ACTOnco® + Report

TW202032020117150224

REPORT SUMMARY

REPORT DETAILS

APPENDIX

PATIENT AND SAMPLE INFORMATION

PATIENT
Name: 葉哲豪
Gender: Male
Date of Birth: Mar 26, 1953
Patient ID: 19342906
Diagnosis: Metastatic neuroendocrine carcinoma

SPECIMEN
Type: FFPE tissue
Date received: Jan 04, 2022
Collection site: Vertebra
Specimen ID: S11024511A
Lab ID: AA-22-00047
D/ID: NA

ORDERING PHYSICIAN
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VARIANT(S) WITH CLINICAL RELEVANCE

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

SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
CDH1	T340A	99	85.9%	COSM19821
RB1	A74fs	87	63.2%	COSM432450

COPY NUMBER VARIANTS (CNVS)

Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on <u>**55%**</u> tumor purity.

Amplification (Copy number ≥ 8)

Chr	Gene	Copy Number
ND	ND	ND

Homozygous deletion (Copy number=0)

Chr	Gene
chr2	*BARD1, LRP1B*

Heterozygous deletion (Copy number=1)

Chr	Gene
chr1	*CDKN2C*
chr9	*TSC1*
chr11	*ATM, CHEK1, MRE11*
chr13	*BRCA2, RB1*
chr16	*CDH1*
chr22	*CHEK2, NF2*

ND, Not Detected

TUMOR MUTATIONAL BURDEN (TMB)

2.5 muts/Mb

Muts/Mb, mutations per megabase

MICROSATELLITE INSTABILITY (MSI)

Microsatellite stable (MSS)

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

Variant Analysis:
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Yun-Yu Chen Ph.D.
檢字第 015647 號

Sign Off
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葉哲豪
Project ID: C22-M001-00020
Report No.: AA-22-00047_ONC
Date Reported: Jan 17, 2022

THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3B		
BARD1 Homozygous deletion	Niraparib, Olaparib	**sensitive**
ATM Heterozygous deletion	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK1 Heterozygous deletion	Olaparib, Rucaparib	**sensitive**
CHEK2 Heterozygous deletion	Niraparib, Rucaparib	**sensitive**
CDKN2C Heterozygous deletion	Abemaciclib, Ribociclib	**sensitive**
Level 4		
CDKN2C Heterozygous deletion	Palbociclib	**sensitive**
BRCA2 Heterozygous deletion	Olaparib, Rucaparib	**sensitive**
CHEK2 Heterozygous deletion	Olaparib	**sensitive**
MRE11 Heterozygous deletion	Olaparib, Talazoparib	**sensitive**
NF2 Heterozygous deletion	Everolimus	**sensitive**
TSC1 Heterozygous deletion	Everolimus, Temsirolimus	**sensitive**
RB1 A74fs	Abemaciclib, Palbociclib, Ribociclib	**resistant**
RB1 Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	**resistant**

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

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICI) THERAPIES

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

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

MMR, mismatch repair; ND, not detected

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

CHEMOTHERAPIES

Therapies	Genomic Alterations	Effect	Gene / Variant Level Evidence	Cancer Type
Cisplatin	***RB1*** A74fs Heterozygous deletion	**sensitive**	Clinical	Bladder carcinoma
FAC T/FAC taxane/doxorubicin	***RB1*** A74fs Heterozygous deletion	**sensitive**	Clinical	Breast cancer

HORMONAL THERAPIES

Therapies	Genomic Alterations	Effect	Gene / Variant Level Evidence	Cancer Type
Tamoxifen	***RB1*** A74fs Heterozygous deletion	**resistant**	Clinical	Breast cancer

OTHERS

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

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

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VARIANT INTERPRETATION

CDH1 T340A, Heterozygous deletion

Biological Impact

The CDH1 gene encodes the epithelial cadherin (E-cadherin) protein, a single-pass transmembrane glycoprotein that is mainly expressed in epithelial cells. Loss of E-cadherin function is hypothesized to promote cancer progression through lack of adhesion-mediated growth inhibition[1][2][3][4][5]. CDH1 germline mutations are associated with increased risk of developing diffuse gastric cancer and breast cancer, with lobular breast cancer being the most characteristic[6]. Impaired E-cadherin function has also been implicated in a variety of sporadic cancer types including gastric cancer[7], pancreatic cancer[8], hepatocellular carcinoma[9], colorectal cancer[10]and esophageal cancer[11].

CDH1 T340A is a missense mutation at codon 340, resulting in a change of amino acid from a threonine to an alanine. This variant has been previously identified in hereditary diffuse gastric cancer (HDGC) and colorectal cancers[12][13][14] and has been demonstrated as a loss-of-function mutation that confers increased EGFR, p38 MAPK signaling and cell motility in vitro[15]. Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

Therapeutic and prognostic relevance

Several studies showed that partial or total loss of E-cadherin expression correlates with loss of differentiation characteristics, acquisition of invasiveness, increased tumor grade, metastatic behavior and poor prognosis in patients with breast cancer[16][17][18][19].

CDH1 mutation was found to be associated with shortened survival in diffuse-type gastric cancer[20].

RB1 A74fs, Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[21]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[22]. RB1 has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[23][24][25]. Deletion or inactivating mutation of RB1 is found in a number of tumors, including lung, prostate, bladder, breast cancers and sarcomas. RB1 mutations are found in approximately half of all retinoblastoma cases[26].

A74fs mutation results in a change in the amino acid sequence beginning at 74, likely to cause premature truncation of the functional RB1 protein (UniProtKB). This mutation is predicted to lead to a loss of RB1 protein function, despite not being characterized in the literature. Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

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Therapeutic and prognostic relevance

A deleterious mutation in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response and better overall survival to cisplatin-based chemotherapy for muscle-invasive bladder cancer patients[27]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytoxan (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy[28].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[29][30].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[31]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[32].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[33][34]. Analyses of repeat biopsy samples from patients with EGFR-mutant adenocarcinoma that had transformed to the SCLC subtype have revealed that 100% of these patients have loss of RB1 and may be the alteration that induces this non-small-cell to small-cell transformation[30][35].

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[36]. 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[37][38][39][40][41]. 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[42]. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies[43][44][45][46]and a board range of tumors such as prostate cancer[47], head and neck squamous cell carcinoma (HNSCC)[48], pancreatic cancer[49], lung adenocarcinoma[50], breast cancer[51], and ovarian cancer[38].

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[52].

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In addition, ATM has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer[53]or prostate cancer[54], 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[55]. 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[27]. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer[56].

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer[57].

***BARD1* Homozygous deletion**

Biological Impact

BARD1 (BRCA1 associated RING domain 1) interacts with BRCA1 to maintain the genomic stability[58][59]. BARD1 mutations have been observed in patients with breast cancer, ovarian cancer and uterine cancer[60][61].

Therapeutic and prognostic relevance

In May 2020, the US 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[52].

In addition, BARD1 has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in breast cancer (NCT04053322), rucaparib efficacy in ovarian cancer[53] or prostate cancer[54], niraparib efficacy in metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma (NCT03840967), pancreatic cancer (NCT03553004), and any malignancy, except prostate(NCT03207347), and talazoparib efficacy in HER2-negative breast cancer (NCT02401347), and lung cancer (NCT03377556), respectively.

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BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[62]. BRCA2 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[63]. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia[64]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[65].

Therapeutic and prognostic relevance

The U.S. FDA has approved olaparib in advanced ovarian cancer under several settings including (1) first-line maintenance treatment for patients with deleterious or suspected deleterious germline or somatic BRCA mutation who are in complete or partial response to first-line platinum-based chemotherapy[66]; (2) in combination with bevacizumab as first-line maintenance treatment for patients with homologous recombination deficiency (HRD)-positive status[67]; (3) maintenance treatment for patients with germline BRCA-mutated recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy[68][69]; (4) treatment for patients with germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy[70]. In addition, olaparib has also been approved in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in either neoadjuvant, adjuvant, or metastatic setting[71]and germline BRCA-mutated metastatic pancreatic cancer[72]. Of note, 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[52].

Rucaparib has been approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and patients with BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more chemotherapies[53][73]. In May 2020, the U.S. FDA also approved rucaparib to treat adult patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy (TRITON2, NCT02952534). The U.S. FDA also approved niraparib for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy and patients who have been treated with three or more prior lines of chemotherapy and associated with HRD positive status[74][75][76]. In addition, talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer[77].

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CDKN2C Heterozygous deletion

Biological Impact

CDKN2C gene encodes for cyclin-dependent kinase inhibitor 2C (CDKN2C) or p18 or INK4C, a member of the INK4 family of cyclin-dependent kinase inhibitors. CDKN2C binds to CDK4 or CDK6 and inhibits the activation of cyclin-dependent kinases (CDK) to prevent cell cycle progression at the G1 phase[78]. CDKN2C has been implicated as a haploinsufficient tumor suppressor gene[79] with one copy loss may promote cell cycle progression and induce proliferation in a variety of cancers[80][81][82]. Loss of CDKN2C by gene deletion or inactivating mutation has been reported in multiple cancer types, including myeloma, lymphoma, glioblastoma, meningioma, testicular cancers, melanoma, hepatocellular carcinomas, thyroid, and parathyroid cancer[83][84][85][86][87][88][89][90][91].

Therapeutic and prognostic relevance

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

An in vitro study demonstrated that loss of CDKN2C activates cyclin-dependent kinases (CDK) and improves the sensitivity to palbociclib in glioblastoma multiforme (GBM) tumor cell[92]. Deletion of CDKN2C was associated with poorer prognosis in myeloma, acute lymphoblastic leukemia, hepatocellular carcinomas, and diffuse large B cell lymphoma (DLBCL)[93][94][90][95].

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[96]. 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[97][98]. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors[99], and CHEK1 mutations are extremely rare[96]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer[100], breast cancer[101], colorectal cancer[102], non-small cell lung (NSCLC) cancer[103], and nasopharyngeal cancer[104].

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[52].

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[53], prostate cancer

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(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[105].

CHEK2 Heterozygous deletion

Biological Impact

The checkpoint kinase 2 (CHEK2 or CHK2) gene encodes a serine/threonine protein kinase involved in transducing DNA damage signals that are required for both the intra-S phase and G2/M checkpoints[106]. CHEK2 heterozygosity has been shown to cause haploinsufficient phenotypes that can contribute to tumorigenesis through inappropriate S phase entry, accumulation of DNA damage during replication, and failure to restrain mitotic entry[97][98]. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers[107][108][109][110][111].

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[52].

In addition, CHEK2 has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer(NCT03533946)[53][54], niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

In a phase 2 trial, two prostate cancer patients harboring CHEK2 homozygous deletion was enrolled. One of the two patients had a response to olaparib[112].

LRP1B Homozygous deletion

Biological Impact

Low-density lipoprotein receptor protein 1B (LRP1B) is a surface protein involved in the receptor-mediated endocytosis and signal transduction (UniProtKB). LRP1B is known as a tumor suppressor and was reported among the top 10 most significantly deleted genes across 3312 human cancer specimens[113]. Besides deletions, mutations and epigenetic silencing of LRP1B have been previously reported in lung adenocarcinoma[50], hepatocellular carcinoma[114], renal cell carcinoma[115], thyroid cancer[116], gastric cancer[117], esophageal squamous cell carcinoma[118], and colon cancer[119].

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Therapeutic and prognostic relevance

The prevalence of genetic alterations (mostly loss-of-function mutations) in the LRP1B gene was significantly higher in patients who responded to PD-1 blockade than that of the non-responders (11 vs. 1 mutations, 34% vs. 3%, respectively, P = 0.008). Moreover, an analysis of TCGA dataset showed that melanomas patients with LRP1B mutations had significantly higher tumor mutational load when compared with those without LRP1B mutations[120][121], as well as prolonged survival in response to immunotherapy. Moreover, a retrospective study has shown that pathogenic and likely pathogenic alternations of LRP1B gene are associated with higher ORR, improved PFS and OS in ICI treated advanced or metastatic malignancies (DOI: 10.1200/JCO.2020.38.15_suppl.3007)[122]. However, there were several limitations in this study, including limited sample size and unmeasured confounders. Therefore, further clinical validations are still needed.

A retrospective study has demonstrated that deletion or downregulation of LRP1B showed significant correlation with acquired chemotherapy resistance in patients with high-grade serous ovarian cancer (HGSC). Functional studies also showed that reducing LRP1B expression was sufficient to reduce the sensitivity of HGSC cell lines to liposomal doxorubicin but not to doxorubicin[123]. Furthermore, deletion of LRP1B has been reported to be significantly associated with poor progression-free survival (6.4 m vs. 10.1 m) and overall survival (13.4 m vs. 17.8 m) in patients with glioblastoma[124].

MRE11 **Heterozygous deletion**

Biological Impact

The MRE11 gene encodes a protein that forms the MRE11-RAD50-NBS (MRN) complex involved in sensing and repairing DNA double-strand breaks via homologous recombination and non-homologous end joining[125][126]. MRE11 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function[125]. The carrier of MRE11 mutation may confer elevated risks for numerous types of cancers including breast cancer, ovarian cancer, endometrial cancer, colorectal cancer, and lymphoid cancer[125][126][127][128][129][130][131].

Therapeutic and prognostic relevance

In a Phase II clinical trial (n=50), one castration-resistant prostate cancer patient harboring an MRE11 inactivating mutation responded to olaparib[112]. Preclinically, loss of MRE11 also predicted sensitivity to PARP inhibitor talazoparib and ABT-888 in endometrial cancer[132]and microsatellite unstable colorectal cancer (CRC) cell lines[133].

CRC patients with tumor deficient of MRE11 showed initially reduced disease-free survival (DFS) and overall survival (OS) but improved long-term DFS and OS compared with patients with an intact MRE11[134].

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NF2 Heterozygous deletion

Biological Impact

The neurofibromin (NF2) gene encodes the protein Merlin, a tumor suppressor that functions as a negative regulator of the PI3K/AKT/mTOR pathway[135][136][137]. NF2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[138]. Inactivation germline mutations in the NF2 are associated with the hereditary neurofibromatosis type 2, a disorder characterized by the growth of noncancerous tumors in the nervous system[135][139]. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas[140], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers[141].

Therapeutic and prognostic relevance

Genomic alterations with activating effects on the mTOR signaling pathway have been identified to confer sensitivity to everolimus across multiple cancer types[142][143][144][145]. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer and urothelial carcinoma[146][147], both harboring NF2 truncating mutations. Preclinical evidence has shown the efficacy of MEK1/2 inhibitor selumetinib in KRAS-mutant thyroid cancer model with NF2 loss[148].

Analysis of afatinib-plus-cetuximab-resistant biopsy specimens revealed a loss-of-function alteration in genes that modulate mTOR signaling pathway, including NF2 and TSC1[149].

TSC1 Heterozygous deletion

Biological Impact

The tuberous sclerosis complex 1 (TSC1) gene encodes a tumor suppressor, hamartin, a key negative regulator of the mammalian target of rapamycin (mTOR) pathway[150][151]. Mutations in TSC1/TSC2 tumor suppressor genes that result in inactivation of the complex are commonly found in patients with tuberous sclerosis[152][153][154], while LOH in TSC1/TSC2 has been identified in head and neck squamous cell carcinoma (HNSCC)[155]and endometrial cancer[156]. Loss of single TSC1 allele (haploinsufficiency) may provide a growth advantage to bladder epithelial cells, contributing to bladder cancer development[157]. Both TSC1 and TSC2 mutations cause the autosomal dominant genetic disorder tuberous sclerosis complex (TSC), in which individuals develop a variety of benign but often progressive neoplasms[158].

Therapeutic and prognostic relevance

Genomic alterations with activating effects of the mTOR signaling pathway (including deletion/inactivation of TSC1/TSC2) have been shown to confer sensitivity to everolimus across multiple neoplasms, such as bladder tumors[146], gastric, sarcoma, thyroid cancer, and HNSCC[145]. There were case reports demonstrated the efficacy of sirolimus in malignant uterine perivascular epithelioid cell tumors (PEComa) patients harboring mutations/deletions in TSC1 and TSC2 genes, and temsirolimus in PEComa patients with hyperactivated mTOR

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pathway. Genomic profiling analysis of GOG248, a Phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer showed that mutations in AKT1, TSC1 and TSC2 may predict clinical benefit from temsirolimus[159]. Recent studies indicate that there are mTORC1-independent signaling pathways downstream of hamartin-tuberin, which may represent new therapeutic targets[160].

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US FDA-APPROVED DRUG(S)

Abemaciclib (VERZENIO)

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

FDA Approval Summary of Abemaciclib (VERZENIO)

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[161] NCT00246621	**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 1[162] NCT02102490	**Breast cancer** (Approved on 2017/09/28) **HR-positive, HER2-negative** Abemaciclib [ORR(%): 19.7 vs. 17.4]
MONARCH 2[163] NCT02107703	**Breast cancer** (Approved on 2017/09/28) **HR-positive, HER2-negative** Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]

Everolimus (AFINITOR)

Everolimus, a derivative of sirolimus, works as an inhibitor of mammalian target of rapamycin complex 1 (mTORC1) and blocks mTORC1-mediated downstream signals for cell growth, proliferation, and survival. Everolimus is developed and marketed by Novartis under the trade name AFINITOR.

FDA Approval Summary of Everolimus (AFINITOR)

RADIANT-4[164] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26) - Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[165] NCT00863655	**Breast cancer** (Approved on 2012/07/20) **ER+/HER2-** Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]

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RADIANT-3[166] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[167] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[168] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

Niraparib (ZEJULA)

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

FDA Approval Summary of Niraparib (ZEJULA)

QUADRA[76] NCT02354586	**Ovarian cancer** (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[75] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27)
	gBRCA+ CR/PR to platinum-based chemotherapy
	Niraparib vs. Placebo [PFS(M): 21 vs. 5.5]
NOVA[75] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27)
	gBRCA- CR/PR to platinum-based chemotherapy
	Niraparib vs. Placebo [PFS(M): 9.3 vs. 3.9]

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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)

PROfound[52] 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[67] 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[72] 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[66] 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[71] 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[169] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA+
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]

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行動基因僅提供技術檢測服務及檢測報告，檢測結果之臨床解釋及相關醫療處置，請諮詢專業醫師。報告結果僅對此試驗件有效。

Study19[170] 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[171] 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[172] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+, HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[173] 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[174] NCT01958021	**Breast cancer** (Approved on 2017/03/13)
	HR+, HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

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Rucaparib (RUBRACA)

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

FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA+, sBRCA
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[53] 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[175] 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[77] 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]

TW-P1003220117 15024

葉哲豪
Project ID: C22-M001-00020
Report No.: AA-22-00047_ONC
Date Reported: Jan 17, 2022

Temsirolimus (TORISEL)

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

FDA Approval Summary of Temsirolimus (TORISEL)

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

d=day; w=week; m=month

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葉哲豪

ONGOING CLINICAL TRIALS

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

No trial has been found.

TW2107002032022011715024

葉哲豪
Project ID: C22-M001-00020
Report No.: AA-22-00047_ONC
Date Reported: Jan 17, 2022

DETAILED TEST RESULTS

SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Chr	Exon	Accession Number	cDNA Change	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
ALK	2	9	NM_004304	c.1648C>T	L550F	2077	35.0%	-
BIRC2	11	2	NM_001166	c.185T>G	V62G	2203	53.7%	-
BRCA2	13	11	NM_000059	c.6322C>T	R2108C	278	10.4%	-
CDH1	**16**	**8**	**NM_004360**	**c.1018A>G**	**T340A**	**99**	**85.9%**	**COSM19821**
CYP2C8	10	8	NM_000770	c.1189G>A	D397N	76	57.9%	COSM5714566
FBXW7	4	-	NM_033632	c.1644+6A>C	Splice region	1269	44.4%	-
KAT6A	8	15	NM_006766	c.2986A>G	S996G	615	86.0%	-
KIT	4	16	NM_000222	c.2263G>A	A755T	880	54.3%	COSM7335355
MUC16	19	3	NM_024690	c.20635G>A	A6879T	1731	57.8%	-
MUC16	19	3	NM_024690	c.23778C>A	S7926R	1042	39.1%	-
NOTCH4	6	30	NM_004557	c.5635G>C	A1879P	293	82.6%	-
NOTCH4	6	21	NM_004557	c.3670T>G	F1224V	513	62.8%	-
PMS2	7	11	NM_000535	c.1928A>G	Q643R	1316	49.8%	-
RB1	**13**	**2**	**NM_000321**	**c.219_220dup**	**A74fs**	**87**	**63.2%**	**COSM432450**
RET	10	6	NM_020975	c.1084C>A	L362I	1057	34.9%	-

Mutations with clinical relevance are highlighted in red.

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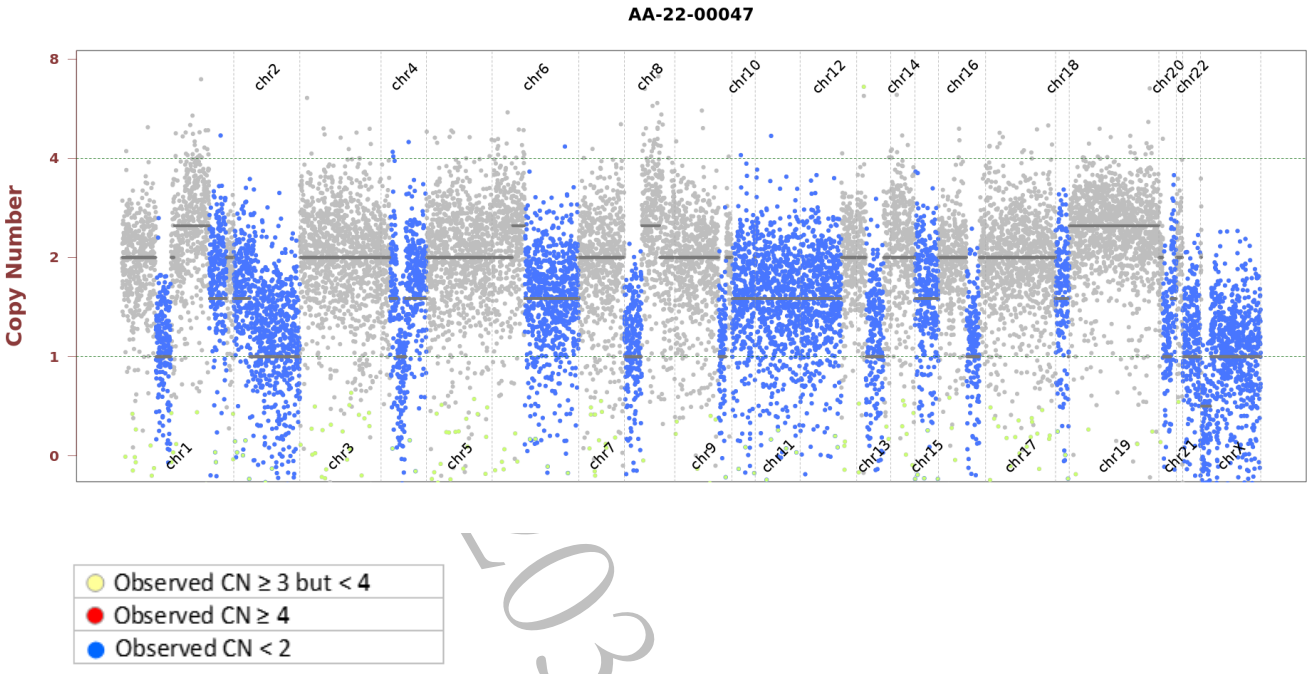
葉哲豪
Project ID: C22-M001-00020
Report No.: AA-22-00047_ONC
Date Reported: Jan 17, 2022

COPY NUMBER VARIANTS (CNVS)

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



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葉哲豪
Project ID: C22-M001-00020
Report No.: AA-22-00047_ONC
Date Reported: Jan 17, 2022

HOTSPOT GENOTYPES

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

Gene	Variant	Genotype Detected
BRAF	V600X	Not detected
EGFR	A763_Y764insFQEA, E709K, E709_T710delinsD, Exon 19 deletion, Exon 19 insertion, Exon 20 insertion, G719A/C/D/S, L747P, L833V, L858R, L861Q/R, S768I, T790M	Not detected
IDH2	R140Q, R172G/K/M/S	Not detected
KIT	A502_Y503dup, D419del, D579del, D816F/V/Y, D820A/E/G/Y, E554_I571del, E554_K558del, E554_V559del, Exon 11 mutation, F522C, H697Y, I563_L576del, I653T, K550_W557del, K558N, K558_E562del, K558_V559del, K558delinsNP, K642E, M552_W557del, N505I, N564_Y578del, N822H/I/K/Y, P551_M552del, P573_D579del, P577_D579del, P577_W582delinsPYD, P838L, Q556_K558del, T417_D419delinsI, T417_D419delinsRG, T574_Q575insTQLPYD, V530I, V555_L576del, V555_V559del, V559A/C/D/G, V559_V560del, V559del, V560D/G, V560del, V569_L576del, V654A, W557G/R, W557_K558del, Y553N, Y553_K558del, Y570H, Y578C	Not detected
KRAS	A146T/V/P, G12X, G13X, Q61X	Not detected
MET	D1028H/N/Y	Not detected
NRAS	G12X, G13X, Q61X	Not detected
PDGFRA	A633T, C450_K451insMIEWMI, C456_N468del, C456_R481del, D568N, D842I/V, D842_H845del, D842_M844del, D846Y, E311_K312del, G853D, H650Q, H845Y, H845_N848delinsP, I843del, N659K/R/S, N848K, P577S, Q579R, R560_V561insER, R748G, R841K, S566_E571delinsR, S584L, V469A, V536E, V544_L545insAVLVLLVIVIISLI, V561A/D, V561_I562insER, V658A, W559_R560del, Y375_K455del, Y555C, Y849C/S	Not detected
PIK3CA	C420R, E542K/V, E545A/D/G/K, H1047X, Q546E/R	Not detected

V600X= any mutation in the valine (V) at amino acid 600 being replaced by a different amino acid.
G12X = any mutation in the glycine (G) at amino acid 12 being replaced by a different amino acid.
G13X= any mutation in the glycine (G) at amino acid 13 being replaced by a different amino acid.
Q61X = any mutation in the glutamine (Q) at amino acid 61 being replaced by a different amino acid.
H1047X = any mutation in the histidine (H) at amino acid 1047 being replaced by a different amino acid.

Gene	Copy Number Detected
CDK4	2
EGFR	2
ERBB2	2
MET	2

Copy number ≥ 8 is considered amplification

行動基因僅提供技術檢測服務及檢測報告，檢測結果之臨床解釋及相關醫療處置，請諮詢專業醫師。報告結果僅對此試驗件有效。

葉哲豪
Project ID: C22-M001-00020
Report No.: AA-22-00047_ONC
Date Reported: Jan 17, 2022

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

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

Gene	Copy Number Detected
FGFR1	1
MDM2	2
MDM4	3

Copy number ≥ 8 is considered amplification

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TEST DETAILS

ABOUT ACTOnco®+

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

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

DATABASE USED

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

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

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite (version 5.10). Coverage depth was calculated using Torrent Coverage Analysis plug-in. Single nucleotide variants (SNVs) and short insertions/deletions (INDELs) were identified using the Torrent Variant Caller plug-in (version 5.10). The coverage was down-sampled to 4000. VEP (Variant Effect Predictor) (version 100) was used to annotate every variant using databases from Clinvar (version 20210208), COSMIC v.92 and Genome Aggregation database r2.1.1. Variants with coverage ≥ 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 r2.1.1 with > 1% minor allele frequency (MAF) were

considered as polymorphisms. ACT Genomics in-house database was used to determine technical errors. Clinically actionable and biologically significant variants were determined based on the published medical literature.

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

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

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

STANDARD OPERATING PROCEDURES (SOPS)

Standard operating procedures (SOPs) are shown below:

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

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

LIMITATIONS

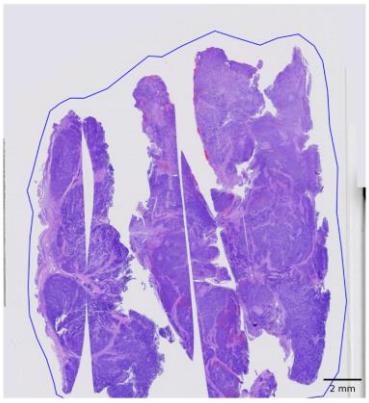
This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject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

NOTES

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

PATHOLOGY EVALUATION

- H&E-stained section No.: S11024511A
- Collection site: Vertebra
- Examined by: Dr. Pei-Yi Chu
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 85%
  The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 85%
  The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
  The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
  Additional comment: NA
- Manual macrodissection: Not performed



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

S11024511A

SPECIMEN PHOTO(S)

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

RUN QC

- Panel: ACTOnco®+
- Mean Depth: 999x
- Target Base Coverage at 100x: 91%

32022017 15024

葉哲豪

ACTOnco®+ GENE LIST

ABCB1*	AURKB	CBL	CDKN2B	E2F3	FAT1	GRIN2A	JAK2	MED12	NOTCH4	PMS1	RAD51D	SLCO1B3*	TNFRSF14
ABCC2*	AXIN1	CCNA1	CDKN2C	EGFR	FBXW7	GSK3B	JAK3	MEF2B	NPM1	PMS2	RAD52	SMAD2	TNFSF11
ABCG2*	AXIN2	CCNA2	CEBPA*	EP300	FCGR2B	GSTP1*	JUN*	MEN1	NQO1*	POLB	RAD54L	SMAD3	TOP1
ABL1	AXL	CCNB1	CHEK1	EPCAM	FGF1*	GSTT1*	KAT6A	MET	NRAS	POLD1	RAF1	SMAD4	TP53
ABL2	B2M	CCNB2	CHEK2	EPHA2	FGF10	HGF	KDM5A	MITF	NSD1	POLE	RARA	SMARCA4	TPMT*
ADAMTS1	BAP1	CCNB3	CIC	EPHA3	FGF14	HIF1A	KDM5C	MLH1	NTRK1	PPARG	RB1	SMARCB1	TSC1
ADAMTS13	BARD1	CCND1	CREBBP	EPHA5	FGF19*	HIST1H1C*	KDM6A	MPL	NTRK2	PPP2R1A	RBM10	SMO	TSC2
ADAMTS15	BCL10	CCND2	CRKL	EPHA7	FGF23	HIST1H1E*	KDR	MRE11	NTRK3	PRDM1	RECQL4	SOCS1*	TSHR
ADAMTS16	BCL2*	CCND3	CRLF2	EPHB1	FGF3	HNF1A	KEAP1	MSH2	PAK3	PRKAR1A	REL	SOX2*	TYMS
ADAMTS18	BCL2L1	CCNE1	CSF1R	ERBB2	FGF4*	HR	KIT	MSH6	PALB2	PRKCA	RET	SOX9	U2AF1
ADAMTS6	BCL2L2*	CCNE2	CTCF	ERBB3	FGF6	HRAS*	KMT2A	MTHFR*	PARP1	PRKCB	RHOA	SPEN	UBE2A*
ADAMTS9	BCL6	CCNH	CTLA4	ERBB4	FGFR1	HSP90AA1	KMT2C	MTOR	PAX5	PRKCG	RICTOR	SPOP	UBE2K
ADAMTSL1	BCL9	CD19	CTNNA1	ERCC1	FGFR2	HSP90AB1	KMT2D	MUC16	PAX8	PRKCI	RNF43	SRC	UBR5
ADGRA2	BCOR	CD274	CTNNB1	ERCC2	FGFR3	HSPA4	KRAS	MUC4	PBRM1	PRKCQ	ROS1	STAG2	UGT1A1*
ADH1C*	BIRC2	CD58	CUL3	ERCC3	FGFR4	HSPA5	LCK	MUC6	PDCD1	PRKDC	RPPH1	STAT3	USH2A
AKT1	BIRC3	CD70*	CYLD	ERCC4	FH	IDH1	LIG1	MUTYH	PDCD1LG2	PRKN	RPTOR	STK11	VDR*
AKT2	BLM	CD79A	CYP1A1*	ERCC5	FLCN	IDH2	LIG3	MYC	PDGFRA	PSMB8	RUNX1	SUFU	VEGFA
AKT3	BMPR1A	CD79B	CYP2B6*	ERG	FLT1	IFNL3*	LMO1	MYCL	PDGFRB	PSMB9	RUNX1T1	SYK	VEGFB
ALDH1A1*	BRAF	CDC73	CYP2C19*	ESR1	FLT3	IGF1	LRP1B	MYCN	PDIA3	PSME1	RXRA	SYNE1	VHL
ALK	BRCA1	CDH1	CYP2C8*	ESR2	FLT4	IGF1R	LYN	MYD88	PGF	PSME2	SDHA	TAF1	WT1
AMER1	BRCA2	CDK1	CYP2D6	ETV1	FOXL2*	IGF2	MALT1	NAT2*	PHOX2B*	PSME3	SDHB	TAP1	XIAP
APC	BRD4	CDK12	CYP2E1*	ETV4	FOXP1	IKBKB	MAP2K1	NBN	PIK3C2B	PTCH1	SDHC	TAP2	XPO1
AR	BRIP1	CDK2	CYP3A4*	EZH2	FRG1	IKBKE	MAP2K2	NEFH	PIK3C2G	PTEN	SDHD	TAPBP	XRCC2
ARAF	BTG1*	CDK4	CYP3A5*	FAM46C	FUBP1	IKZF1	MAP2K4	NF1	PIK3C3	PTGS2	SERPINB3	TBX3	ZNF217
ARID1A	BTG2*	CDK5	DAXX	FANCA	GATA1	IL6	MAP3K1	NF2	PIK3CA	PTPN11	SERPINB4	TEK	
ARID1B	BTK	CDK6	DCUN1D1	FANCC	GATA2	IL7R	MAP3K7	NFE2L2	PIK3CB	PTPRD	SETD2	TERT	
ARID2	BUB1B	CDK7	DDR2	FANCD2	GATA3	INPP4B	MAPK1	NFKB1	PIK3CD	PTPRT	SF3B1	TET1	
ASXL1	CALR	CDK8	DICER1	FANCE	GNA11	INSR	MAPK3	NFKBIA	PIK3CG	RAC1	SGK1	TET2	
ATM	CANX	CDK9	DNMT3A	FANCF	GNA13	IRF4	MAX	NKX2-1*	PIK3R1	RAD50	SH2D1A*	TGFBR2	
ATR	CARD11	CDKN1A	DOT1L	FANCG	GNAQ	IRS1	MCL1	NOTCH1	PIK3R2	RAD51	SLC19A1*	TMSB4X*	
ATRX	CASP8	CDKN1B	DPYD	FANCL	GNAS	IRS2*	MDM2	NOTCH2	PIK3R3	RAD51B	SLC22A2*	TNF	
AURKA	CBFB	CDKN2A	DTX1	FAS	GREM1	JAK1	MDM4	NOTCH3	PIM1	RAD51C	SLCO1B1*	TNFAIP3	

*Analysis of copy number alteration not available.

行動基因僅提供技術檢測服務及檢測報告，檢測結果之臨床解釋及相關醫療處置，請諮詢專業醫師。報告結果僅對此試驗件有效。

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Level of Evidence Provided

Drugs with a potential clinical benefit (or potential lack of clinical benefit) are evaluated for level of published evidence with at least one clinical efficacy case report or preclinical study. We endeavor to keep the information in the report up to date. However, customers must be aware that scientific understanding and technologies change over time, and we make no warranty as to the accuracy, suitability or currency of information provided in this report at any time.

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葉哲豪
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Date Reported: Jan 17, 2022

免責聲明

法律聲明

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

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

醫療決策需由醫師決定

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

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

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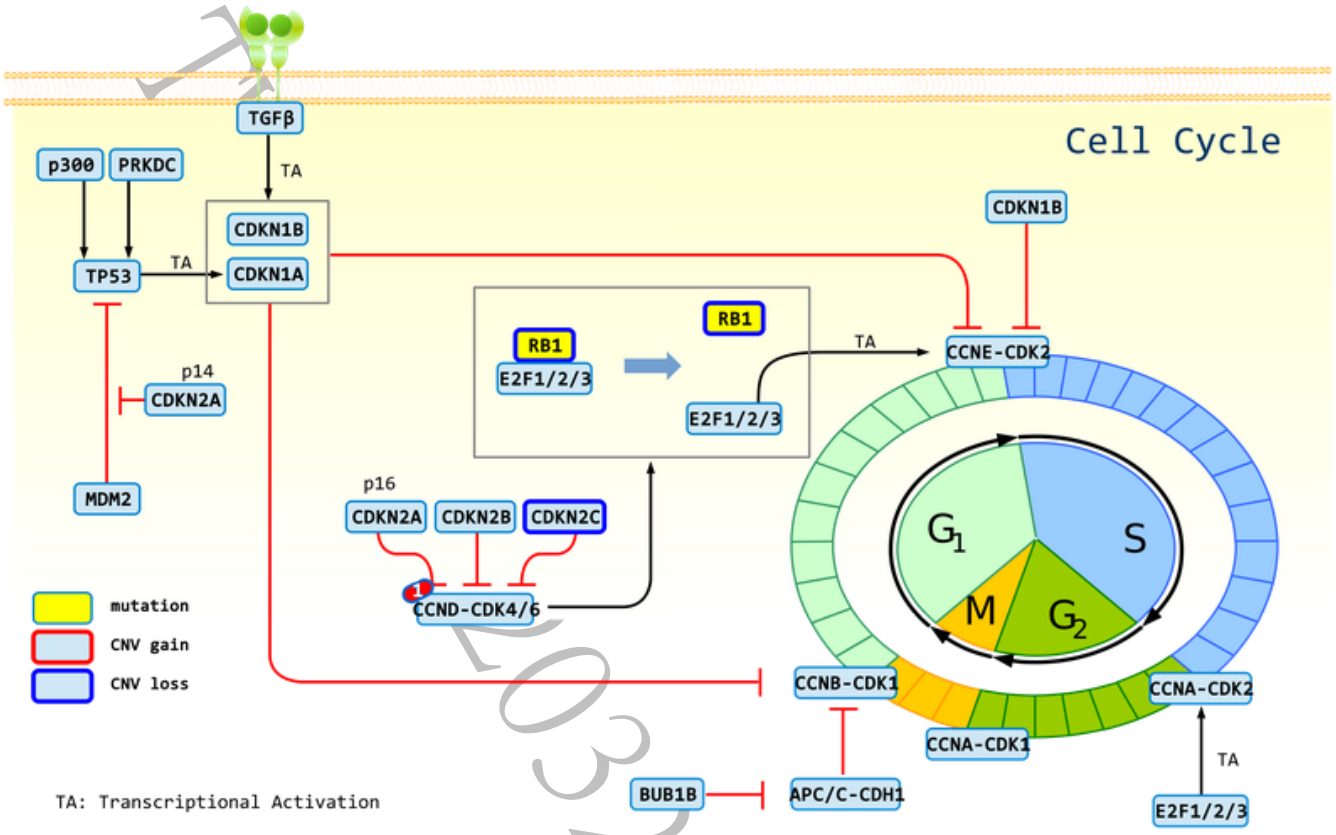
SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Palbociclib, Ribociclib, Abemaciclib

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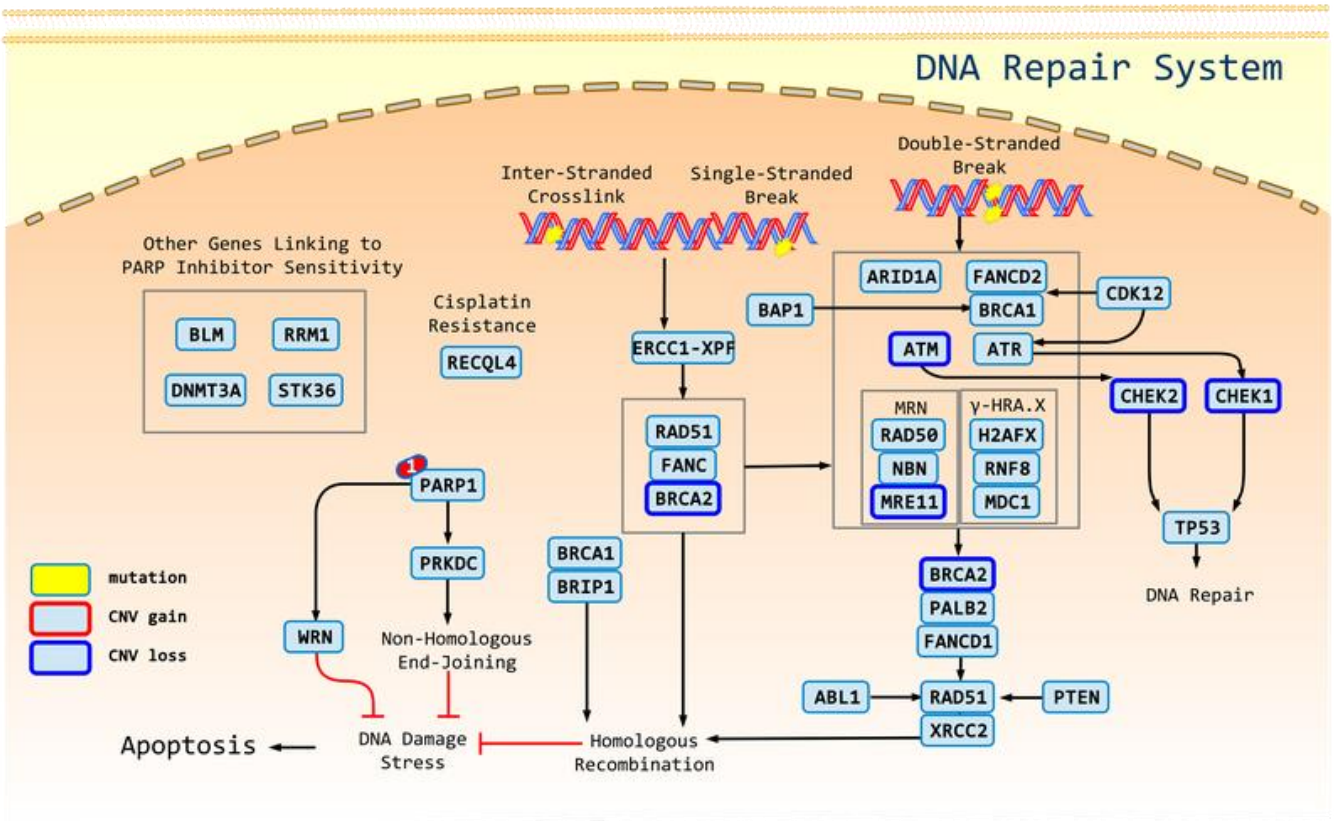

1: Olaparib, Niraparib, Rucaparib, Talazoparib

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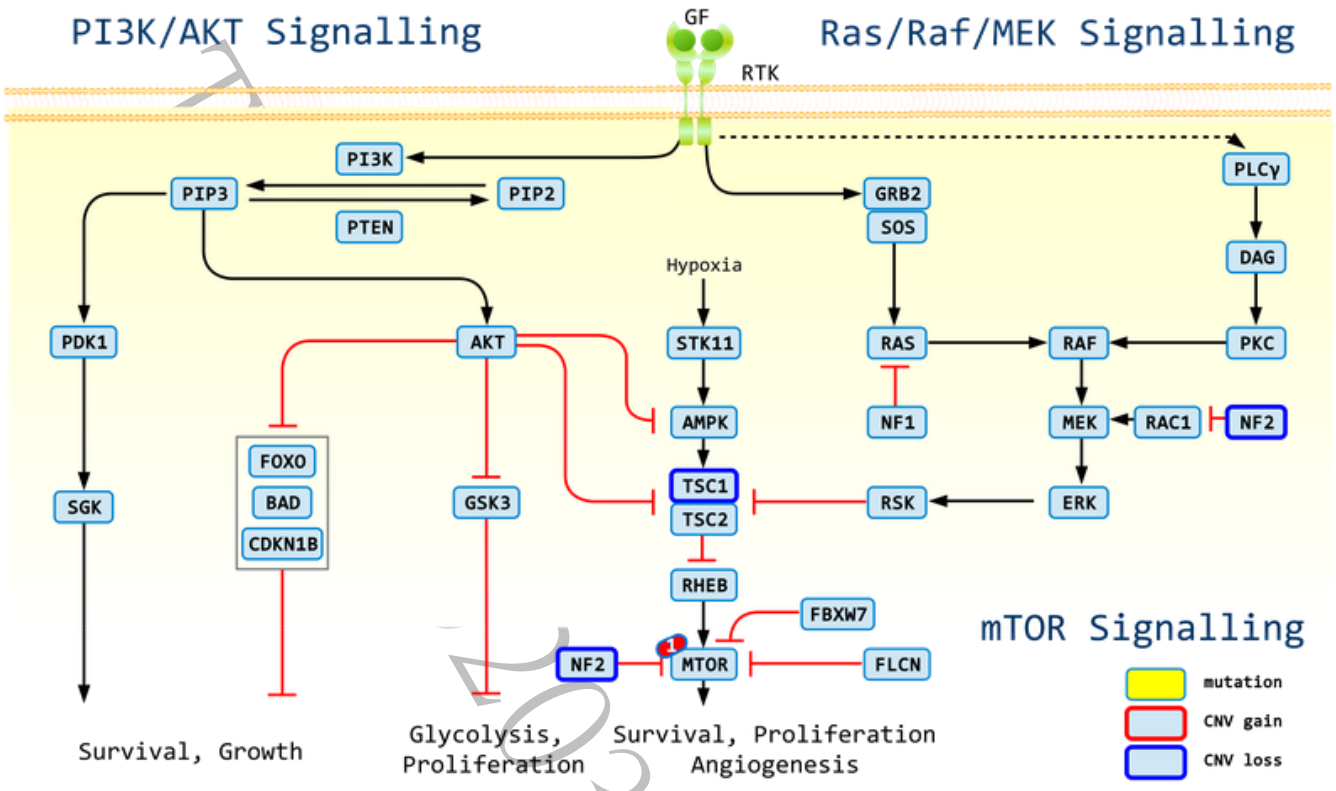

1: Everolimus, Temsirolimus

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行動基因僅提供技術檢測服務及檢測報告，檢測結果之臨床解釋及相關醫療處置，請諮詢專業醫師。報告結果僅對此試驗件有效。

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葉哲豪
Project ID: C22-M001-00020
Report No.: AA-22-00047_FUSION
Date Reported: Jan 17, 2022

ACTFusion™ Report

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PATIENT		
Name: 葉哲豪		Patient ID: 19342906
Date of Birth: Mar 26, 1953		Gender: Male
Diagnosis: Metastatic neuroendocrine carcinoma		
ORDERING PHYSICIAN		
Name: 賴峻毅醫師		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: S11024511A	Collection site: Vertebra	Date received: Jan 04, 2022
Lab ID: AA-22-00047	Type: FFPE tissue	D/ID: NA

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

TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Fusions

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

ACTFusion™ Report

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THERAPEUTIC IMPLICATION

Not Applicable.

VARIANT INTERPRETATION

Not Applicable.

US FDA-APPROVED DRUG(S)

Not Applicable.

ACTFusion™ Report

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ONGOING CLINICAL TRIALS

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

No trial has been found.

ACTFusion™ Report

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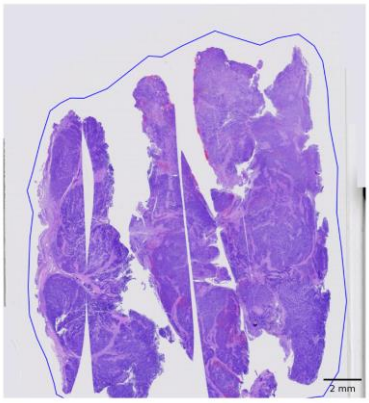
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Aug 2021
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11024511A
- Collection site: Vertebra
- Examined by: Dr. Pei-Yi Chu
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 85%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 85%
  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: ACTFusion™
- Total reads: 502870
- Average unique RNA Start Sites per control GSP2: 137

LIMITATIONS

This test has been designed to detect fusions in 13 genes sequenced. Therefore, fusion in genes not covered by this test would not be reported. For novel fusions detected in this test, Sanger sequencing confirmation is recommended if residue specimen is available.

ACTFusion™ Report

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NEXT-GENERATION SEQUENCING (NGS) METHODS

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

The fusion analysis pipeline aligned sequenced reads to the human reference genome, identified regions that map to noncontiguous regions of the genome, applied filters to exclude probable false-positive events and, annotated previously characterized fusion events according to Quiver Gene Fusion Database, a curated database owned and maintained by ArcherDX.

STANDARD OPERATING PROCEDURES (SOPs)

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

DATABAES USED

- Quiver Gene Fusion Database version 5.1.18

GENE LIST

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

Variant Analysis:
醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

Sign Off
醫檢師陳韻仔 博士
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Yun Yu Chen

ACTFusion™ Report

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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。

責任

本檢驗報告僅提供專業醫療參考，本公司及其員工不對任何由使用本報告之內容引起的直接、間接、特殊、連帶或衍生的損失或損害承擔責任。

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REFERENCE

Not Applicable.