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PATIENT AND SAMPLE INFORMATION

PATIENT

Name: 陳添壽
Gender: Male
Date of Birth: Feb 18, 1966
Patient ID: 47526567
Diagnosis: Squamous cell carcinoma

SPECIMEN

Type: FFPE tissue
Date received: Nov 24, 2021
Collection site: Soft tissue
Specimen ID: S11027641P
Lab ID: AA-21-05698
D/ID: NA

ORDERING PHYSICIAN

Name: 陳三奇醫師
Facility: 臺北榮總
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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
BAP1	S468fs	839	67.7%	-
PIK3CA	E545K	2014	34.4%	COSM763
TP53	S227*	1433	34.8%	COSM45211
TP53	R248Q	1409	25.3%	COSM10662

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 **60%** tumor purity.

Amplification (Copy number ≥ 8)

Chr	Gene	Copy Number
ND	ND	ND

Homozygous deletion (Copy number=0)

Chr	Gene
ND	ND

Heterozygous deletion (Copy number=1)

Chr	Gene
chr7	KMT2C
chr9	CDKN2A
chr13	BRCA2, RB1
chr19	ERCC1, STK11

ND, Not Detected

TUMOR MUTATIONAL BURDEN (TMB)

< 1 muts/Mb

Muts/Mb, mutations per megabase

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%.

MICROSATELLITE INSTABILITY (MSI)

Microsatellite stable (MSS)

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

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Yun Yu Chen

THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3A		
PIK3CA E545K	Alpelisib	sensitive
Level 3B		
PIK3CA E545K	Everolimus, Temsirolimus	sensitive
BAP1 S468fs	Niraparib, Olaparib	sensitive
CDKN2A Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	sensitive
Level 4		
PIK3CA E545K	Trametinib	sensitive
BRCA2 Heterozygous deletion	Olaparib, Rucaparib	sensitive
ERCC1 Heterozygous deletion	Olaparib, Rucaparib	sensitive
KMT2C Heterozygous deletion	Olaparib	sensitive
STK11 Heterozygous deletion	Everolimus, Trametinib	sensitive
PIK3CA E545K	Lapatinib, Trastuzumab	less sensitive
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

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
Platinum- and taxane-based regimens	TP53 R248Q	less sensitive	Clinical	Ovarian cancer

HORMONAL THERAPIES

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

OTHERS

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

Note:

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

VARIANT INTERPRETATION

BAP1 S468fs

Biological Impact

Breast cancer type 1 susceptibility protein (BRCA1)-associated protein (BAP1) encodes an enzyme with ubiquitin carboxyl hydrolase activity involved in the regulation of cell cycle, transcription, and double-strand DNA repair^{[1][2][3]}. BAP1 acts as a tumor suppressor by forming a complex with BRCA1^[4]. BAP1 is a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is related to renal cell carcinoma (RCC)^[5]. Inactivating mutations of BAP1 were frequently observed in uveal melanoma with high metastatic risk, malignant mesothelioma and other carcinoma types, including a subtype of renal cell carcinoma and intrahepatic cholangiocarcinoma^{[2][6][7][8][9][10][11]}.

S468fs mutation results in a change in the amino acid sequence beginning at 468, likely to cause premature truncation of the functional BAP1 protein (UniProtKB). This mutation is predicted to lead to a loss of BAP1 protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

The loss of BAP1 was shown to be associated with increased sensitivity to PARP inhibitor, olaparib, in renal cell carcinoma (RCC)^[8] and mesothelioma cell lines^[12]. However, no difference in sensitivity to the PARP inhibitor MK4827 was observed between BAP1-mutant and wild-type mesothelioma cell^[2]. BAP1 deficiency was also linked to a high tumor grade and was correlated with metastasis development in uveal melanoma^[6]. An open-label, non-randomized, Phase II study (NCT03207347) has been initiated, aimed at investigating the use of niraparib in mesothelioma, uveal melanoma, renal cell carcinoma, and cholangiocarcinoma patients with tumors known to have mutations in BAP1 and other selected DNA double-strand break repair pathway genes. BAP1 loss of function mutation has been selected as an inclusion criteria for the trial examining olaparib in urothelial cancer (NCT03375307) and malignant mesothelioma (NCT04515836).

PIK3CA E545K

Biological Impact

The PIK3CA gene encodes the catalytic subunit (p110 α) of phosphatidylinositol 3-kinase (PI3K) that plays a key role in the PI3K/AKT signaling pathway and is involved in the regulation of cellular functions such as proliferation, metabolism and protein synthesis, angiogenesis and apoptosis. PIK3CA has long been described as an oncogene and the PIK3CA gene amplification, deletion, and mutations have been reported in a wide range of cancers, including colorectal, breast, brain, liver, ovarian, stomach and lung cancers^{[13][14][15][16]}. Mutations located in the exon 9 that encodes the PI3K helical (like E542K, E545K) and the exon 20 that encodes the catalytic/kinase domain (like H1047R, H1047L, H1047Y) have been shown to result in the constitutively activated mutant, which could enhance downstream signaling and oncogenic transformation in vitro and in vivo^{[14][17][18][19]}.

The PIK3CA E545K/E542K is the second most prevalent activating mutations in breast cancer and are also highly recurrent in other cancer types.

Therapeutic and prognostic relevance

In a preclinical study, cells harbored different activating PIK3CA mutations (H1047R, E545K, G1049R, Q546K, N345K, H1047L, E542K) were significantly more sensitive to PIK3 pathway inhibitors (dactolisib, MK2206, alpelisib), and MEK1/2 inhibitor trametinib, compared to wild-type^[20]. According to ExteNET trial, PIK3CA activating mutation was not an appropriate predictive biomarker of response to neratinib in HER2-positive early breast cancer^[21].

In 2019 May, alpelisib, the PI3K inhibitor, in combination with fulvestrant received U.S. FDA approval for the treatment of postmenopausal women and men, with HR+, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced breast cancer following progression on or after an endocrine-based regimen. The approval is based on the results of the SOLAR-1 trial (NCT02437318), a randomized phase III trial of 572 patients with breast cancers showed that addition of alpelisib to fulvestrant significantly prolonged progression-free survival (median of 11 months vs. 5.7 months) in patients whose tumors had a PIK3CA mutation including C420R, E542K, E545A, E545D, E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y^[22].

An early phase study demonstrated that alpelisib has potential treatment benefits in a subset of PIK3CA-mutated tumors. Of the 114 patients with PIK3CA-mutated tumors, one patient with endometrial cancer achieved a complete response and seven had partial responses (including cervical, breast, endometrial, colon and rectal cancers). Besides, stable disease was observed in 70 patients and disease control rate was 58.2%^[23].

Given that compared to patients with wild-type PIK3CA, those carrying PIK3CA mutations have a favorable response to mTOR inhibitors-containing monotherapy like everolimus and temsirolimus in several clinical studies of advanced malignancies^{[24][25][26][27][28]} or temsirolimus in combination with doxorubicin and bevacizumab^{[29][30]}, combining PI3K-targeted agent with endocrine therapy was suggested.

Meanwhile, clinical benefit and response were observed when everolimus, an mTOR kinase inhibitor, was added to trastuzumab for the treatment of patients with HER2-overexpressing metastatic breast cancer, who progressed on trastuzumab-based therapy^[31]. BOLERO-1 and BOLERO-3 (Breast Cancer Trials of Oral Everolimus) also suggested that patients with HER2-positive advanced breast cancer carrying PIK3CA mutations, PTEN loss, or hyperactive PI3K pathway could derive progression-free survival (PFS) benefit from everolimus^[32]. In addition, BOLERO-3 study also showed that the addition of everolimus to trastuzumab plus vinorelbine significantly prolonged PFS in patients with trastuzumab-resistant and taxane-pretreated, HER2-positive, advanced breast cancer. However, the clinical benefit should be considered in the context of the adverse event profile in this population^[33]. According to ExteNET trial, PIK3CA activating mutation was not an appropriate predictive biomarker of response to neratinib in HER2-positive early breast cancer^[21].

PIK3CA mutations have been determined as an inclusion criterion for the trials evaluating everolimus efficacy in patients with malignant glioma and different types of tumors (NCT03834740, NCT01827384) and trials examining temsirolimus in malignant solid tumors, multiple myeloma, B-cell non-Hodgkin lymphoma and malignant uterine neoplasm (NCT03297606, NCT02693535). On the other hand, there are several investigational PI3K inhibitors, including taselisib and buparlisib, which are currently in clinical development^{[34][35]}.

A retrospective study indicated that CRC patients with PIK3CA mutation and wild-type KRAS/BRAF showed fair responses to anti-EGFR therapies^[36].

Hyperactivation of the PI3K signaling pathway is common and has been implicated in resistance to endocrine therapy^{[37][34]} and HER2-targeting neoadjuvant therapies such as trastuzumab and lapatinib^{[38][39][40][41][42][43]} in patients with advanced breast cancer.

Results from a clinical study showed that PIK3CA mutations occur in approximately 5% (2/37) of EGFR-mutated lung cancers who developed acquired resistance to EGFR TKI therapy^[44]. Preclinical data also showed that PI3K/AKT/mTOR signaling was implicated in gefitinib resistance in EGFR-mutated lung cancer cell lines^[45]. Although preclinical data suggested that addition of everolimus restored gefitinib sensitivity in NSCLC cancer cell lines^{[46][47]}, the efficacy was not evidenced in the clinical settings^{[48][49]}.

Two meta-analyses involving five studies demonstrated a significant correlation of PIK3CA mutations with better recurrence-free survival (RFS) in patients with unsorted breast cancer^{[50][51][41]}.

In patients with advanced EGFR- or KRAS-mutant lung adenocarcinoma, a concurrent PIK3CA mutation has been reported as a poor prognostic factor^[52].

TP53 R248Q, S227*

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[53]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[54].

R248Q is a missense mutation located in the DNA-binding domain (DBD) of the p53 protein (UniProtKB). This mutation causes oncogenic gain-of-function phenotypes in a breast cancer cell line^[55] and has been reported to target the proteasome activator REG gamma to promote endometrial cancer progression^[56].

S227* mutation results in a premature truncation of the p53 protein at amino acid 227 (UniProtKB). This mutation is predicted to lead to a loss of p53 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

Despite having a high mutation rate in cancers, there are currently no approved targeted therapies for TP53 mutations. A phase II trial demonstrated that Wee1 inhibitor (AZD1775) in combination with carboplatin was well tolerated and showed promising anti-tumor activity in TP53-mutated ovarian cancer refractory or resistant (< 3 months) to standard first-line therapy (NCT01164995)^[57].

In a retrospective study (n=19), advanced sarcoma patients with TP53 loss-of-function mutations displayed improved progression-free survival (208 days versus 136 days) relative to patients with wild-type TP53 when treated with pazopanib^[58]. Results from another Phase I trial of advanced solid tumors (n=78) demonstrated that TP53 hotspot mutations are associated with better clinical response to the combination of pazopanib and vorinostat^[59].

Advanced solid tumor and colorectal cancer patients harboring a TP53 mutation have been shown to be more sensitive to bevacizumab when compared with patients harboring wild-type TP53^{[60][61][62]}. In a pilot trial (n=21), TP53-negative breast cancer patients demonstrated increased survival following treatment with bevacizumab in combination with chemotherapy agents, Adriamycin (doxorubicin) and Taxotere (docetaxel)^[63]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[64][65]}. In a retrospective study of non-small cell lung cancer (NSCLC), TP53 mutations were associated with high expression of VEGF-A, the primary target of bevacizumab, offering a mechanistic explanation for why patients exhibit improved outcomes after bevacizumab treatment when their tumors harbor mutant TP53 versus wild-type TP53^[66].

TP53 oncomorphic mutations, including P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L and R282W have been shown to predict resistance to platinum- and taxane-based chemotherapy in advanced serous ovarian carcinoma patients^[67].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair^[68]. 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^[69]. 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^[70]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers^[71].

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^[72]; (2) in combination with bevacizumab as first-line maintenance treatment for patients with homologous recombination deficiency (HRD)-positive status^[73]; (3) maintenance treatment for patients with germline BRCA-mutated recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy^{[74][75]}; (4) treatment for patients with germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy^[76]. 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^[77] and germline BRCA-mutated metastatic pancreatic cancer^[78]. 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^[79].

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^[80] and patients with BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more chemotherapies^[81]. 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^{[82][83]} and patients who have been treated with three or more prior lines of chemotherapy and associated with HRD positive status^[84]. In addition, talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer^[85].

CDKN2A Heterozygous deletion

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein^{[86][87]} whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53^[88]. CDKN2A has been reported as a haploinsufficient tumor suppressor with one copy loss that may lead to weak protein expression and is insufficient to execute its original physiological functions^[89]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation^{[90][91]}.

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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AG4-QP4001-02(05)

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors^{[92][93]}. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments^{[94][95][96]}. However, there are clinical studies that demonstrated CDKN2A nuclear expression, CDKN2A/CDKN2B co-deletion, or CDKN2A inactivating mutation was not associated with clinical benefit from CDK4/6 inhibitors, such as palbociclib and ribociclib, in RB-positive patients^{[97][98][99]}. However, CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for the treatment of ER+ and HER2- breast cancer^{[93][100][101]}.

In a Phase I trial, a KRAS wild-type squamous non-small cell lung cancer (NSCLC) patient with CDKN2A loss had a partial response when treated with CDK4/6 inhibitor abemaciclib^[95]. Administration of combined palbociclib and MEK inhibitor PD-0325901 yield promising progression-free survival among patients with KRAS mutant non-small cell lung cancer (NSCLC) (AACR 2017, Abstract CT046). Moreover, MEK inhibitor in combination with CDK4/6 inhibitor demonstrates significant anti-KRAS-mutant NSCLC activity and radiosensitizing effect in preclinical models^[102].

A retrospective analysis demonstrated that concurrent deletion of CDKN2A with EGFR mutation in patients with non-small cell lung cancer (NSCLC), predicts worse overall survival after EGFR-TKI treatment^[103].

ERCC1 Heterozygous deletion

Biological Impact

The Excision Repair Cross-Complementation Group 1 (ERCC1) gene encodes a non-catalytic component of a structure-specific DNA repair endonuclease that is responsible for 5' incision. This endonuclease is a heterodimer containing ERCC1 and ERCC4 and is involved in recombinational DNA repair and in the repair of inter-strand crosslinks (ICL). In addition, ERCC1 participates in the processing of anaphase bridge-generating DNA structures. Other genes associated with the nucleotide excision repair pathway includes ERCC1-5, CDK7, DDB1-2, XPA, and XPC^[104]. ERCC1 haploinsufficiency is associated with tumorigenesis in the mouse model^[105].

Therapeutic and prognostic relevance

Loss of expression of ERCC1 has long been implicated in increased sensitivity towards cisplatin in non-small cell lung cancer (NSCLC)^[106] and ovarian carcinoma^{[107][108][109]}. PARP inhibitors demonstrated anti-tumor activity against ERCC1-deficient non-small cell lung cancer (NSCLC) cell line^{[110][111][112]}. Preclinical studies also showed that inhibiting topoisomerase I and PARP1 in combination, as was demonstrated with the combination of ABT-888 and CPT-11, may result in the synergistic decrease in tumor regression for women with triple-negative breast cancer (TNBC)^[113].

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KMT2C Heterozygous deletion

Biological Impact

Lysine methyltransferase 2C (KMT2C) gene encodes the histone methyltransferase MLL3, which methylates lysine residue four on the tail of histone H3 (H3K4)^[114] and regulates the gene expression during development and hematopoiesis^{[115][116][117]}. KMT2C is ubiquitously expressed, and its function is essential for normal embryonal development and cell proliferation^[118]. Genetic deletion of the region containing KMT2C is the most common chromosomal abnormality in acute myeloid leukemia^{[119][120]}, and KMT2C mutation has been reported in breast cancer, cutaneous squamous cell carcinoma, and leukemia^{[121][122][123][124][125]}. KMT2C was implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^[126]. Animal studies revealed that MLL3 haploinsufficiency enhances hematopoietic stem cells (HSCs) self-renewal capacity and induces extensive division of HSCs (AACR; Cancer Res 2018;78(13 Suppl): Abstract nr 4996).

Therapeutic and prognostic relevance

Preclinical studies of cell lines and xenograft models demonstrated that cells with reduced KMT2C expression and activity are deficient in homologous recombination-mediated double-strand break DNA repair and therefore, are more sensitive to olaparib, a PARP1/2 inhibitor^[127].

A meta-analysis indicated that low levels of KMT2C expression was associated with better overall survival in pancreatic ductal adenocarcinoma (PDAC) patients^[128]. However, another study of ER-positive breast cancer patients (n = 401) demonstrated that low KMT2C expression was associated with worse overall survival^[129].

RB1 Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication^[130]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis^[131]. 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^{[132][133][134]}. 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^[135].

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^[136]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytosine (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy^[137].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer^{[138][139]}.

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment^[140]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib^[141].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)^{[142][143]}. 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^{[139][144]}.

STK11 Heterozygous deletion

Biological Impact

The serine/threonine kinase 11 (STK11, also known as LKB1) gene encodes the multifunctional serine/threonine kinase, a tumor suppressor that functions as an inhibitor for the mTOR signaling pathway^{[145][146]}. STK11 is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^{[147][148]}. In the mouse model, loss of STK11 promotes aggressive endometrial and squamous cell carcinomas^{[149][150]}. Mutations in STK11 have been found in lung, breast, cervical, testicular, and liver cancers, as well as malignant melanoma, pancreatic and biliary carcinoma^[151]. Germline mutations in STK11 are found in 30-70% of Peutz-Jeghers syndrome^[152].

Therapeutic and prognostic relevance

A clinical study in a pancreatic cancer patient with Peutz-Jeghers syndrome whose tumor harboring an STK11 D194E mutation coupled with the loss of heterozygosity of the other STK11 allele displayed partial response to the everolimus treatment^[153]. In another clinical case study, an adrenocorticotrophic pituitary carcinoma patient whose tumor bearing an STK11 inactivating mutation responded to a combination of everolimus and radiotherapy^[154].

Preclinical data suggested that lung cancer cell lines with STK11 inactivating mutations may confer increased sensitivity to the MEK-1 and MEK-2 inhibitor, trametinib^[155].

Inactivating mutations of STK11 was shown to be associated with resistance to immune checkpoint blockade in KRAS-mutant lung adenocarcinoma (LUAC) and NSCLC (DOI: 10.1200/JCO.2017.35.15_suppl.9016)^{[156][157][158]}. It was proposed that loss of STK11 negatively impacts the number and function of tumor-infiltrating T cells (TILs) and PD-L1 expression on tumor cells and therefore results in an ineffective response to PD-1-targeting antibodies^[159].

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^[160] 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^[161] NCT02102490	Breast cancer (Approved on 2017/09/28)
	HR-positive, HER2-negative Abemaciclib [ORR(%): 19.7 vs. 17.4]
MONARCH 2^[101] NCT02107703	Breast cancer (Approved on 2017/09/28)
	HR-positive, HER2-negative Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]

Alpelisib (PIQRAY)

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3K α . Gain-of-function mutations in the gene encoding the catalytic α -subunit of PI3K (PIK3CA) lead to activation of PI3K α and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models. Alpelisib is developed and marketed by Novartis under the trade name PIQRAY.

FDA Approval Summary of Alpelisib (PIQRAY)

SOLAR-1^[22] NCT02437318	Hr-positive, her2-negative breast cancer (Approved on 2019/05/24)
	PIK3CA mutation Alpelisib plus fulvestrant vs. Placebo plus fulvestrant [PFS(M): 11 vs. 5.7]

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 ^[162] NCT01524783	Lung or gastrointestinal neuroendocrine tumor (Approved on 2016/02/26)
	- Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2 ^[163] NCT00863655	Breast cancer (Approved on 2012/07/20) ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
RADIANT-3 ^[164] NCT00510068	Pancreatic neuroendocrine tumor (Approved on 2011/05/05)
	- Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1 ^[165] NCT00789828	Subependymal giant cell astrocytoma (Approved on 2010/10/29)
	- Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1 ^[166] 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 ^[84] 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^[83] 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^[83] 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]

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^[79] 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^[73] 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^[78] 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^[72] 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^[77] 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^[167] 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^[168] 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^[169] 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^[170] NCT01740427	Breast cancer (Approved on 2017/03/31)
	ER+, HER2- Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3^[171] 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^[100] 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^[80] 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^[172] NCT01482715, NCT01891344	Ovarian cancer (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation
	Rucaparib [ORR(%): 54.0]

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)

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

Trametinib (MEKINIST)

Trametinib is an anti-cancer inhibitor which targets MEK1 and MEK2. Trametinib is developed and marketed by GlaxoSmithKline (GSK) under the trade name MEKINIST.

FDA Approval Summary of Trametinib (MEKINIST)

BRF117019 ^[174] NCT02034110	Anaplastic thyroid cancer (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928 ^[175] NCT01336634	Non-small cell lung cancer (Approved on 2017/06/22)
	BRAF V600E
	Trametinib + dabrafenib vs. Dabrafenib [ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9]
COMBI-d ^[176] NCT01584648	Melanoma (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC ^[177] NCT01245062	Melanoma (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

d=day; w=week; m=month

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.

DETAILED TEST RESULTS

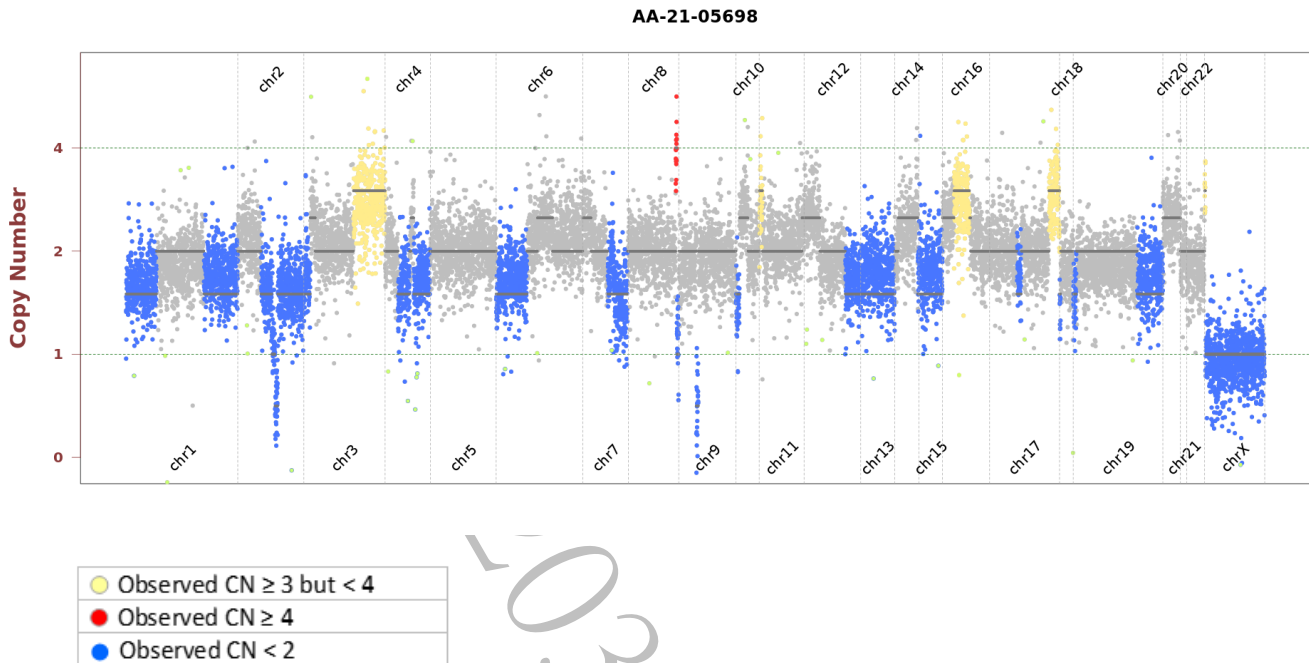
SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Chr	Exon	Accession Number	cDNA Change	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
ATR	3	3	NM_001184	c.190A>G	T64A	1843	42.0%	-
BAP1	3	13	NM_004656	c.1401del	S468fs	839	67.7%	-
CASP8	2	9	NM_033355	c.982G>A	G328R	965	80.7%	COSM3576299
CYLD	16	4	NM_015247	c.121G>A	V41I	1436	14.2%	-
DPYD	1	20	NM_000110	c.2528T>C	I843T	1646	82.6%	-
FANCF	11	1	NM_022725	c.1063C>T	R355C	1774	58.0%	-
FANCG	9	7	NM_004629	c.881G>A	G294E	1644	74.1%	-
MSH2	2	2	NM_000251	c.279_281del	L94del	395	47.1%	-
NTRK1	1	7	NM_002529	c.824A>C	E275A	870	83.2%	-
PDGFRB	5	7	NM_002609	c.1108C>T	R370C	1682	42.3%	COSM6743163
PIK3CA	3	10	NM_006218	c.1633G>A	E545K	2014	34.4%	COSM763
RAD51B	14	2	NM_133509	c.8G>A	S3N	628	37.4%	-
REL	2	11	NM_002908	c.1804A>G	S602G	935	60.6%	-
ROS1	6	10	NM_002944	c.1013A>G	Y338C	1799	61.3%	-
SETD2	3	3	NM_014159	c.3809C>T	T1270M	1117	16.9%	COSM4442501
SYNE1	6	105	NM_182961	c.19483G>A	V6495M	1325	56.7%	-
SYNE1	6	-	NM_182961	c.10443+2T>C	Splice donor	1725	24.8%	-
TP53	17	7	NM_000546	c.680_681del	S227*	1433	34.8%	COSM45211
TP53	17	7	NM_000546	c.743G>A	R248Q	1409	25.3%	COSM10662

Mutations with clinical relevance are highlighted in red.

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.



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
<i>BRAF</i>	V600X	Not detected
<i>EGFR</i>	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
<i>IDH2</i>	R140Q, R172G/K/M/S	Not detected
<i>KIT</i>	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
<i>KRAS</i>	A146T/V/P, G12X, G13X, Q61X	Not detected
<i>MET</i>	D1028H/N/Y	Not detected
<i>NRAS</i>	G12X, G13X, Q61X	Not detected
<i>PDGFRA</i>	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_L545insAVLVLLVIVISLI, V561A/D, V561_I562insER, V658A, W559_R560del, Y375_K455del, Y555C, Y849C/S	Not detected
<i>PIK3CA</i>	C420R, E542K/V, E545A/D/G/K, H1047X, Q546E/R	E545K

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
<i>CDK4</i>	2
<i>EGFR</i>	2
<i>ERBB2</i>	2
<i>MET</i>	2

Copy number ≥ 8 is considered amplification

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

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

Gene	Copy Number Detected
<i>FGFR1</i>	2
<i>MDM2</i>	1
<i>MDM4</i>	2

 Copy number ≥ 8 is considered amplification

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 $\geq 5\%$ and actionable variants with allele frequency $\geq 2\%$ were retained.

This test provides uniform coverage of the targeted regions, enabling target base coverage at $100x \geq 85\%$ with a mean coverage $\geq 500x$.

Variants reported in Genome Aggregation database 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 QIAasympyphony 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

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。

行動基因臨床分子醫學實驗室 台北市內湖區新湖二路 345 號 3F

Email: service@actgenomics.com T: +886-2-2795-3660 | F: +886-2-2795-5016

AG4-QP4001-02(05)

- AG3-QP16-35 SOP of Variant Annotation
- AG3-QP16-96 SOP of Manual Inspection for SNV/Indel 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

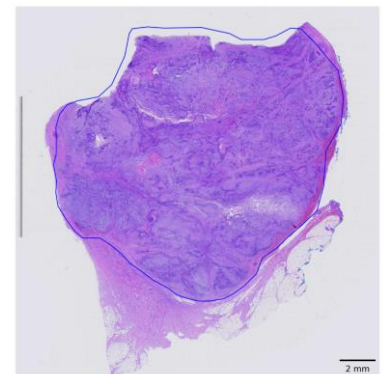
This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject 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.: S11027641P
- Collection site: Soft tissue
- Examined by: Dr. Pei-Yi Chu
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 25%
The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 40%
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: Performed on the highlighted region



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

SPECIMEN PHOTO(S)



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

RUN QC

- Panel: ACTOnco®+
- Mean Depth: 1052x
- Target Base Coverage at 100x: 95%

202111207163427

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	SOC1*	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	IKKB	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.

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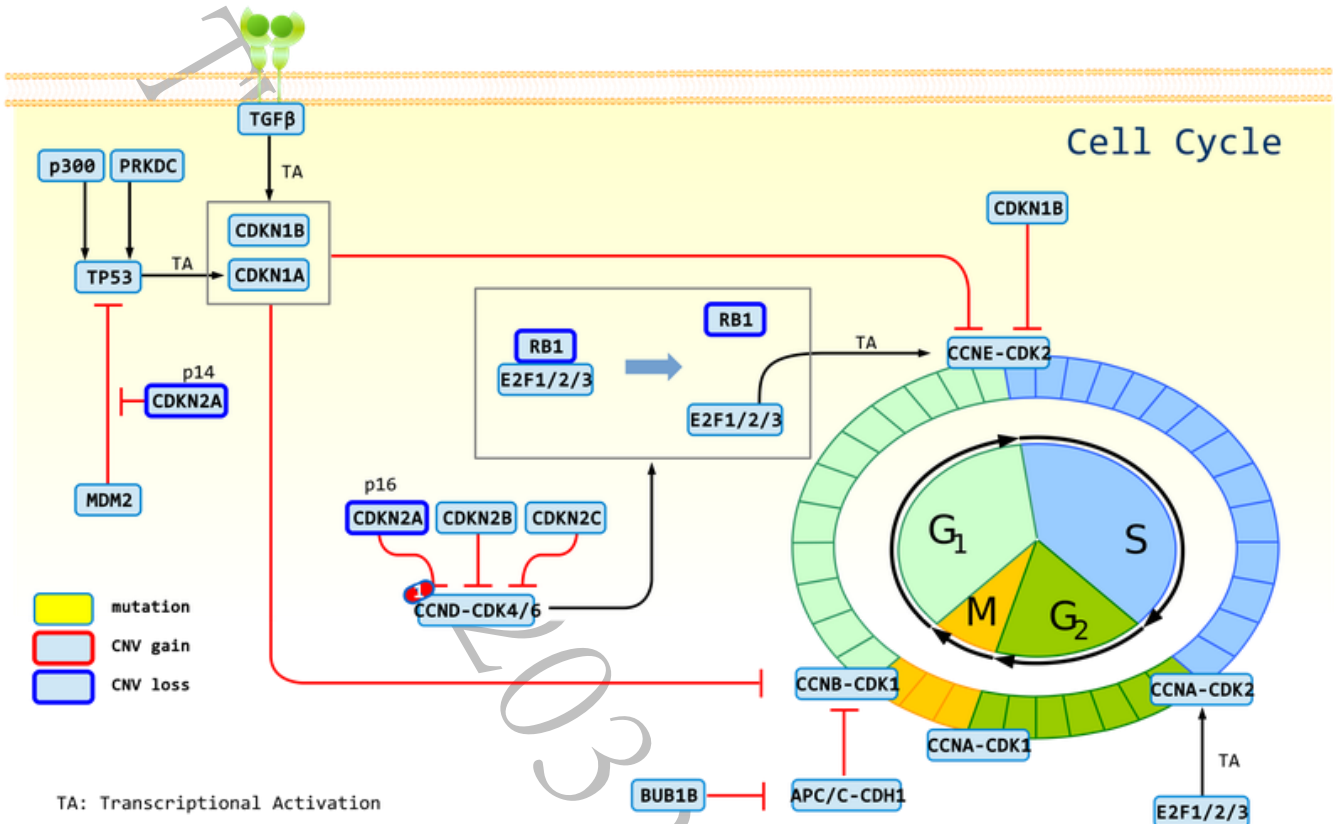
證據等級

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。

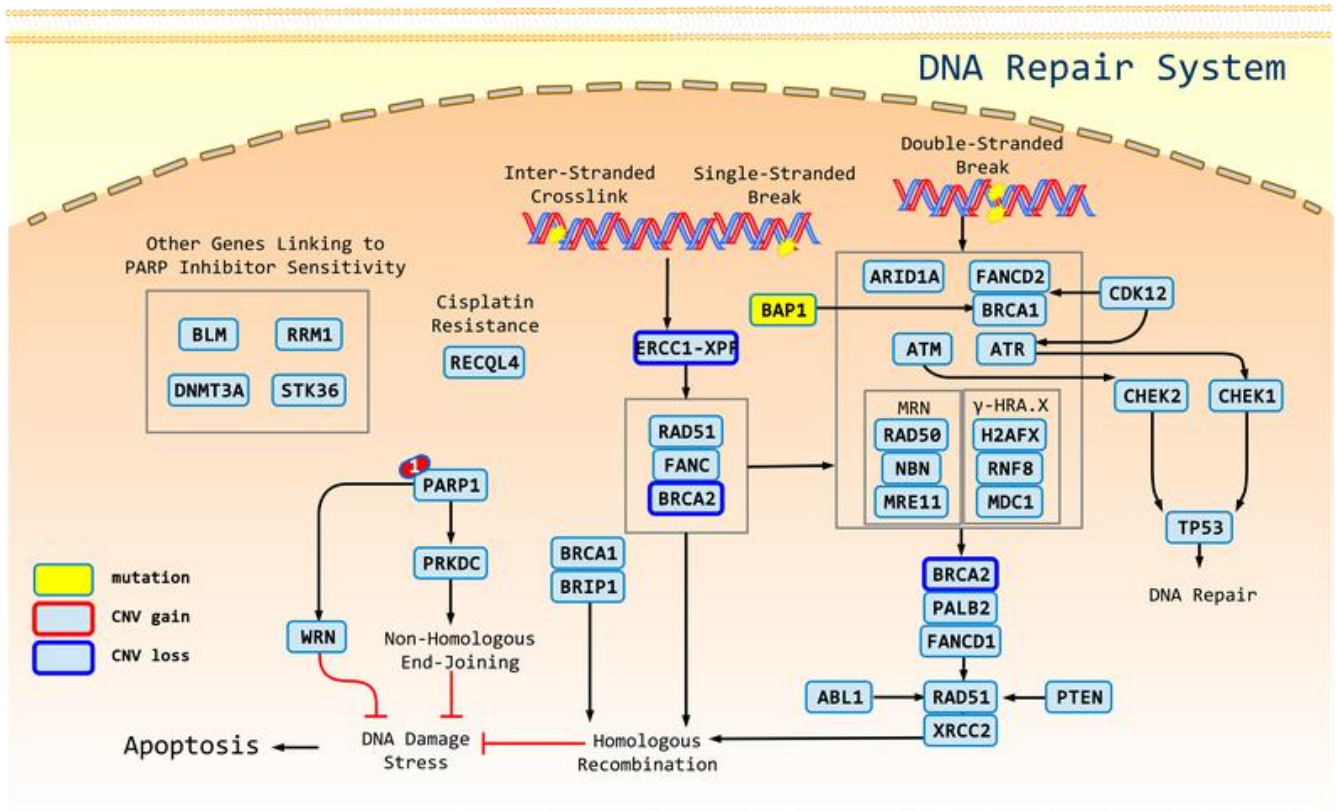
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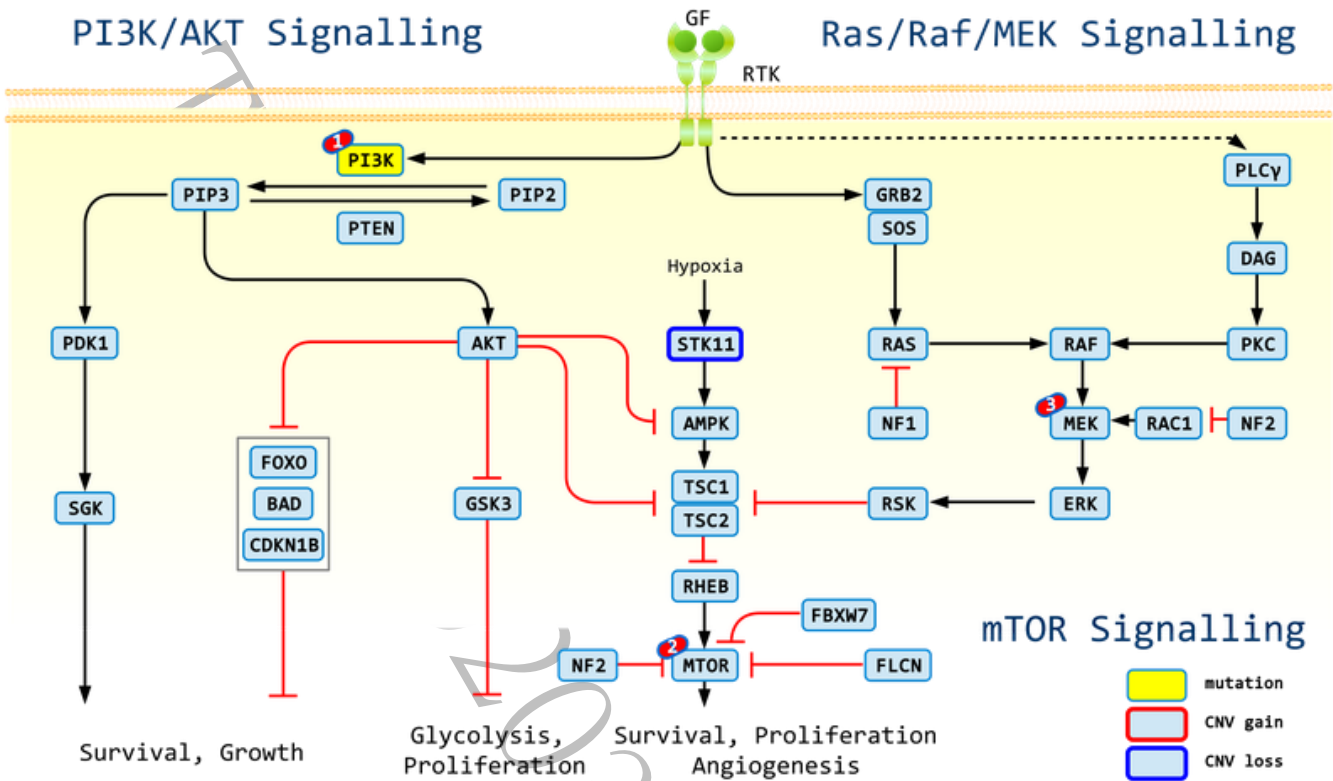
SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Abemaciclib, Palbociclib, Ribociclib



1: Olaparib, Niraparib, Rucaparib



1: Alpelisib; 2: Everolimus, Temsirolimus; 3: Trametinib

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ACTFusion™ Report

PATIENT		
Name: 陳添壽		Patient ID: 47526567
Date of Birth: Feb 18, 1966		Gender: Male
Diagnosis: Squamous cell carcinoma		
ORDERING PHYSICIAN		
Name: 陳三奇醫師		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: S11027641P		Date received: Nov 24, 2021
Lab ID: AA-21-05698		D/ID: NA
Collection site: Soft tissue		
Type: FFPE tissue		

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

THERAPEUTIC IMPLICATION

Not Applicable.

VARIANT INTERPRETATION

Not Applicable.

US FDA-APPROVED DRUG(S)

Not Applicable.

ACTFusion™ Report

ONGOING CLINICAL TRIALS

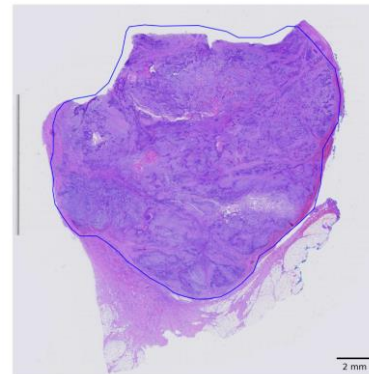
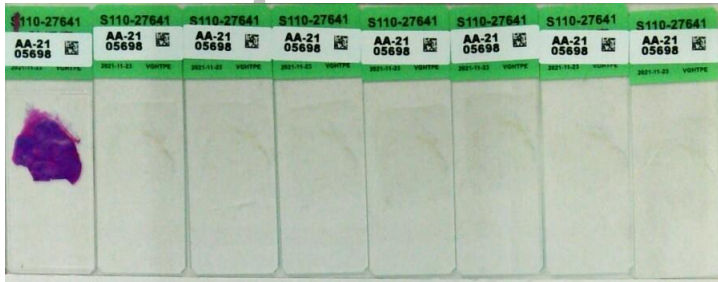
Trials were searched by applying filters: study status, patient's diagnosis, intervention, location and/or biomarker(s). Please visit <https://clinicaltrials.gov> to search and view for a complete list of open available and updated matched trials.

No trial has been found.

ACTFusion™ Report

TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Sep 2021
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11027641P
- Collection site: Soft tissue
- Examined by: Dr. Pei-Yi Chu
 1. The percentage of viable tumor cells in total cells in the whole slide (%): 25%
 2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 40%
 3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
 4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
 5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTFusion™
- Total reads: 890589
- Average unique RNA Start Sites per control GSP2: 169

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

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)

DATABASES 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

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ACTFusion™ Report

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.