王彥儒
Project ID: C22-M001-01604
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PATIENT		
Name: 王彥儒		Patient ID: 48485978
Date of Birth: Oct 21, 1981		Gender: Male
Diagnosis: Neuroendocrine tumor		
ORDERING PHYSICIAN		
Name: 陳明晃醫師		Tel: 886-228712121
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SPECIMEN		
Specimen ID: S11170743A	Collection site: Liver	Type: FFPE tissue
Date received: May 30, 2022	Lab ID: AA-22-02827	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
CCND1 Amplification	Abemaciclib, Palbociclib, Ribociclib	-
CDK4 Amplification	Abemaciclib, Palbociclib, Ribociclib	-
MDM2 Amplification	-	Cabozantinib

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
Not detected		

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr11	*ATM, CHEK1*	Heterozygous deletion	1
Chr12	*ERBB3*	Amplification	6¥
Chr11	*BIRC2*	Amplification	8
Chr8	*MYC*	Amplification	16
Chr12	*CDK4*	Amplification	19
Chr11	*CCND1*	Amplification	37
Chr12	*MDM2*	Amplification	40

¥ 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 50% 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		
CCND1 Amplification	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
CDK4 Amplification	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
Level 4		
MDM2 Amplification	Cabozantinib	**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
MDM2/MDM4 amplification	Likely associated with WORSE response to ICIs

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
MYC Amplification	FAC CMF and P-FEC regimens	**Sensitive**	Clinical	Breast cancer
	Platinum-based regimens	**Sensitive**	Clinical	Ovarian cancer
MDM2 Amplification	Cisplatin	**Less sensitive**	Clinical	Germ cell cancer

HORMONAL THERAPIES

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

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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

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[1]. 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[2][3][4][5][6]. 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[7]. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies[8][9][10][11]and a board range of tumors such as prostate cancer[12], head and neck squamous cell carcinoma (HNSCC)[13], pancreatic cancer[14], lung adenocarcinoma[15], breast cancer[16], and ovarian cancer[3].

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[17].

In addition, ATM has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer[18]or prostate cancer[19], 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[20]. Also, a prospective study in muscle-invasive bladder cancer patients suggested that genomic alternations in the DNA repair genes ATMs, RB1 and FANCC could be recognized as biomarkers predictive of response to cisplatin-based neoadjuvant chemotherapy[21]. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer[22].

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer[23].

BIRC2 Amplification

Biological Impact

Baculoviral IAP repeat containing 2 (BIRC2) gene encodes cellular inhibitor of apoptosis protein 1 and is involved in regulating TNF and NF-kB activated signaling pathways[24].

BIRC2 amplification has been identified in squamous cell carcinomas of the uterine cervix, head and neck squamous cellular carcinoma and oral squamous cell carcinoma[25][26]. Increased BIRC2 copy number was associated with higher expression level of BIRC2 protein[27]. BIRC2 is required for cell migration in vitro[25], and inhibits non-canonical NF-κB activity, resulting in reduction of CXCL9 and immunosuppression[28].

Therapeutic and prognostic relevance
In oral squamous cell carcinoma (OSCC), BIRC2 amplification was associated with poor clinical outcome[25].

A preclinical study demonstrated BIRC2 expression impairs the sensitivity of anti-CTLA4 and/or anti-PD1 immune checkpoint inhibitors in animal models[28].

CCND1 Amplification
Biological Impact
The cyclin D1 (CCND1) gene encodes a protein involved in the control of cell growth, proliferation, transcription, and DNA repair[29]. CCND1 forms a complex with CDK4 and CDK6, leading to G1-S cell-cycle transition by inhibiting the retinoblastoma (RB) protein[29]. Amplification or overexpression of CCND1 could be oncogenic and is associated with carcinogenesis of various cancer types[30].

Therapeutic and prognostic relevance
Several CDK4 inhibitors, including palbociclib (PD0332991), LEE011, and LY2835219 have entered clinical trials for tumors with CCND1 amplification[31][32]. In the Phase II study of palbociclib and letrozole in patients with ER-positive HER2-negative metastatic breast cancer, patient selection based on CCND1 amplification or p16 loss did not further improve patient outcome[33]. Preclinical studies also demonstrated conflicting results regarding the correlation between high-level CCND1 and palbociclib sensitivity[34][35][36].

CCND1 amplification has been implicated in predicting poor clinical outcomes in postmenopausal breast cancer patients treated with either anastrozole or tamoxifen[37]. In lung cancer patients, the increased CCND1 copy number is associated with poorer overall survival[38].

A retrospective study showed that melanoma patients whose tumor harboring CCND1, cRAF or KRAS gene copy number gain had better treatment response with CPS (carboplatin, paclitaxel, and sorafenib)[39].

Amplification of CCND1 are frequent and contributes to dedifferentiation and cellular proliferative activity of intrahepatic cholangiocarcinoma (ICC), and also indicates a poor prognosis for ICC patients[40].

Of note, CCND1 amplification has been selected as an inclusion criterion for the trial examining CDK4/6 inhibitors in different types of malignant solid tumors (NCT02187783, NCT02896335, NCT03526250, NCT02693535, NCT01037790, NCT03454919, NCT03310879, and NCT03356223).

CDK4 Amplification
Biological Impact
The cyclin-dependent kinase 4 (CDK4) gene encodes a serine/threonine kinase that functions in the regulation of CDK kinases in the cell cycle. CDK4 forms a complex with cyclin-dependent kinase 6 (CDK6) and cyclin D, leading to G1-S cell-cycle transition by inhibiting the retinoblastoma (RB) protein[30]. Dysregulation of CDK4/6 activity by gene amplification, activating mutations or loss of CDKN2A has been reported in breast cancer, melanoma, glioblastoma and sarcomas[41][42][43][44][45].

Therapeutic and prognostic relevance
Results from clinical studies of liposarcoma and endocrine-resistant, hormone receptor-positive breast cancer showed that CDK4 amplification is predictive of sensitivity to CDK4/6 inhibitor palbociclib in RB-expressing tumors[46][47][48].

Abemaciclib, another CDK4/6 inhibitor, showed acceptable toxicity profile and preliminary efficacy in a Phase I trial of multiple tumor types, including breast cancer, non-small cell lung cancer (NSCLC) and other solid tumors[49].

Of note, CDK4 amplification has been selected as an inclusion criterion for the trial examining CDK4/6 inhibitors in different types of malignant solid tumors (NCT03310879, NCT02187783, NCT02154490).

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[50]. 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[51][52]. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors[53], and CHEK1 mutations are extremely rare[50]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer[54], breast cancer[55], colorectal cancer[56], non-small cell lung (NSCLC) cancer[57], and nasopharyngeal cancer[58].

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[17].

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[18], 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[59].

ERBB3 Amplification

Biological Impact

The ERBB3 (also known as HER3) gene encodes a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases[60]. HER3 lacks or has little intrinsic tyrosine kinase activity. Upon binding of its ligand, neu differentiation factor (NDF), HER3 forms a heterodimer with ErbB2[61]and subsequently activates various mitogenic signaling cascades, including the PI3K/AKT/mTOR, STAT and RAS/RAF/MAPK[62][63][64]. Aberrant expression or alterations of the ErbB family play crucial roles in the development and progression of cancer[65]. Enhanced expression of HER2 has been observed in a broad spectrum of human cancers, including gastric, bladder, uterine, colorectal, and breast cancers[66]. HER3 is the preferred heterodimeric partner for EGFR in melanoma and pancreatic carcinoma[67][68], while in breast cancer, HER3 preferably heterodimerizes with HER2 and plays a critical role in HER2-mediated tumorigenesis.

Therapeutic and prognostic relevance

Currently, there are no FDA-approved anti-HER3 therapies for patients with solid tumors. A variety of strategies targeting HER3 including pan HER approach, abrogating its dimerization partners' kinase activity using small molecule inhibitors (e.g. lapatinib, erlotinib, gefitinib, afatinib, and neratinib) or direct targeting of its extracellular domain (e.g. including AV-203 (Abstract nr 2509, AACR 2012)) are under investigation[69][70].

Preclinical data indicated that HER3 expression level is a predictive biomarker of pertuzumab (an anti-HER2 antibody) efficacy in HER2 low-expressing pancreatic cancer[71].

ERBB3 mutation has been selected as an inclusion criteria for the trial examining afatinib in urothelial tract carcinoma, non-small cell lung carcinoma (NSCLC) and malignant solid tumor (NCT02780687, NCT01523587, NCT03810872)[72][73].

Accumulating evidence indicates that overexpression of HER3 associates with worse survival in cancer patients with solid tumors[74], besides, HER3 signaling plays a major role causing treatment failure in cancer therapy[75][76][69]. For example, elevated HER3 expression of HER3 in HER2-overexpressing breast cancer cells results in resistance to hormone therapy (tamoxifen)[77], HER2-targeted therapy (trastuzumab and lapatinib)[78], and chemotherapy (paclitaxel). Besides, the high expression of ERBB3 has associated with gefitinib resistance in head and neck squamous cell carcinoma (HNSCC) cell lines[79].

The amplification of ERBB3 was associated with poor response to chemotherapy, higher distant metastasis rate, poor PFS and OS of primary osteosarcoma patients[80].

In a prospective study, a gallbladder cancer patient harboring ERBB3 amplification demonstrated a partial response for 1.8 months by lapatinib and capecitabine treatment[81].

MDM2 Amplification

Biological Impact

The Mouse double minute 2 proto-oncogene (MDM2) gene encodes a E3-ubiquitin ligase that negatively regulates the protein level of p53[82][83][84]. Overexpression or amplification of MDM2 has been shown to disrupt the MDM2/p53 balance, leading to the malignant transformation in a wide range of cancers[85].

Therapeutic and prognostic relevance

Small molecules inhibiting the MDM2-p53 protein-protein interaction to reactivate p53 function are currently under preclinical studies and in early clinical trials[86]. Nutlin-3, a MDM2 inhibitor, when synergized with cisplatin, has been shown to disrupt the interaction between MDM2 and TP53, and induce apoptosis in TP53 wild-type ovarian cancer cells[87], non-small cell lung cancer (NSCLC) cells[88], and nasopharyngeal carcinoma cells[89]. Clinical and preclinical studies showed that overexpression of MDM2 can confer resistance to cisplatin[90][91].

The retrospective studies demonstrated that EGFR-mutated NSCLC patients harboring MDM2 amplification were associated with resistance to EGFR-TKIs and showed poor prognosis after treatment[92][93][94][95].

MDM2 amplification was shown to be a potential mechanism of primary or acquired resistance to cabozantinib and MDM2 inhibitors in clinical development can be targeted therapeutics (Journal of Clinical Oncology, 34, 9068-9068).

Importantly, results from a study suggested that patients with amplification of the MDM2 family members, including MDM2 and MDM4, or EGFR aberrations exhibited poor clinical outcome and demonstrated a significantly increased rate of tumor growth (hyper-progression) after receiving immune checkpoint (PD-1/PD-L1) therapy[96].

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[97][98][99]. Dysregulated MYC expression is implicated in a wide range of human cancers[100].

Therapeutic and prognostic relevance

MYC amplification was associated with better clinical outcome in breast cancer patients treated with FAC (5-fluorouracil,

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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[101][102][103].

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[104][105].

Overexpression of MYC has been reported as a favorable prognostic biomarker in colorectal carcinoma (CRC)[106][107]. However, the favorable prognostic value of MYC in CRC is abrogated by the TP53 mutation[107].

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[104][108].

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)

monarchE NCT03155997	**Breast cancer** (Approved on 2021/10/12)
	HR-positive, HER2-negative
	Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3[109] NCT02246621	**Breast cancer** (Approved on 2018/02/26)
	HR-positive, HER2-negative
	Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 2[110] NCT02107703	**Breast cancer** (Approved on 2017/09/28)
	HR-positive, HER2-negative
	Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1[111] NCT02102490	**Breast cancer** (Approved on 2017/09/28)
	HR-positive, HER2-negative
	Abemaciclib [ORR(%): 19.7 vs. 17.4]

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[112] 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[113] 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[17] 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[114] 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[115] 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[116] 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[117] 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[118] 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[119] 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[120] NCT01078662	**Ovarian cancer** (Approved on 2014/12/19)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

Palbociclib (IBRANCE)

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

- FDA Approval Summary of Palbociclib (IBRANCE)

PALOMA-2[121] 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[122] 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[123] 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+, sBRCA
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[18] 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[124] 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[125] 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]

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

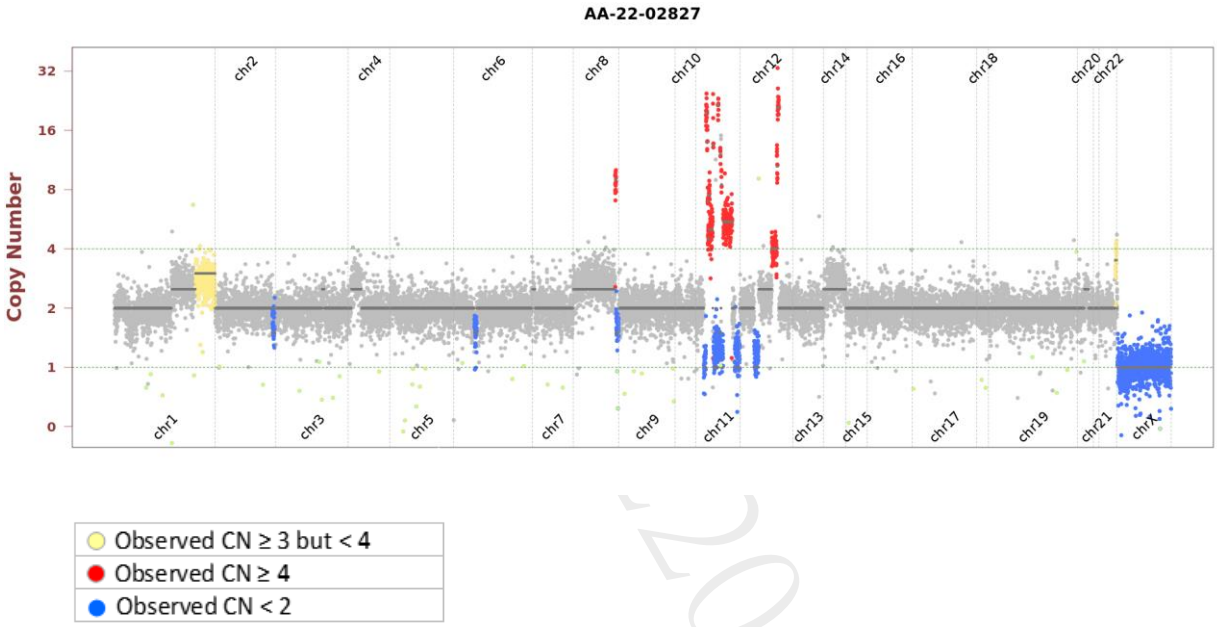
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- 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
ADGRA2	A127T	3	c.379G>A	NM_032777	COSM6673605	48.8%	1781
CCNB1	P107S	3	c.319C>T	NM_031966	COSM5014497	52.9%	1366
DAXX	L500P	6	c.1499T>C	NM_001141969	-	49.0%	1101
DOT1L	Splice acceptor	-	c.1924-1G>T	NM_032482	-	37.9%	428
ERBB3	R1173Q	28	c.3518G>A	NM_001982	-	74.9%	1468
HIST1H1C	T154A	1	c.460A>G	NM_005319	COSM8401514	46.9%	665
KMT2C	C385F	8	c.1154G>T	NM_170606	COSM9180259	6.9%	3991
KMT2D	Splice region	-	c.10741-7A>G	NM_003482	-	55.6%	36
MEN1	Y307*	6	c.921C>G	NM_130802	-	56.7%	584
MRE11	I263M	8	c.789C>G	NM_005591	-	13.5%	4000
PRKCI	R405W	13	c.1213C>T	NM_002740	COSM3204228	32.7%	733
RAD54L	Splice region	-	c.477+6T>C	NM_003579	-	51.3%	881
SDHA	R554Q	12	c.1661G>A	NM_004168	-	50.5%	1375
SYNE1	S4678F	78	c.14033C>T	NM_182961	-	49.6%	1707
TNFAIP3	G456V	7	c.1367G>T	NM_006290	COSM303677	42.9%	856
USH2A	D3463G	53	c.10388A>G	NM_206933	COSM9281064	66.2%	382

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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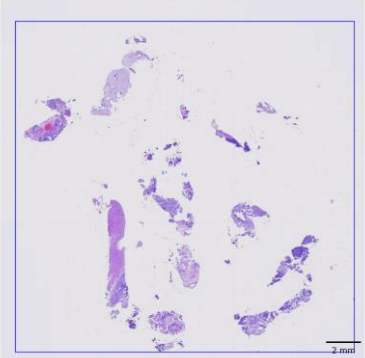
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: May 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11170743A
- Collection site: Liver
- Examined by: Dr. Yeh-Han Wang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 50%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 50%
    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: 1262x
- Target Base Coverage at 100x: 96%

RNA test

- Average unique RNA Start Sites per control GSP2: 67

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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 ≥ 25, 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:
醫檢師張筑芠 博士
Chu-Yuan Chang Ph.D.
檢字第 020115 號

Sign Off
醫檢師張筑芠 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*	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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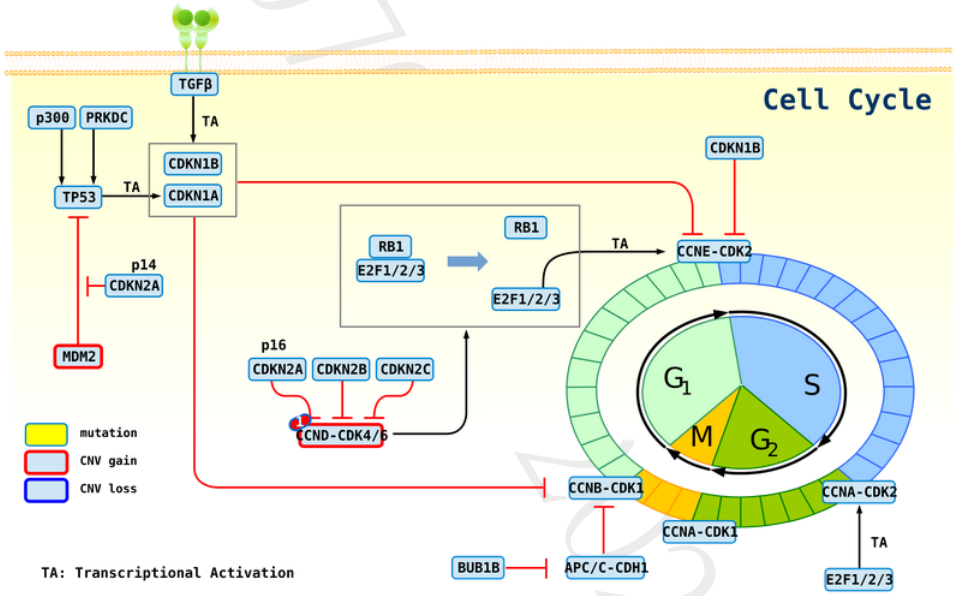
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

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

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Palbociclib, Ribociclib, Abemaciclib

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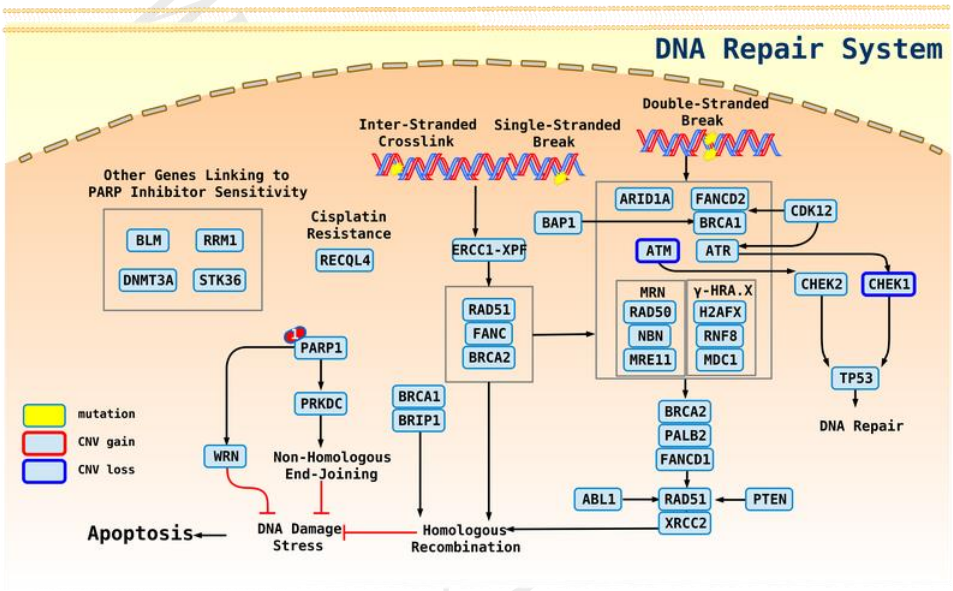

1: Olaparib, Niraparib, Rucaparib, Talazoparib

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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。
本檢驗報告非經本公司許可，不得私自變造、塗改，或以任何方式作為廣告及其他宣傳之用途。
本公司於提供檢驗報告後，即已完成本次契約義務，後續之報告解釋、判讀及用藥、治療，應自行尋求相關專業醫師協助，若需將報告移件其他醫師，本人應取得該醫師同意並填寫移件申請書，主動告知行動基因，行動基因僅能配合該醫師意願與時間提供醫師解說。

醫療決策需由醫師決定

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

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

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REFERENCE

1. PMID: 22079189; 2012, Trends Biochem Sci;37(1):15-22
The ATM protein kinase and cellular redox signaling: beyond the DNA damage response.

2. PMID: 1548942; 1992, Leukemia;6 Suppl 1():8-13
Cancer susceptibility in ataxia-telangiectasia.

3. PMID: 12810666; 2003, Cancer Res;63(12):3325-33
Contributions of ATM mutations to familial breast and ovarian cancer.

4. PMID: 1961222; 1991, N Engl J Med;325(26):1831-6
Incidence of cancer in 161 families affected by ataxia-telangiectasia.

5. PMID: 28779002; 2017, J Med Genet;54(11):732-741
Rare, protein-truncating variants in ATM, CHEK2 and PALB2, but not XRCC2, are associated with increased breast cancer risks.

6. PMID: 16400190; 2006, Carcinogenesis;27(4):848-55
Atm-haploinsufficiency enhances susceptibility to carcinogen-induced mammary tumors.

7. PMID: 29478780; 2018, Am J Hum Genet;102(3):401-414
Inherited DNA-Repair Defects in Colorectal Cancer.

8. PMID: 9488043; 1998, Oncogene;16(6):789-96
ATM is usually rearranged in T-cell prolymphocytic leukaemia.

9. PMID: 11429421; 2001, J Clin Pathol;54(7):512-6
Ataxia telangiectasia gene mutations in leukaemia and lymphoma.

10. PMID: 11756177; 2002, Blood;99(1):238-44
ATM gene inactivation in mantle cell lymphoma mainly occurs by truncating mutations and missense mutations involving the phosphatidylinositol-3 kinase domain and is associated with increasing numbers of chromosomal imbalances.

11. PMID: 21993670; 2012, Haematologica;97(1):47-55
ATM gene alterations in chronic lymphocytic leukemia patients induce a distinct gene expression profile and predict disease progression.

12. PMID: 22981675; 2013, Eur Urol;63(5):920-6
Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity.

13. PMID: 22410096; 2012, Oral Oncol;48(8):698-702
Correlation of Ataxia-Telangiectasia-Mutated (ATM) gene loss with outcome in head and neck squamous cell carcinoma.

14. PMID: 23103869; 2012, Nature;491(7424):399-405
Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes.

15. PMID: 18948947; 2008, Nature;455(7216):1069-75
Somatic mutations affect key pathways in lung adenocarcinoma.

16. PMID: 30537493; 2019, Hum Pathol;86():85-92
Molecular characterization of metaplastic breast carcinoma via next-generation sequencing.

17. PMID: 32343890; 2020, N Engl J Med;382(22):2091-2102
Olaparib for Metastatic Castration-Resistant Prostate Cancer.

18. PMID: 28916367; 2017, Lancet;390(10106):1949-1961
Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial.

19. PMID: 32086346; 2020, Clin Cancer Res;26(11):2487-2496

Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: Analysis From the Phase II TRITON2 Study.

20. PMID: 26282658; 2015, J Clin Oncol;33(33):3858-65
Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer.

21. PMID: 26238431; 2015, Eur Urol;68(6):959-67
Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy in Muscle-invasive Bladder Cancer.

22. PMID: 22420423; 2012, Breast Cancer Res;14(2):R47
Low expression levels of ATM may substitute for CHEK2 /TP53 mutations predicting resistance towards anthracycline and mitomycin chemotherapy in breast cancer.

23. PMID: 23154512; 2012, Oncotarget;3(11):1348-55
Loss of expression of the double strand break repair protein ATM is associated with worse prognosis in colorectal cancer and loss of Ku70 expression is associated with CIN.

24. PMID: 21653699; 2011, J Biol Chem;286(30):26406-17
Cellular inhibitor of apoptosis protein-1 (cIAP1) can regulate E2F1 transcription factor-mediated control of cyclin transcription.

25. PMID: 29167558; 2017, Sci Rep;7(1):16051
Recurring Amplification at 11q22.1-q22.2 Locus Plays an Important Role in Lymph Node Metastasis and Radioresistance in OSCC.

26. PMID: 22733500; 2012, Virchows Arch;461(2):123-8
BIRC2 amplification in squamous cell carcinomas of the uterine cervix.

27. PMID: 27469115; 2016, Cancer Res;76(18):5442-5454
SMAC Mimetic Birinapant plus Radiation Eradicates Human Head and Neck Cancers with Genomic Amplifications of Cell Death Genes FADD and BIRC2.

28. PMID: 32846130; 2020, Cell Rep;32(8):108073
BIRC2 Expression Impairs Anti-Cancer Immunity and Immunotherapy Efficacy.

29. PMID: 8114739; 1994, Mol Cell Biol;14(3):2077-86
Identification of G1 kinase activity for cdk6, a novel cyclin D partner.

30. PMID: 12432268; 2002, Cancer Biol Ther;1(3):226-31
Cycling to cancer with cyclin D1.

31. PMID: 24795392; 2014, Clin Cancer Res;20(13):3379-83
Molecular pathways: CDK4 inhibitors for cancer therapy.

32. PMID: 27030077; 2016, Nat Rev Clin Oncol;13(7):417-30
Treating cancer with selective CDK4/6 inhibitors.

33. PMID: 25524798; 2015, Lancet Oncol;16(1):25-35
The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.

34. PMID: 27334220; 2016, Ann Surg Oncol;23(9):2745-52
Targeting Cyclin-Dependent Kinases in Synovial Sarcoma: Palbociclib as a Potential Treatment for Synovial Sarcoma Patients.

35. PMID: 19874578; 2009, Breast Cancer Res;11(5):R77
PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro.

36. PMID: 23898052; 2013, Anticancer Res;33(8):2997-3004
PD-0332991, a potent and selective inhibitor of cyclin-dependent kinase 4/6, demonstrates inhibition of proliferation in renal cell carcinoma at nanomolar concentrations and molecular markers predict for sensitivity.

ACT Onco® + Report

37. PMID: 22475046; 2012, Breast Cancer Res;14(2):R57
Effects of cyclin D1 gene amplification and protein expression on time to recurrence in postmenopausal breast cancer patients treated with anastrozole or tamoxifen: a TransATAC study.

38. PMID: 17070615; 2007, Lung Cancer;55(1):1-14
Cyclin D1 in non-small cell lung cancer: a key driver of malignant transformation.

39. PMID: 26307133; 2016, Clin Cancer Res;22(2):374-82
Copy Number Changes Are Associated with Response to Treatment with Carboplatin, Paclitaxel, and Sorafenib in Melanoma.

40. PMID: 11495045; 2001, J Hepatol;35(1):74-9
The role of overexpression and gene amplification of cyclin D1 in intrahepatic cholangiocarcinoma.

41. PMID: 8101826; 1993, Genes Dev;7(8):1572-83
Subunit rearrangement of the cyclin-dependent kinases is associated with cellular transformation.

42. PMID: 8221695; 1993, Cancer Res;53(22):5535-41
Coamplification of the CDK4 gene with MDM2 and GLI in human sarcomas.

43. PMID: 8586464; 1995, Glia;15(3):289-96
Gene amplification in human gliomas.

44. PMID: 9916925; 1999, Am J Pathol;154(1):113-8
Gene amplification and overexpression of CDK4 in sporadic breast carcinomas is associated with high tumor cell proliferation.

45. PMID: 24089445; 2013, Clin Cancer Res;19(19):5320-8
The cell-cycle regulator CDK4: an emerging therapeutic target in melanoma.

46. PMID: 23569312; 2013, J Clin Oncol;31(16):2024-8
Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma.

47. PMID: 27124835; 2016, JAMA Oncol;2(7):937-40
Progression-Free Survival Among Patients With Well-Differentiated or Dedifferentiated Liposarcoma Treated With CDK4 Inhibitor Palbociclib: A Phase 2 Clinical Trial.

48. PMID: 25501126; 2015, Clin Cancer Res;21(5):995-1001
CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment.

49. PMID: 27217383; 2016, Cancer Discov;6(7):740-53
Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non-Small Cell Lung Cancer, and Other Solid Tumors.

50. PMID: 12781359; 2003, Cancer Cell;3(5):421-9
Chk1 and Chk2 kinases in checkpoint control and cancer.

51. PMID: 15261141; 2004, Cancer Cell;6(1):45-59
Chk1 is haploinsufficient for multiple functions critical to tumor suppression.

52. PMID: 15539958; 2005, Cell Cycle;4(1):131-9
Chk1 is essential for tumor cell viability following activation of the replication checkpoint.

53. PMID: 15459660; 2004, Nat Rev Mol Cell Biol;5(10):792-804
Checking on DNA damage in S phase.

54. PMID: 22585575; 2012, J Clin Invest;122(6):2165-75
CHK1 targets spleen tyrosine kinase (L) for proteolysis in hepatocellular carcinoma.

55. PMID: 17638866; 2007, Cancer Res;67(14):6574-81
The E2F-regulated gene Chk1 is highly expressed in triple-negative estrogen receptor /progesterone receptor /HER-2 breast carcinomas.

ACT Onco® + Report

56. PMID: 17848589; 2007, Mol Cell Proteomics;6(12):2150-64
A proteomics analysis of cell signaling alterations in colorectal cancer.

57. PMID: 24418519; 2014, J Surg Res;187(1):6-13
Checkpoint kinase 1 protein expression indicates sensitization to therapy by checkpoint kinase 1 inhibition in non-small cell lung cancer.

58. PMID: 15297395; 2004, Clin Cancer Res;10(15):4944-58
Global gene expression profile of nasopharyngeal carcinoma by laser capture microdissection and complementary DNA microarrays.

59. PMID: 21458083; 2011, Trends Pharmacol Sci;32(5):308-16
Anticancer therapy with checkpoint inhibitors: what, where and when?

60. PMID: 19536107; 2009, Nat Rev Cancer;9(7):463-75
Novel anticancer targets: revisiting ERBB2 and discovering ERBB3.

61. PMID: 9130710; 1997, EMBO J;16(7):1647-55
ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling.

62. PMID: 22785351; 2012, Nat Rev Cancer;12(8):553-63
The ERBB network: at last, cancer therapy meets systems biology.

63. PMID: 7515147; 1994, Mol Cell Biol;14(6):3550-8
ErbB3 is involved in activation of phosphatidylinositol 3-kinase by epidermal growth factor.

64. PMID: 12853564; 2003, Proc Natl Acad Sci U S A;100(15):8933-8
The ErbB2/ErbB3 heterodimer functions as an oncogenic unit: ErbB2 requires ErbB3 to drive breast tumor cell proliferation.

65. PMID: 19208461; 2009, Curr Opin Cell Biol;21(2):177-84
ErbB receptors and signaling pathways in cancer.

66. PMID: 23680147; 2013, Cancer Cell;23(5):603-17
Oncogenic ERBB3 mutations in human cancers.

67. PMID: 18698037; 2008, Clin Cancer Res;14(16):5188-97
HER3 is a determinant for poor prognosis in melanoma.

68. PMID: 20647770; 2010, Cancer Biol Ther;10(6):555-63
ErbB3 expression promotes tumorigenesis in pancreatic adenocarcinoma.

69. PMID: 30057690; 2018, Oncol Rev;12(1):355
HER3 signaling and targeted therapy in cancer.

70. PMID: 30109175; 2018, Acta Pharm Sin B;8(4):503-510
Understanding the biology of HER3 receptor as a therapeutic target in human cancer.

71. PMID: 25216528; 2014, Oncotarget;5(16):7138-48
HER3 as biomarker and therapeutic target in pancreatic cancer: new insights in pertuzumab therapy in preclinical models.

72. PMID: 27044931; 2016, J Clin Oncol;34(18):2165-71
Afatinib Activity in Platinum-Refractory Metastatic Urothelial Carcinoma in Patients With ERBB Alterations.

73. PMID: 29902295; 2018, JAMA Oncol;4(9):1189-1197
Association of ERBB Mutations With Clinical Outcomes of Afatinib- or Erlotinib-Treated Patients With Lung Squamous Cell Carcinoma: Secondary Analysis of the LUX-Lung 8 Randomized Clinical Trial.

74. PMID: 20485140; 2010, Ann Surg;251(6):1107-16
HER-3 overexpression is prognostic of reduced breast cancer survival: a study of 4046 patients.

75. PMID: 20816829; 2010, Semin Cell Dev Biol;21(9):944-50

ACT Onco® + Report

The role of HER3, the unpretentious member of the HER family, in cancer biology and cancer therapeutics.

76. PMID: 24886126; 2014, Mol Cancer;13():105
Targeting of erbB3 receptor to overcome resistance in cancer treatment.

77. PMID: 16000581; 2005, Clin Cancer Res;11(13):4835-42
Can molecular markers predict when to implement treatment with aromatase inhibitors in invasive breast cancer?

78. PMID: 20064507; 2010, Exp Cell Res;316(7):1083-100
Mechanisms of resistance to HER family targeting antibodies.

79. PMID: 16818711; 2006, Clin Cancer Res;12(13):4103-11
Signaling via ErbB2 and ErbB3 associates with resistance and epidermal growth factor receptor (EGFR) amplification with sensitivity to EGFR inhibitor gefitinib in head and neck squamous cell carcinoma cells.

80. PMID: 31663373; 2019, Scand J Clin Lab Invest;79(8):601-612
Clinicopathological and prognostic values of ErbB receptor family amplification in primary osteosarcoma.

81. PMID: 33354548; 2020, South Asian J Cancer;9(2):74-79
Genomic Landscape and Targeted Treatment of Gallbladder Cancer: Results of a First Ongoing Prospective Study.

82. PMID: 25550088; 2015, Immunol Res;61(3):250-9
The roles of IL-2 and IL-10 enhance anti-CD45RBmAb immune inhibition in allograft skin.

83. PMID: 8875929; 1996, Science;274(5289):948-53
Structure of the MDM2 oncoprotein bound to the p53 tumor suppressor transactivation domain.

84. PMID: 1535557; 1992, Cell;69(7):1237-45
The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivation.

85. PMID: 9671804; 1998, Nucleic Acids Res;26(15):3453-9
The MDM2 gene amplification database.

86. PMID: 18834305; 2009, Annu Rev Pharmacol Toxicol;49():223-41
Small-molecule inhibitors of the MDM2-p53 protein-protein interaction to reactivate p53 function: a novel approach for cancer therapy.

87. PMID: 24136147; 2013, Br J Cancer;109(10):2685-95
Nutlin-3 preferentially sensitises wild-type p53-expressing cancer cells to DR5-selective TRAIL over rhTRAIL.

88. PMID: 26125230; 2015, Oncotarget;6(26):22666-79
The MDM2-inhibitor Nutlin-3 synergizes with cisplatin to induce p53 dependent tumor cell apoptosis in non-small cell lung cancer.

89. PMID: 26252575; 2015, Oncol Rep;34(4):1692-700
Nutlin-3 sensitizes nasopharyngeal carcinoma cells to cisplatin-induced cytotoxicity.

90. PMID: 16815295; 2006, Biochem Biophys Res Commun;347(1):60-6
p73 and MDM2 confer the resistance of epidermoid carcinoma to cisplatin by blocking p53.

91. PMID: 27646943; 2016, J Clin Oncol;34(33):4000-4007
Genetic Determinants of Cisplatin Resistance in Patients With Advanced Germ Cell Tumors.

92. PMID: 32391110; 2020, Oncol Lett;19(6):4169-4176
Genetic alterations in epidermal growth factor receptor-tyrosine kinase inhibitor-naïve non-small cell lung carcinoma.

93. PMID: 30391576; 2019, J Thorac Oncol;14(2):193-202
Concurrent Genetic Alterations Predict the Progression to Target Therapy in EGFR-Mutated Advanced NSCLC.

94. PMID: 32611363; 2020, Mol Med;26(1):66
Primary resistance to first-generation EGFR-TKIs induced by MDM2 amplification in NSCLC.

ACT Onco® + Report

95. PMID: 15165086; 2004, Lung Cancer;43(3):285-95
MDM2 gene amplification: a new independent factor of adverse prognosis in non-small cell lung cancer (NSCLC).

96. PMID: 28351930; 2017, Clin Cancer Res;23(15):4242-4250
Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate.

97. PMID: 19029958; 2008, Nat Rev Cancer;8(12):976-90
Reflecting on 25 years with MYC.

98. PMID: 22464321; 2012, Cell;149(1):22-35
MYC on the path to cancer.

99. PMID: 10378696; 1999, Oncogene;18(19):3004-16
MYC oncogenes and human neoplastic disease.

100. PMID: 16934487; 2006, Semin Cancer Biol;16(4):318-30
The Myc oncoprotein as a therapeutic target for human cancer.

101. PMID: 22113465; 2012, Clin Exp Med;12(4):217-23
C-myc as a predictive marker for chemotherapy in metastatic breast cancer.

102. PMID: 21741827; 2011, Eur J Cancer;47(12):1779-88
Association between c-myc amplification and pathological complete response to neoadjuvant chemotherapy in breast cancer.

103. PMID: 15132769; 2004, Cancer Sci;95(5):418-23
Expression of the c-myc gene as a predictor of chemotherapy response and a prognostic factor in patients with ovarian cancer.

104. PMID: 22430491; 2012, J Exp Med;209(4):679-96
MYC pathway activation in triple-negative breast cancer is synthetic lethal with CDK inhibition.

105. PMID: 27486754; 2016, Oncotarget;7(35):56864-56875
Inhibition of cyclin dependent kinase 9 by dinaciclib suppresses cyclin B1 expression and tumor growth in triple negative breast cancer.

106. PMID: 24503701; 2014, PLoS One;9(2):e87456
Immunohistochemistry for myc predicts survival in colorectal cancer.

107. PMID: 9816266; 1996, Clin Cancer Res;2(6):1049-53
Overexpression of the c-myc proto-oncogene in colorectal carcinoma is associated with a reduced mortality that is abrogated by point mutation of the p53 tumor suppressor gene.

108. PMID: 23860775; 2013, Tumour Biol;34(6):3945-58
MYC overexpression and poor prognosis in sporadic breast cancer with BRCA1 deficiency.

109. PMID: 28968163; 2017, J Clin Oncol;35(32):3638-3646
MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer.

110. PMID: 28580882; 2017, J Clin Oncol;35(25):2875-2884
MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy.

111. PMID: 28533223; 2017, Clin Cancer Res;23(17):5218-5224
MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer.

112. PMID: 30948273; 2019, Lancet Oncol;20(5):636-648
Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial.

113. PMID: 27717299; 2016, N Engl J Med;375(22):2154-2164
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer.

ACT Onco® + Report

114. PMID: 31851799; 2019, N Engl J Med;381(25):2416-2428
Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer.

115. PMID: 31157963; 2019, N Engl J Med;381(4):317-327
Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer.

116. PMID: 30345884; 2018, N Engl J Med;379(26):2495-2505
Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.

117. PMID: 28578601; 2017, N Engl J Med;377(6):523-533
Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation.

118. PMID: 28754483; 2017, Lancet Oncol;18(9):1274-1284
Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial.

119. PMID: 27617661; 2016, Lancet Oncol;17(11):1579-1589
Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial.

120. PMID: 25366685; 2015, J Clin Oncol;33(3):244-50
Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation.

121. PMID: 27959613; 2016, N Engl J Med;375(20):1925-1936
Palbociclib and Letrozole in Advanced Breast Cancer.

122. PMID: 26030518; 2015, N Engl J Med;373(3):209-19
Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer.

123. PMID: 27717303; 2016, N Engl J Med;375(18):1738-1748
Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer.

124. PMID: 27908594; 2017, Lancet Oncol;18(1):75-87
Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial.

125. PMID: 30110579; 2018, N Engl J Med;379(8):753-763
Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation.