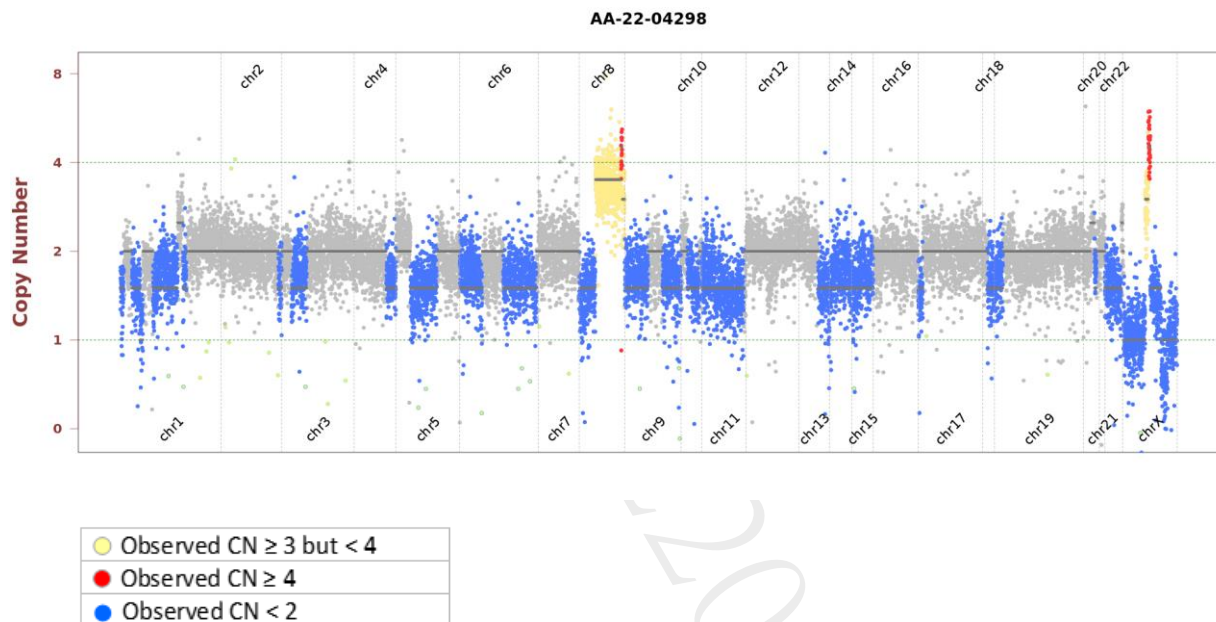
## SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

### - Single Nucleotide and Small InDel Variants

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

### - Copy Number Alterations

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



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## OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ADAMTSL1	G1461S	24	c.4381G>A	NM_001040272	-	48.6%	2056
CARD11	S694L	16	c.2081C>T	NM_032415	COSM5505215	54.6%	577
CDK12	V605A	2	c.1814T>C	NM_016507	COSM9248152	19.9%	1835
DAXX	Y89C	3	c.266A>G	NM_001141969	-	53.4%	554
EP300	P747L	12	c.2240C>T	NM_001429	-	40.1%	1138
FAT1	T2377M	10	c.7130C>T	NM_005245	-	43.1%	888
IGF1	P114A	3	c.340C>G	NM_001111285	-	52.4%	1144
INSR	R1128H	19	c.3383G>A	NM_000208	COSM2728443	58.0%	958
PRKCQ	G314D	10	c.941G>A	NM_006257	-	51.7%	1123

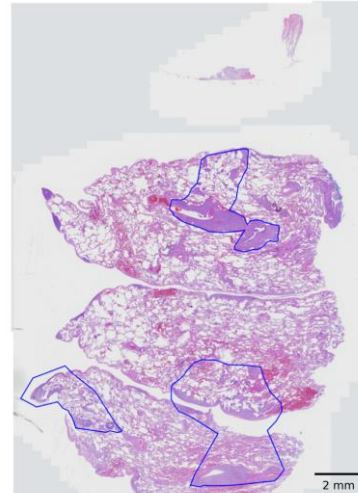
Note:

- 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.: S11127271C
- Collection site: Lung
- Examined by: Dr. Chien-Ta Chiang
  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 (%): 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<sup>®</sup>+

### DNA test

- Mean Depth: 873x
- Target Base Coverage at 100x: 94%

### RNA test

- Average unique RNA Start Sites per control GSP2: 177



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## LIMITATIONS

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

## NEXT-GENERATION SEQUENCING (NGS) METHODS

### DNA test

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

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

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

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

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

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

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

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## RNA test

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

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

## DATABASE USED

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

## Variant Analysis:

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



## Sign Off

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



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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	SOC1*	SOX2*	SOX9	SPEN	SPOP
SRC	STAG2	STAT3	STK11	SUFU	SYK	SYNE1	TAF1	TAP1	TAP2	TAPBP	TBX3
TEK	TERT	TET1	TET2	TGFBR2	TMSB4X*	TNF	TNFAIP3	TNFRSF14	TNFSF11	TOP1	TP53
TPMT*	TSC1	TSC2	TSHR	TYMS	U2AF1	UBE2A*	UBE2K	UBR5	UGT1A1*	USH2A	VDR*
VEGFA	VEGFB	VHL	WT1	XIAP	XPO1	XRCC2	ZNF217				

\*Analysis of copy number alterations NOT available.

## FUSION

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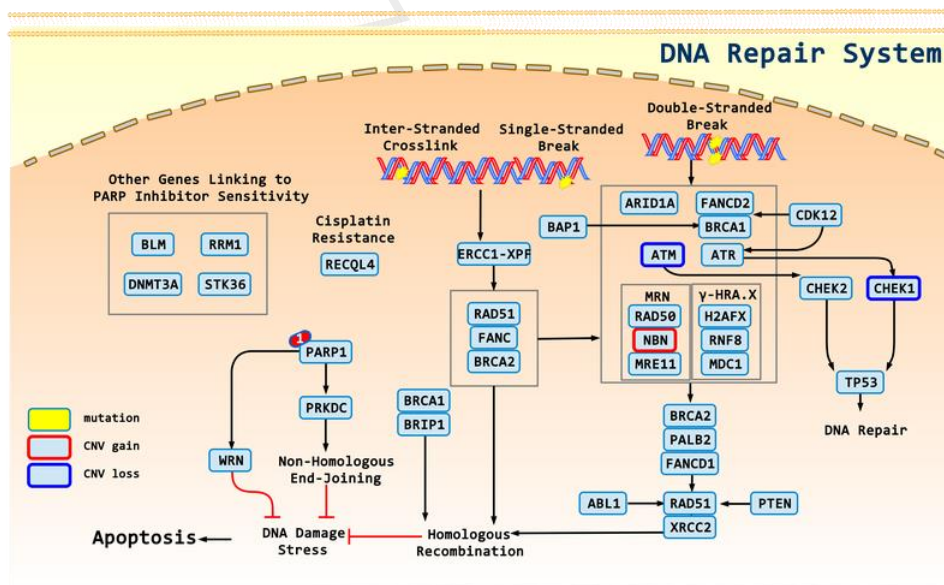
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## APPENDIX

### POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
ATM	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
CHEK1	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive

### SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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## DISCLAIMER

### 法律聲明

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

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### 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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