ACTOnco® + Report

REPORT SUMMARY

PATIENT AND SAMPLE INFORMATION 2
VARIANT(S) WITH CLINICAL RELEVANCE 2
THERAPEUTIC IMPLICATIONS 3

REPORT DETAILS

VARIANT INTERPRETATION 5
US FDA-APPROVED DRUG(S) 14
ONGOING CLINICAL TRIALS 22
DETAILED TEST RESULTS 23
HOTSPOT GENOTYPES 25
TEST DETAILS 27
ACTOnco®+ GENE LIST 31
DISCLAIMER 32

APPENDIX

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS 34
REFERENCES 38

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_ONC
Date Reported: Nov 09, 2021

PATIENT AND SAMPLE INFORMATION

PATIENT	SPECIMEN	ORDERING PHYSICIAN
Name: 賴鼎曜	Type: FFPE tissue	Name: 陳三奇醫師
Gender: Male	Date received: Oct 27, 2021	Facility: 臺北榮總
Date of Birth: Jan 20, 1967	Collection site: Bone	Tel: 886-228712121
Patient ID: 47708009	Specimen ID: S11030849	Address: 臺北市北投區石牌路二段 201 號
Diagnosis: Cholangiocarcinoma	Lab ID: AA-21-04817	
	D/ID: NA	

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
PBRM1	Splice acceptor	782	29.3%	-
TP53	P47fs	381	37.0%	COSM13161

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 **50%** tumor purity.

Amplification (Copy number ≥ 8)

Chr	Gene	Copy Number
ND	ND	ND

Homozygous deletion (Copy number=0)

Chr	Gene
ND	ND

ND, Not Detected

Heterozygous deletion (Copy number=1)

Chr	Gene
chr1	*ARID1A*
chr3	*BAP1, PBRM1*
chr4	*FBXW7*
chr9	*CDKN2A, PTCH1*
chr10	*PTEN*
chr13	*BRCA2, RB1*
chr17	*FLCN*
chr19	*STK11*

TUMOR MUTATIONAL BURDEN (TMB)

< 1 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:
醫檢師黃靖婷 博士
Ching-Ting Huang Ph.D.
檢字第 016511 號

CT Huang

Sign Off
解剖病理專科醫師王業翰
Yeh-Han Wang M.D.
病解字第 000545 號

Yehn

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_ONC
Date Reported: Nov 09, 2021

THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3B		
ARID1A Heterozygous deletion	Niraparib	sensitive
PTCH1 Heterozygous deletion	Sonidegib, Vismodegib	sensitive
CDKN2A Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	sensitive
PTEN Heterozygous deletion	Everolimus, Temsirolimus, Olaparib	sensitive
Level 4		
FLCN Heterozygous deletion	Everolimus	sensitive
STK11 Heterozygous deletion	Everolimus, Trametinib	sensitive
FBXW7 Heterozygous deletion	Everolimus, Temsirolimus	sensitive
BAP1 Heterozygous deletion	Olaparib	sensitive
BRCA2 Heterozygous deletion	Olaparib, Rucaparib	sensitive
ARID1A Heterozygous deletion	Olaparib, Rucaparib, Talazoparib, Dasatinib	sensitive
FBXW7 Heterozygous deletion	Gefitinib, Regorafenib	resistant
RB1 Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	resistant
PTEN Heterozygous deletion	Erlotinib, Gefitinib, Cetuximab, Panitumumab, Trastuzumab	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: **Yes**	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.

The patient's tumor harbored biallelic PBRM1 loss. Biallelic loss of PBRM1 has been shown be correlated with clinical benefit in clear cell carcinoma (ccRCC)[1], melanoma, lung cancer, bladder cancer, and head and neck squamous carcinoma (HNSCC) patients[2] treated with immune checkpoint inhibitors.

CHEMOTHERAPIES

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

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.

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_ONC
Date Reported: Nov 09, 2021

VARIANT INTERPRETATION

PBRM1 Splice acceptor, Heterozygous deletion

Biological Impact

The PBRM1 gene encodes the protein BAF180 tumor suppressor, which is a component of the nucleosome-remodeling complex switching defective/sucrose non-fermenting (SWI/SNF)[3]. Loss of PBRM1 activity is associated with chromosomal instability[4]. PBRM1, BAP1 and SETD2 are three frequently altered tumor suppressor genes on chromosome 3p in a region that is deleted in over 90% of clear cell renal cell carcinoma (ccRCC)[5][6].

PBRM1 c.2966-1G>T is a variant located at the splice acceptor region, which may result in the exon skipping. Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

Therapeutic and prognostic relevance

Biallelic loss of PBRM1 has been shown to correlate with clinical benefit in clear cell renal cell carcinoma (ccRCC)[1], melanoma, lung cancer, bladder cancer, and head and neck squamous carcinoma (HNSCC) patients[2] treated with immune checkpoint inhibitors.

Decreased expression of PBRM1 has been shown to predict unfavorable clinical outcome in patients with ccRCC[7].

TP53 P47fs

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[8]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[9].

P47fs mutation results in a change in the amino acid sequence beginning at 47, likely to cause premature truncation of the functional p53 protein (UniProtKB). This mutation is predicted to lead to a loss of p53 protein function, despite not being 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)[10].

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[11]. 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[12].

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[13][14][15]. 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)[16]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[17][18]. 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[19].

***ARID1A* Heterozygous deletion**

Biological Impact

The AT-rich interactive domain 1A (ARID1A) gene encodes the BAF250A protein, a component of the SWI/SNF chromatin remodeling complex that plays a role in various cellular functions, including DNA repair, DNA synthesis, and transcription[20][21]. Haploinsufficiency of ARID1A is associated with tumor formation in some cancers[22]. Inactivation of ARID1A is commonly observed in ovarian, endometrial, uterine, and, gastric cancers[23][24][25][26][27].

Therapeutic and prognostic relevance

ARID1A is the most frequently mutated genes in ovarian clear cell carcinoma and several synthetic lethality hypothesis-based therapeutic targets in ARID1A mutated cancer are in development. For examples, 1) EZH2 inhibitor[28][29]; 2) AKT-inhibitors MK-2206 and perifosine, as well as PI3K-inhibitor buparlisib[30]; 3) multiple kinase inhibitor, dasatinib[31].

Some preclinical evidences suggested that reduced ARID1A expression confers resistance to several HER2/PI3K/mTOR signaling cascade inhibitors such as AZD8055 and trastuzumab, through activation of annexin A1 expression[32]. Loss or decreased expression of ARID1A has been reported to associate with resistance to platinum-based chemotherapies, shorter overall survival and lower complete response rate in ovarian cancer patients[33][34].

Low expression of ARID1A is a significant and independent prognostic factor for poor disease-free and overall survival in breast cancer patients[35][36]. Besides, loss of ARID1A expression was more frequently seen in mismatch repair (MMR)-deficient colorectal cancers, predominantly in tumor with MLH1 promoter hypermethylation[37]. Positive ARID1A expression could independently predict worse overall survival in stage IV CRC patients compared with negative ARID1A expression[38].

ARID1A mutation has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in metastatic biliary tract cancer (NCT04042831), and niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), or any malignancy, except prostate cancer (NCT03207347).

The preclinical study discovered that ARID1A deficiency sensitized some tumors to PARP inhibitor drugs, such as olaparib, rucaparib, talazoparib, and veliparib, which block DNA damage repair pathways[39].

BAP1 Heterozygous deletion

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[40][41][42]. BAP1 acts as a tumor suppressor by forming a complex with BRCA1[43]. BAP1 is a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is related to renal cell carcinoma (RCC)[44]. 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[41][45][46][47][48][49][50].

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)[47] and mesothelioma cell lines[51]. However, no difference in sensitivity to the PARP inhibitor MK4827 was observed between BAP1-mutant and wild-type mesothelioma cell[41]. BAP1 deficiency was also linked to a high tumor grade and was correlated with metastasis development in uveal melanoma[45]. 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).

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[52]. 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[53]. 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[54]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[55].

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[56]; (2) in combination with bevacizumab as first-line maintenance treatment for patients with homologous recombination deficiency (HRD)-positive status[57]; (3) maintenance treatment for patients with germline BRCA-mutated recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy[58][59]; (4) treatment for patients with germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy[60]. 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[61] and germline BRCA-mutated metastatic pancreatic cancer[62]. 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[63].

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[64] and patients with BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more chemotherapies[65]. 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[66][67] and patients who have been treated with three or more prior lines of chemotherapy and associated with HRD positive status[68]. In addition, talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer[69].

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[70][71] whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53[72]. 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[73]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[74][75].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[76][77]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[78][79][80]. 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[81][82][83]. 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[77][84][85].

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[79]. 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[86].

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[87].

***FBXW7* Heterozygous deletion**

Biological Impact

The F-box/WD repeat-containing protein 7 (FBXW7) gene encodes a protein that belongs to the SCF (SKP1-CUL1-F-box protein) E3 ligase complex. FBXW7 is recognized as a tumor suppressor which is involved in the negative regulation of oncogenes such as c-Myc[88][89], c-Jun[90], cyclin E[91], Notch family members[92][93], Aurora-A[94], mTOR[95], KLF5[96], and MCL-1[97]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation[98]. FBXW7 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[96][97][99].

Therapeutic and prognostic relevance

Clinical efficacy of mTOR inhibitors was seen in patients harboring aberrations in the FBXW7 gene (one patient with refractory fibrolamellar hepatocellular carcinoma, and one patient with lung adenocarcinoma)[100][101]. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor[95].

Preclinical studies suggested that mutations or loss of FBXW7 were associated with regorafenib and oxaliplatin resistance in CRC cell lines[102][103] and gefitinib resistance in lung cancer cells[104][105].

Retrospective studies have indicated that a relatively low expression level of FBXW7 is an independent prognostic marker of poor survival for patients with hepatocellular carcinoma, lung adenocarcinoma and squamous cell carcinoma[106][104].

FLCN Heterozygous deletion

Biological Impact

The FLCN gene encodes the tumor suppressor, Folliculin, a GTPase activating protein (GAP) for RagC/D GTPase proteins involved in amino acid sensing and signaling to mTORC1[107]. FLCN 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[108][109]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[110][111]. Germline mutation of the FLCN gene causes the Birt-Hogg-Dubé syndrome, a rare disorder that is characterized by benign hamartomatous skin lesions and an increased risk of pneumothorax and renal tumors[112].

Therapeutic and prognostic relevance

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTC) patients who had PI3K/mTOR/AKT alterations, including TSC2, FLCN or NF1, showed impressive progression-free survival (PFS) of 15.2 months after receiving everolimus[113]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[114].

PTCH1 Heterozygous deletion

Biological Impact

The PTCH1 (protein patched homolog 1) gene encodes a multi-pass transmembrane receptor for sonic hedgehog (shh), a tumor suppressor that acts to repress shh signaling in the absence of ligand[115]. Inactivation of PTCH1 results in hedgehog ligand-independent activation of SMO, causing a downstream activation of the pathway and lead to the neoplastic growth[116][117]. Recurrent PTCH1 mutations have been reported in sporadic basal cell carcinoma (BCCs) and medulloblastoma[118][119][120][121]. Germline PTCH1 mutations are associated with the nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome), predisposing patients to basal cell carcinoma and medulloblastoma[119]. PTCH1 is a haploinsufficient tumor suppressor gene with one copy loss may be sufficient to promote tumor development in mice[116][122].

Therapeutic and prognostic relevance

Vismodegib is a small molecule inhibitor of SMO approved by the FDA for the treatment of patients with basal cell carcinoma. A heavily-pretreated patient with metastatic medulloblastoma harboring loss of heterozygosity and somatic mutation of PTCH1, showed rapid regression of the tumor after treated with vismodegib[123]. Furthermore,

a phase II study demonstrated that vismodegib treatment results in extended progression-free survival (PFS) in patients with loss-of-heterozygosity, SHH-driven medulloblastoma[124][125]. In a phase II trial (MyPathway), 3 advanced solid tumors patients harboring PTCH1 loss-of-function mutations had partial responses to vismodegib treatment[126].

PTEN Heterozygous deletion

Biological Impact

The phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene encodes a lipid/protein phosphatase that is important for the regulation of cell proliferation, survival, homologous recombination and maintenance of genomic integrity[127][128]. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway[129]. PTEN is a haploinsufficient tumor suppressor gene, in which having only one copy of the wild-type allele does not produce enough protein product to execute wild-type functions[9][130][131]. Germline loss-of-function PTEN mutations are found in approximately 80% of patients with Cowden syndrome, a disorder that is associated with high-penetrance breast and thyroid cancer[132][133][134]. Somatic mutations or monoallelic loss of PTEN is regularly observed in a significant fraction of human cancers, including sporadic breast cancer, colon cancer, endometrial cancer, prostate cancer, and glioblastoma[135][136][137][138][139].

Therapeutic and prognostic relevance

Somatic loss of PTEN results in aberrant activation of PI3K/AKT/mTOR signaling pathway and provides a mechanistic rationale for PI3K pathway inhibitors treatment[140][141]. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes[142][143][144][145][146][147]. Moreover, early clinical data also indicated that PTEN loss was associated with improved response and longer PFS in patients with advanced breast cancer[148], advanced pancreatic neuroendocrine tumors[149] and metastatic castration-resistant prostate cancer[150] treated with mTORC1 inhibitor, everolimus.

Several groups found that PTEN loss was generally associated with poor response to trastuzumab therapy, whether this agent was administered in the neoadjuvant, adjuvant, or metastatic settings[151][152][153][154][155].

Loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab[156][157][158][159][160][161]. However, encouraging anti-tumor activity of the combination of an EGFR antibody and a mTORC1 inhibitor (everolimus or temsirolimus) have been reported in early-phase clinical studies (J Clin Oncol. 2011;29 (suppl): abstr 3587; J Clin Oncol. 2013;31 (suppl): abstr 608). Ongoing phase I/II studies testing combinations of EGFR antibodies and PI3K/AKT/mTOR pathway inhibitors (e.g., NCT01816984, NCT01252628, NCT01719380) will provide larger numbers of patients to assess the role of PTEN status in therapeutic response.

Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib[162][163]. Inhibition of the PI3K/AKT/mTOR signal pathway has been shown to be an effective strategy to radiosensitize NSCLC cells harboring the EGFR activating mutation that acquires resistance to both TKIs due to PTEN loss or inactivation mutations[164].

Loss or biallelic inactivation of PTEN is associated with resistance to anti-PD-1 checkpoint blockade therapies, including pembrolizumab and nivolumab in melanoma and leiomyosarcoma patients[165][166][2].

PTEN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in metastatic biliary tract cancer (NCT04042831); talazoparib efficacy in HER2-negative breast cancer (NCT02401347), and niraparib efficacy in breast cancer (NCT04508803) or any malignancy (except prostate) cancer (NCT03207347). Clinical data also suggested that PTEN deficient cancers may be sensitive to olaparib[167].

***RB1* Heterozygous deletion**

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[168]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[169]. 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[170][171][172]. 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[173].

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[174]. 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[175].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[176][177].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[178]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[179].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[180][181]. 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[177][182].

***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[183][184]. STK11 is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[185][186]. In the mouse model, loss of STK11 promotes aggressive endometrial and squamous cell carcinomas[187][188]. Mutations in STK11 have been found in lung, breast, cervical, testicular, and liver cancers, as well as malignant melanoma, pancreatic and biliary carcinoma[189]. Germline mutations in STK11 are found in 30-70% of Peutz-Jeghers syndrome[190].

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[191]. In another clinical case study, an adrenocorticotropic pituitary carcinoma patient whose tumor bearing an STK11 inactivating mutation responded to a combination of everolimus and radiotherapy[192].

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[193].

Inactivating mutations of STK11 was shown to be associated with resistance to immune checkpoint blockade in KRAS-mutant lung adenocarcinoma (LUAC) (Journal of Clinical Oncology, 2017. 35(15_suppl): p. 9016-9016)[194][195] and NSCLC[196]. 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[197].

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[198] 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[199] NCT02102490	**Breast cancer** (Approved on 2017/09/28) **HR-positive, HER2-negative** Abemaciclib [ORR(%): 19.7 vs. 17.4]
MONARCH 2[85] NCT02107703	**Breast cancer** (Approved on 2017/09/28) **HR-positive, HER2-negative** Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]

Dasatinib (SPRYCEL)

Dasatinib is an oral Bcr-Abl tyrosine kinase inhibitor (inhibits the "Philadelphia chromosome") and Src family tyrosine kinase inhibitor. Dasatinib is produced by Bristol-Myers Squibb and sold under the trade name SPRYCEL.

FDA Approval Summary of Dasatinib (SPRYCEL)

DASISION[200] NCT00481247	**Chronic myeloid leukemia** (Approved on 2010/10/28) - Dasatinib vs. Imatinib [ORR(%): 76.8 vs. 66.2]
[201] NCT00123474	**Chronic myeloid leukemia** (Approved on 2007/11/08) - Dasatinib [ORR(%): 63.0]

[202] NCT00123487	**Acute lymphocytic leukemia** (Approved on 2006/06/28)
	-
	Dasatinib [ORR(%): 38.0]

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[203] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[204] NCT00863655	**Breast cancer** (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
RADIANT-3[149] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[205] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[206] 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[68] 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[67] 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[67] 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[63] 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[57] 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[62] 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[56] 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[61] 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[207] 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[208] 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[209] 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[210] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+, HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[211] 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[84] 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[64] 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[212] NCT01482715, NCT01891344	**Ovarian cancer** (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation
	Rucaparib [ORR(%): 54.0]

Sonidegib (ODOMZO)

Sonidegib is a Hedgehog signaling pathway inhibitor by blocking its key component, smoothened (smo). Sonidegib is developed and marketed by Novartis under the trade name ODOMZO.

FDA Approval Summary of Sonidegib (ODOMZO)

BOLT[213] NCT01327053	**Basal cell carcinoma** (Approved on 2015/07/24)
	-
	Sonidegib [ORR(%): 58.0]

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[69] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

Temsirolimus (TORISEL)

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

FDA Approval Summary of Temsirolimus (TORISEL)

[214] 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[215] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[216] 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[217] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[218] NCT01245062	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_ONC
Date Reported: Nov 09, 2021

Vismodegib (ERIVEDGE)

Vismodegib is a cyclopamine-competitive antagonist and acts as a first-in-class Hedgehog signaling pathway inhibitor by blocking its key component smoothened (smo). Vismodegib is developed by Genentech and marketed by Roche under the trade name ERIVEDGE.

FDA Approval Summary of Vismodegib (ERIVEDGE)

ERIVANCE BCC[219] NCT00833417	**Basal cell carcinoma** (Approved on 2012/01/30)
	-
	Vismodegib [ORR (mBCC)(%): 30.3, ORR (laBCC)(%): 42.9]

d=day; w=week; m=month

賴鼎曜

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.

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_ONC
Date Reported: Nov 09, 2021

DETAILED TEST RESULTS

SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Chr	Exon	Accession Number	cDNA Change	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
FGFR1	8	3	NM_023110	c.304G>A	V102I	494	68.8%	-
MUC16	19	5	NM_024690	c.35757C>A	N11919K	664	62.2%	COSM7813200
MUC16	19	3	NM_024690	c.18964_18965delinsTT	D6322F	916	32.3%	-
MUC6	11	-	NM_005961	c.1453+4C>T	Splice region	197	47.7%	COSM2108620
NFE2L2	2	5	NM_006164	c.779C>G	T260R	1185	50.5%	-
PBRM1	**3**	**-**	**NM_018313**	**c.2966-1G>T**	**Splice acceptor**	**782**	**29.3%**	**-**
TAP1	6	5	NM_000593	c.1313G>A	R438Q	854	52.0%	-
TP53	**17**	**4**	**NM_000546**	**c.140del**	**P47fs**	**381**	**37.0%**	**COSM13161**

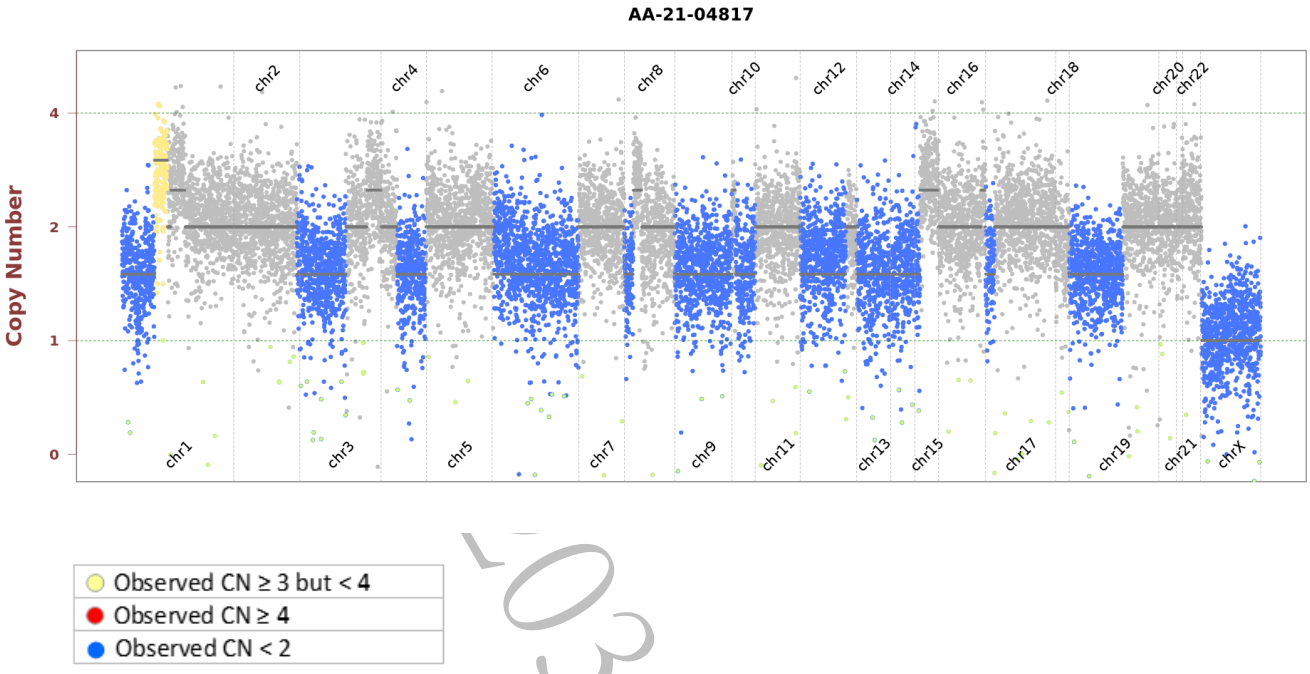
Mutations with clinical relevance are highlighted in red.

賴鼎曜

Project ID: C21-M001-01050
Report No.: AA-21-04817_ONC
Date Reported: Nov 09, 2021

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
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	1
EGFR	2
ERBB2	2
MET	2

Copy number ≥ 8 is considered amplification

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_ONC
Date Reported: Nov 09, 2021

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	1
MDM4	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 ≥ 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

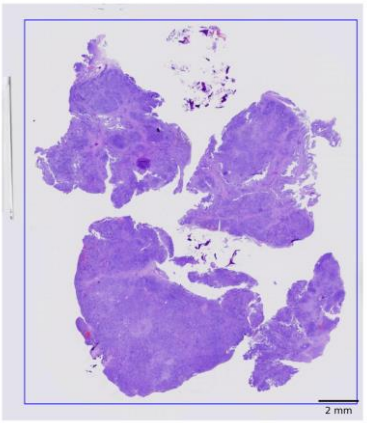
This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject 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.: S11030849
- Collection site: Bone
- Examined by: Dr. Yeh-Han Wang
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 50%
  The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 50%
  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.

賴鼎曜

Project ID: C21-M001-01050
Report No.: AA-21-04817_ONC
Date Reported: Nov 09, 2021

SPECIMEN PHOTO(S)

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

RUN QC

- Panel: ACTOnco®+
- Mean Depth: 844x
- Target Base Coverage at 100x: 94%

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_ONC
Date Reported: Nov 09, 2021

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.

DISCLAIMER

Legal Statement

This test was developed by ACT Genomics and its performing characteristics were determined by ACT Genomics. This test result is to be used for clinical consultative purposes only and is not intended as a substitute for a clinical guidance of your doctor or another qualified medical practitioner. It should not be regarded as investigational or used for research.

The detection of genomic alterations does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; the detection of no genomic alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Treatment Decisions are the Responsibility of the Physician

Decisions on clinical care and treatment should be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, including physical examinations, information from other diagnostics tests and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test, or the information contained in this report.

In terms of consulting a different treating physician, the patient must file an application and fulfill the listed criteria for ACT Genomics to provide the patient's report to the assigned physician. The report may not be copied or reproduced except in its totality.

Genetic Alterations and Drugs Not Presented in Ranked Order

In this report, neither any biomarker alteration nor any drug associated with a potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

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.

No Guarantee of Clinical Benefit

This report makes no promises or guarantees about the effectiveness of a particular drug or any treatment procedure in any disease or in any patient. This report also makes no promises or guarantees that a drug without an association of reportable genomic alteration will, in fact, provide no clinical benefit.

Liability

ACT Genomics is not affiliated with any medical facility or medical practitioner. We provide information for informational purposes only, therefore, ACT Genomics and their employees cannot be held responsible for any direct, indirect, special, incidental or consequential damages that may arise from the use of information provided in the report.

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。

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。

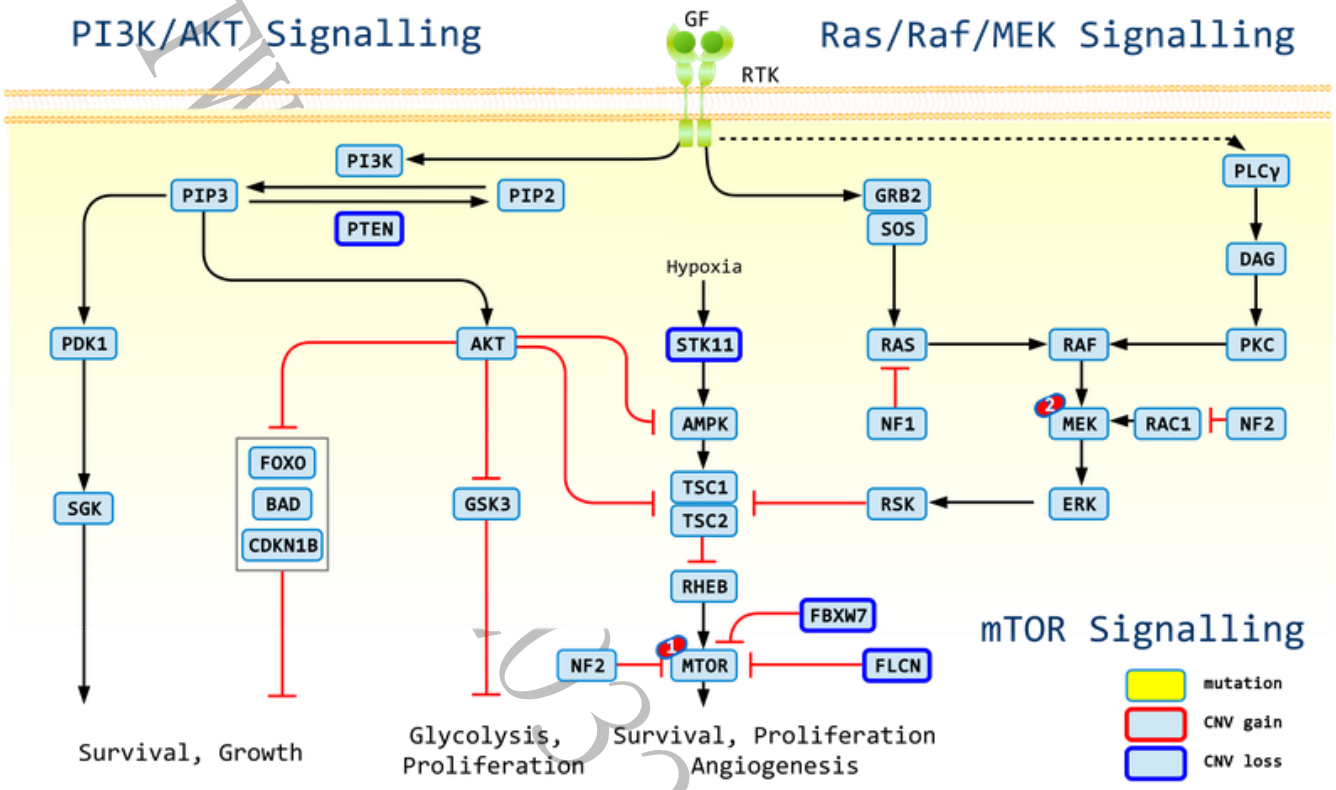
證據等級

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。

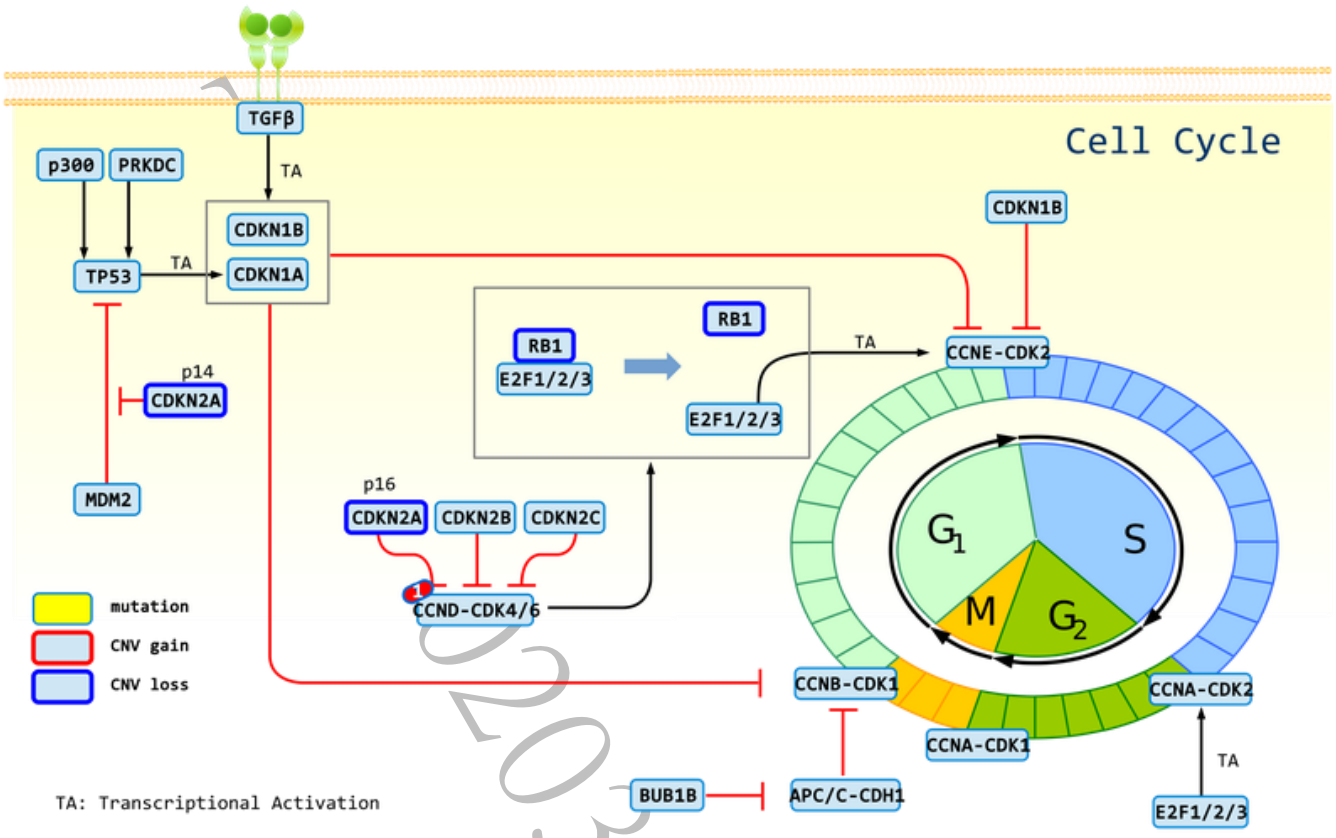
責任

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。

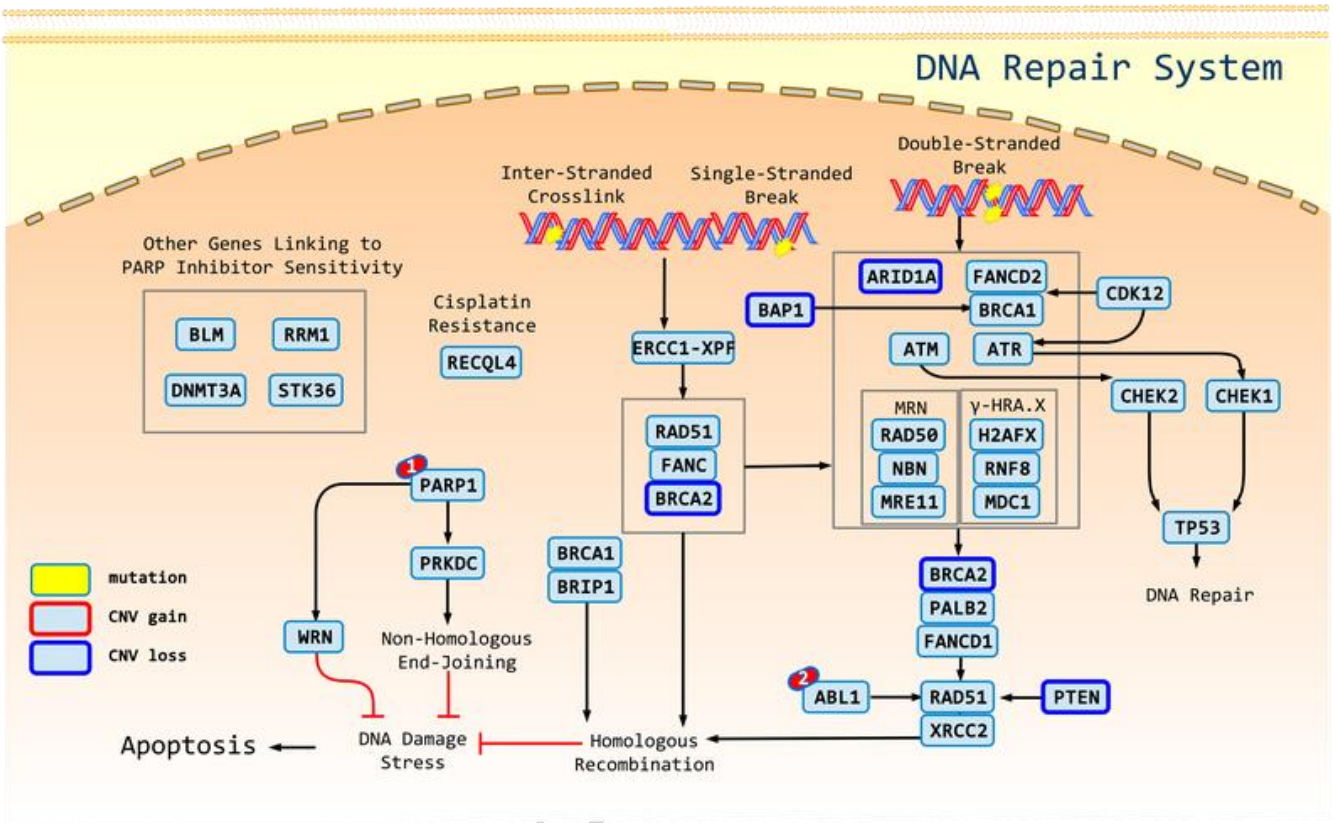
SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



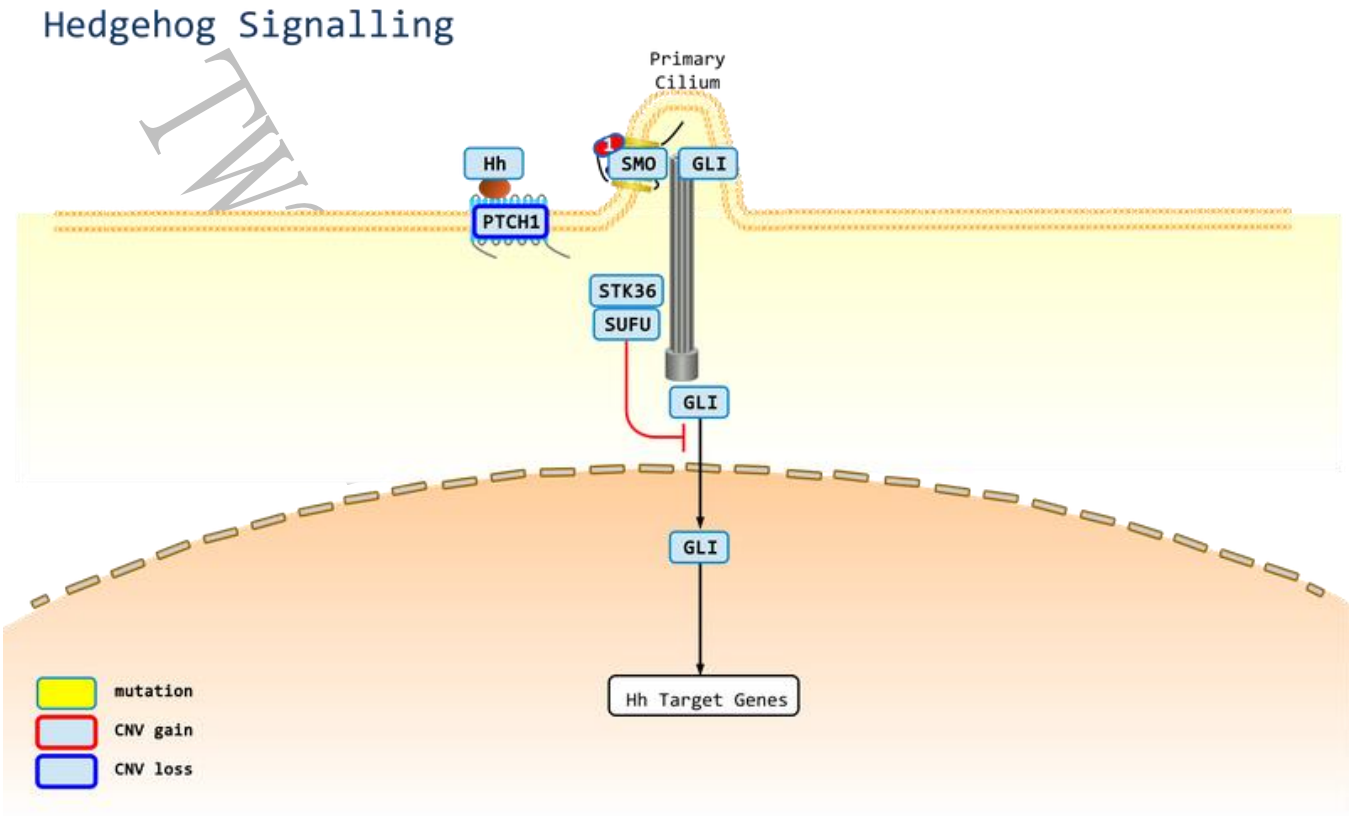
1: Everolimus, Temsirolimus; 2: Trametinib



1: Abemaciclib, Palbociclib, Ribociclib



1: Olaparib, Niraparib, Rucaparib, Talazoparib; 2: Dasatinib



1: Sonidegib, Vismodegib

REFERENCES

1. PMID: 29301960; 2018, Science;359(6377):801-806
Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma.

2. PMID: 30150660; 2018, Nat Genet;50(9):1271-1281
Genomic correlates of response to immune checkpoint blockade in microsatellite-stable solid tumors.

3. PMID: 19234488; 2009, Oncogene;28(14):1653-68
The SWI/SNF complex and cancer.

4. PMID: 24613357; 2014, Cell Rep;6(6):973-981
BAF180 promotes cohesion and prevents genome instability and aneuploidy.

5. PMID: 23867514; 2013, Cancer J;19(4):324-32
PBRM1 and BAP1 as novel targets for renal cell carcinoma.

6. PMID: 10897333; 2000, Mol Pathol;53(3):137-44
Role of chromosome 3p12-p21 tumour suppressor genes in clear cell renal cell carcinoma: analysis of VHL dependent and VHL independent pathways of tumorigenesis.

7. PMID: 26003625; 2015, Urol Oncol;33(8):340.e9-16
Decreased PBRM1 expression predicts unfavorable prognosis in patients with clear cell renal cell carcinoma.

8. PMID: 24739573; 2014, Nat Rev Cancer;14(5):359-70
Unravelling mechanisms of p53-mediated tumour suppression.

9. PMID: 21125671; 2011, J Pathol;223(2):137-46
Haplo-insufficiency: a driving force in cancer.

10. PMID: 27998224; 2016, J Clin Oncol;34(36):4354-4361
Phase II Study of WEE1 Inhibitor AZD1775 Plus Carboplatin in Patients With TP53-Mutated Ovarian Cancer Refractory or Resistant to First-Line Therapy Within 3 Months.

11. PMID: 26646755; 2016, Ann Oncol;27(3):539-43
TP53 mutational status is predictive of pazopanib response in advanced sarcomas.

12. PMID: 25669829; 2015, Ann Oncol;26(5):1012-8
Phase I study of pazopanib and vorinostat: a therapeutic approach for inhibiting mutant p53-mediated angiogenesis and facilitating mutant p53 degradation.

13. PMID: 27466356; 2016, Mol Cancer Ther;15(10):2475-2485
TP53 Alterations Correlate with Response to VEGF/VEGFR Inhibitors: Implications for Targeted Therapeutics.

14. PMID: 23670029; 2013, Oncotarget;4(5):705-14
P53 mutations in advanced cancers: clinical characteristics, outcomes, and correlation between progression-free survival and bevacizumab-containing therapy.

15. PMID: 17145525; 2006, Semin Oncol;33(5 Suppl 10):S8-14
Bevacizumab in combination with chemotherapy: first-line treatment of patients with metastatic colorectal cancer.

16. PMID: 21399868; 2011, Int J Oncol;38(5):1445-52
p53, HER2 and tumor cell apoptosis correlate with clinical outcome after neoadjuvant bevacizumab plus chemotherapy in breast cancer.

17. PMID: 20549698; 2011, Int J Cancer;128(8):1813-21
p53 status influences response to tamoxifen but not to fulvestrant in breast cancer cell lines.

18. PMID: 10786679; 2000, Cancer Res;60(8):2155-62
Complete sequencing of TP53 predicts poor response to systemic therapy of advanced breast cancer.

19. PMID: 25672981; 2015, Cancer Res;75(7):1187-90
VEGF-A Expression Correlates with TP53 Mutations in Non-Small Cell Lung Cancer: Implications for Antiangiogenesis Therapy.

20. PMID: 10757798; 2000, Mol Cell Biol;20(9):3137-46
The human SWI-SNF complex protein p270 is an ARID family member with non-sequence-specific DNA binding activity.

21. PMID: 25387058; 2015, Annu Rev Pathol;10():145-71
SWI/SNF chromatin remodeling and human malignancies.

22. PMID: 23208470; 2013, Cancer Discov;3(1):35-43
ARID1A mutations in cancer: another epigenetic tumor suppressor?

23. PMID: 20826764; 2010, Science;330(6001):228-31
Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma.

24. PMID: 20942669; 2010, N Engl J Med;363(16):1532-43
ARID1A mutations in endometriosis-associated ovarian carcinomas.

25. PMID: 21590771; 2011, J Pathol;224(3):328-33
Loss of BAF250a (ARID1A) is frequent in high-grade endometrial carcinomas.

26. PMID: 21412130; 2011, Am J Surg Pathol;35(5):625-32
Mutation and loss of expression of ARID1A in uterine low-grade endometrioid carcinoma.

27. PMID: 22037554; 2011, Nat Genet;43(12):1219-23
Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer.

28. PMID: 26125128; 2015, Expert Opin Ther Targets;19(11):1419-22
Potential therapeutic targets in ARID1A-mutated cancers.

29. PMID: 29093822; 2017, Gynecol Oncol Res Pract;4():17
EZH2 inhibition in ARID1A mutated clear cell and endometrioid ovarian and endometrioid endometrial cancers.

30. PMID: 24979463; 2014, Oncotarget;5(14):5295-303
Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition.

31. PMID: 27364904; 2016, Mol Cancer Ther;15(7):1472-84
Synthetic Lethal Targeting of ARID1A-Mutant Ovarian Clear Cell Tumors with Dasatinib.

32. PMID: 27172896; 2016, Clin Cancer Res;22(21):5238-5248
Loss of ARID1A Activates ANXA1, which Serves as a Predictive Biomarker for Trastuzumab Resistance.

33. PMID: 22101352; 2012, Mod Pathol;25(2):282-8
Loss of ARID1A expression is related to shorter progression-free survival and chemoresistance in ovarian clear cell carcinoma.

34. PMID: 24459582; 2014, J Gynecol Oncol;25(1):58-63
Decreased ARID1A expression is correlated with chemoresistance in epithelial ovarian cancer.

35. PMID: 26770240; 2015, J Breast Cancer;18(4):339-46
Loss of Tumor Suppressor ARID1A Protein Expression Correlates with Poor Prognosis in Patients with Primary Breast Cancer.

36. PMID: 21889920; 2012, Cancer Epidemiol;36(3):288-93
Frequent low expression of chromatin remodeling gene ARID1A in breast cancer and its clinical significance.

37. PMID: 25311944; 2014, Hum Pathol;45(12):2430-6
Immunohistochemical detection of ARID1A in colorectal carcinoma: loss of staining is associated with sporadic microsatellite unstable tumors with medullary histology and high TNM stage.

38. PMID: 25561809; 2014, World J Gastroenterol;20(48):18404-12
Clinicopathologic and prognostic relevance of ARID1A protein loss in colorectal cancer.

39. PMID: 26069190; 2015, Cancer Discov;5(7):752-67
ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors.

40. PMID: 20302916; 2010, Biochim Biophys Acta;1806(1):1-6
The potential role of ubiquitin c-terminal hydrolases in oncogenesis.

41. PMID: 21642991; 2011, Nat Genet;43(7):668-72
The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma.

42. PMID: 19188440; 2009, Mol Cell Biol;29(8):2181-92
Association of C-terminal ubiquitin hydrolase BRCA1-associated protein 1 with cell cycle regulator host cell factor 1.

43. PMID: 18757409; 2008, Cancer Res;68(17):6953-62
BRCA1-associated protein-1 is a tumor suppressor that requires deubiquitinating activity and nuclear localization.

44. PMID: 26891804; 2016, Int J Oncol;48(4):1571-80
Genomic profiling of the genes on chromosome 3p in sporadic clear cell renal cell carcinoma.

45. PMID: 21051595; 2010, Science;330(6009):1410-3
Frequent mutation of BAP1 in metastasizing uveal melanomas.

46. PMID: 24128712; 2013, J Thorac Oncol;8(11):1430-3
Clinical characteristics of patients with malignant pleural mesothelioma harboring somatic BAP1 mutations.

47. PMID: 22683710; 2012, Nat Genet;44(7):751-9
BAP1 loss defines a new class of renal cell carcinoma.

48. PMID: 23333114; 2013, Lancet Oncol;14(2):159-167
Effects on survival of BAP1 and PBRM1 mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation.

49. PMID: 24185509; 2013, Nat Genet;45(12):1470-3
Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas.

50. PMID: 25889843; 2015, J Transl Med;13():122
BAP1 mutation is a frequent somatic event in peritoneal malignant mesothelioma.

51. PMID: 28389374; 2017, J Thorac Oncol;12(8):1309-1319
A Novel BRCA1-Associated Protein-1 Isoform Affects Response of Mesothelioma Cells to Drugs Impairing BRCA1-Mediated DNA Repair.

52. PMID: 11239455; 2001, Mol Cell;7(2):263-72
BRCA2 is required for homology-directed repair of chromosomal breaks.

53. PMID: 17597348; 2007, Ann Surg Oncol;14(9):2510-8
Heterogenic loss of the wild-type BRCA allele in human breast tumorigenesis.

54. PMID: 22193408; 2011, Nat Rev Cancer;12(1):68-78
BRCA1 and BRCA2: different roles in a common pathway of genome protection.

55. PMID: 27283171; 2016, J Natl Compr Canc Netw;14(6):795-806
The Relevance of Hereditary Cancer Risks to Precision Oncology: What Should Providers Consider When Conducting Tumor Genomic Profiling?

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

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

58. PMID: 28884698; 2017, Lancet Oncol;18(9):e510
Correction to Lancet Oncol 2017; 18: 1274-84.

59. PMID: 22452356; 2012, N Engl J Med;366(15):1382-92
Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.

60. PMID: 26187614; 2015, Clin Cancer Res;21(19):4257-61
FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy.

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

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

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

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

65. PMID: 28882436; 2017, Gynecol Oncol;147(2):267-275
Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2.

66. PMID: 31562799; 2019, N Engl J Med;381(25):2391-2402
Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.

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

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

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

70. PMID: 17055429; 2006, Cell;127(2):265-75
The regulation of INK4/ARF in cancer and aging.

71. PMID: 8521522; 1995, Cell;83(6):993-1000
Alternative reading frames of the INK4a tumor suppressor gene encode two unrelated proteins capable of inducing cell cycle arrest.

72. PMID: 9529249; 1998, Cell;92(6):725-34
ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways.

73. PMID: 16115911; 2005, Clin Cancer Res;11(16):5740-7
Comprehensive analysis of CDKN2A status in microdissected urothelial cell carcinoma reveals potential haploinsufficiency, a high frequency of homozygous co-deletion and associations with clinical phenotype.

74. PMID: 7550353; 1995, Nat Genet;11(2):210-2
Frequency of homozygous deletion at p16/CDKN2 in primary human tumours.

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

76. PMID: 27849562; 2017, Gut;66(7):1286-1296
Palbociclib (PD-0332991), a selective CDK4/6 inhibitor, restricts tumour growth in preclinical models of hepatocellular carcinoma.

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

78. PMID: 28283584; 2017, Oncologist;22(4):416-421
Clinical Benefit in Response to Palbociclib Treatment in Refractory Uterine Leiomyosarcomas with a Common CDKN2A Alteration.

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

80. PMID: 26715889; 2015, Curr Oncol;22(6):e498-501
Does CDKN2A loss predict palbociclib benefit?

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

82. PMID: 27542767; 2016, Clin Cancer Res;22(23):5696-5705
A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas.

83. PMID: 24797823; 2014, Oncologist;19(6):616-22
Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel.

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

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

86. PMID: 26728409; 2016, Clin Cancer Res;22(1):122-33
Coadministration of Trametinib and Palbociclib Radiosensitizes KRAS-Mutant Non-Small Cell Lung Cancers In Vitro and In Vivo.

87. PMID: 31401335; 2019, Transl Oncol;12(11):1425-1431
Concomitant Genetic Alterations are Associated with Worse Clinical Outcome in EGFR Mutant NSCLC Patients Treated with Tyrosine Kinase Inhibitors.

88. PMID: 15498494; 2004, Curr Biol;14(20):1852-7
A nucleolar isoform of the Fbw7 ubiquitin ligase regulates c-Myc and cell size.

89. PMID: 15103331; 2004, EMBO J;23(10):2116-25
Phosphorylation-dependent degradation of c-Myc is mediated by the F-box protein Fbw7.

90. PMID: 16023596; 2005, Cancer Cell;8(1):25-33
The v-Jun point mutation allows c-Jun to escape GSK3-dependent recognition and destruction by the Fbw7 ubiquitin ligase.

91. PMID: 11533444; 2001, Science;294(5540):173-7
Phosphorylation-dependent ubiquitination of cyclin E by the SCFFbw7 ubiquitin ligase.

92. PMID: 11461910; 2001, J Biol Chem;276(38):35847-53
The Notch intracellular domain is ubiquitinated and negatively regulated by the mammalian Sel-10 homolog.

93. PMID: 11425854; 2001, J Biol Chem;276(37):34371-8
Functional interaction between SEL-10, an F-box protein, and the nuclear form of activated Notch1 receptor.

94. PMID: 16863506; 2006, Cancer Sci;97(8):729-36
Fbxw7 contributes to tumor suppression by targeting multiple proteins for ubiquitin-dependent degradation.

95. PMID: 18787170; 2008, Science;321(5895):1499-502
FBXW7 targets mTOR for degradation and cooperates with PTEN in tumor suppression.

96. PMID: 20484041; 2010, Cancer Res;70(11):4728-38
The Fbw7 tumor suppressor targets KLF5 for ubiquitin-mediated degradation and suppresses breast cell proliferation.

97. PMID: 21368833; 2011, Nature;471(7336):104-9
SCF(FBW7) regulates cellular apoptosis by targeting MCL1 for ubiquitylation and destruction.

98. PMID: 18094723; 2008, Nat Rev Cancer;8(2):83-93
FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation.

99. PMID: 23032637; 2012, Cancer Inform;11():157-71
Haploinsufficiency of Tumor Suppressor Genes is Driven by the Cumulative Effect of microRNAs, microRNA Binding Site Polymorphisms and microRNA Polymorphisms: An In silico Approach.

100. PMID: 24586741; 2014, PLoS One;9(2):e89388
FBXW7 mutations in patients with advanced cancers: clinical and molecular characteristics and outcomes with mTOR inhibitors.

101. PMID: 24360397; 2014, Lung Cancer;83(2):300-1
Temsirolimus therapy in a patient with lung adenocarcinoma harboring an FBXW7 mutation.

102. PMID: 27399335; 2017, Oncogene;36(6):787-796
FBW7 mutations mediate resistance of colorectal cancer to targeted therapies by blocking Mcl-1 degradation.

103. PMID: 25860929; 2015, Oncotarget;6(11):9240-56
FBXW7-mutated colorectal cancer cells exhibit aberrant expression of phosphorylated-p53 at Serine-15.

104. PMID: 29633504; 2018, Mol Oncol;12(6):883-895
FBXW7 deletion contributes to lung tumor development and confers resistance to gefitinib therapy.

105. PMID: 28522751; 2017, Cancer Res;77(13):3527-3539
Targeting FBW7 as a Strategy to Overcome Resistance to Targeted Therapy in Non-Small Cell Lung Cancer.

106. PMID: 24884509; 2014, Mol Cancer;13():110
Fbxw7 is an independent prognostic marker and induces apoptosis and growth arrest by regulating YAP abundance in hepatocellular carcinoma.

107. PMID: 24095279; 2013, Mol Cell;52(4):495-505
The folliculin tumor suppressor is a GAP for the RagC/D GTPases that signal amino acid levels to mTORC1.

108. PMID: 26342594; 2016, Fam Cancer;15(1):127-32
Birt-Hogg-Dubé syndrome: novel FLCN frameshift deletion in daughter and father with renal cell carcinomas.

109. PMID: 23223565; 2013, J Clin Pathol;66(3):178-86
Birt-Hogg-Dube syndrome: clinicopathological features of the lung.

110. PMID: 19850877; 2009, Proc Natl Acad Sci U S A;106(44):18722-7
Homozygous loss of BHD causes early embryonic lethality and kidney tumor development with activation of mTORC1 and mTORC2.

111. PMID: 24908670; 2014, Hum Mol Genet;23(21):5706-19
Folliculin (Flcn) inactivation leads to murine cardiac hypertrophy through mTORC1 deregulation.

112. PMID: 15956655; 2005, J Natl Cancer Inst;97(12):931-5
High frequency of somatic frameshift BHD gene mutations in Birt-Hogg-Dubé-associated renal tumors.

113. PMID: 29301825; 2018, Clin Cancer Res;24(7):1546-1553
Genomic Correlates of Response to Everolimus in Aggressive Radioiodine-refractory Thyroid Cancer: A Phase II Study.

114. PMID: 26418749; 2015, Oncotarget;6(32):32761-73
Flcn-deficient renal cells are tumorigenic and sensitive to mTOR suppression.

115. PMID: 8906794; 1996, Nature;384(6605):176-9
Biochemical evidence that patched is the Hedgehog receptor.

116. PMID: 12016144; 2002, Carcinogenesis;23(5):727-33
Unbalanced overexpression of the mutant allele in murine Patched mutants.

117. PMID: 11130178; 2000, Cell Mol Life Sci;57(12):1720-31
Hedgehog signalling in cancer.

118. PMID: 8782823; 1996, Nat Genet;14(1):78-81
The role of the human homologue of Drosophila patched in sporadic basal cell carcinomas.

119. PMID: 8658145; 1996, Science;272(5268):1668-71
Human homolog of patched, a candidate gene for the basal cell nevus syndrome.

120. PMID: 9422511; 1998, Nature;391(6662):90-2
Activating Smoothened mutations in sporadic basal-cell carcinoma.

121. PMID: 22832583; 2012, Nature;488(7409):100-5
Dissecting the genomic complexity underlying medulloblastoma.

122. PMID: 10738305; 2000, Genes Chromosomes Cancer;28(1):77-81
Evidence that haploinsufficiency of Ptch leads to medulloblastoma in mice.

123. PMID: 19726761; 2009, N Engl J Med;361(12):1173-8
Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449.

124. PMID: 26169613; 2015, J Clin Oncol;33(24):2646-54
Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog-Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032.

125. PMID: 25595896; 2015, Oncotarget;6(2):1190-201
Temozolomide resistance in glioblastoma occurs by miRNA-9-targeted PTCH1, independent of sonic hedgehog level.

126. PMID: 29320312; 2018, J Clin Oncol;36(6):536-542
Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study.

127. PMID: 17218262; 2007, Cell;128(1):157-70
Essential role for nuclear PTEN in maintaining chromosomal integrity.

128. PMID: 18794879; 2008, Oncogene;27(41):5443-53
PTEN: a new guardian of the genome.

129. PMID: 18767981; 2009, Annu Rev Pathol;4():127-50
PTEN and the PI3-kinase pathway in cancer.

130. PMID: 11553783; 2001, Proc Natl Acad Sci U S A;98(20):11563-8
Haploinsufficiency of the Pten tumor suppressor gene promotes prostate cancer progression.

131. PMID: 20400965; 2010, Nat Genet;42(5):454-8
Subtle variations in Pten dose determine cancer susceptibility.

132. PMID: 9467011; 1998, Hum Mol Genet;7(3):507-15
Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation.

133. PMID: 24136893; 2013, J Natl Cancer Inst;105(21):1607-16
Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria.

134. PMID: 21430697; 2011, Nat Rev Cancer;11(4):289-301
PTEN loss in the continuum of common cancers, rare syndromes and mouse models.

135. PMID: 18455982; 2008, Cell;133(3):403-14
Tenets of PTEN tumor suppression.

136. PMID: 9393738; 1997, Cancer Res;57(23):5221-5
MMAC1/PTEN mutations in primary tumor specimens and tumor cell lines.

137. PMID: 9829719; 1998, Clin Cancer Res;4(11):2577-83
Loss of heterozygosity and mutational analysis of the PTEN/MMAC1 gene in synchronous endometrial and ovarian carcinomas.

138. PMID: 9582022; 1998, Oncogene;16(13):1743-8
Analysis of PTEN and the 10q23 region in primary prostate carcinomas.

139. PMID: 9671321; 1998, Oncogene;17(1):123-7
Allelic loss of chromosome 10q23 is associated with tumor progression in breast carcinomas.

140. PMID: 11504908; 2001, Proc Natl Acad Sci U S A;98(18):10314-9
Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR.

141. PMID: 23714559; 2013, Am Soc Clin Oncol Educ Book;():
Targeting the PI3K/AKT/mTOR pathway: biomarkers of success and tribulation.

142. PMID: 20231295; 2010, J Biol Chem;285(20):14980-9
Phosphoinositide 3-kinase pathway activation in phosphate and tensin homolog (PTEN)-deficient prostate cancer cells is independent of receptor tyrosine kinases and mediated by the p110beta and p110delta catalytic subunits.

143. PMID: 23287563; 2013, Clin Cancer Res;19(7):1760-72
Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models.

144. PMID: 17047067; 2006, Cancer Res;66(20):10040-7
Inhibition of mammalian target of rapamycin or apoptotic pathway induces autophagy and radiosensitizes PTEN null prostate cancer cells.

145. PMID: 22422409; 2012, Clin Cancer Res;18(6):1777-89
PIK3CA/PTEN mutations and Akt activation as markers of sensitivity to allosteric mTOR inhibitors.

146. PMID: 22662154; 2012, PLoS One;7(5):e37431
Genotype-dependent efficacy of a dual PI3K/mTOR inhibitor, NVP-BEZ235, and an mTOR inhibitor, RAD001, in endometrial carcinomas.

147. PMID: 23136191; 2012, Clin Cancer Res;18(24):6771-83
Phosphoinositide 3-kinase (PI3K) pathway alterations are associated with histologic subtypes and are predictive of sensitivity to PI3K inhibitors in lung cancer preclinical models.

148. PMID: 27091708; 2016, J Clin Oncol;34(18):2115-24
Molecular Alterations and Everolimus Efficacy in Human Epidermal Growth Factor Receptor 2-Overexpressing Metastatic Breast Cancers: Combined Exploratory Biomarker Analysis From BOLERO-1 and BOLERO-3.

149. PMID: 21306238; 2011, N Engl J Med;364(6):514-23
Everolimus for advanced pancreatic neuroendocrine tumors.

150. PMID: 23582881; 2013, Eur Urol;64(1):150-8
Phase 2 trial of single-agent everolimus in chemotherapy-naive patients with castration-resistant prostate cancer (SAKK 08/08).

151. PMID: 15324695; 2004, Cancer Cell;6(2):117-27
PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients.

152. PMID: 20813970; 2010, Am J Pathol;177(4):1647-56
PTEN, PIK3CA, p-AKT, and p-p70S6K status: association with trastuzumab response and survival in patients with HER2-positive metastatic breast cancer.

153. PMID: 21135276; 2011, J Clin Oncol;29(2):166-73
Loss of phosphatase and tensin homolog or phosphoinositol-3 kinase activation and response to trastuzumab or lapatinib in human epidermal growth factor receptor 2-overexpressing locally advanced breast cancers.

154. PMID: 21594665; 2011, Breast Cancer Res Treat;128(2):447-56
Evaluation of the association of PIK3CA mutations and PTEN loss with efficacy of trastuzumab therapy in metastatic breast cancer.

155. PMID: 17936563; 2007, Cancer Cell;12(4):395-402
A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer.

156. PMID: 18700047; 2008, BMC Cancer;8():234
Potential value of PTEN in predicting cetuximab response in colorectal cancer: an exploratory study.

157. PMID: 17940504; 2007, Br J Cancer;97(8):1139-45
PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients.

158. PMID: 19398573; 2009, J Clin Oncol;27(16):2622-9
PTEN expression and KRAS mutations on primary tumors and metastases in the prediction of benefit from cetuximab plus irinotecan for patients with metastatic colorectal cancer.

159. PMID: 19953097; 2010, Br J Cancer;102(1):162-4
PTEN status in advanced colorectal cancer treated with cetuximab.

160. PMID: 27605871; 2016, World J Gastroenterol;22(28):6345-61
Mechanisms of resistance to anti-epidermal growth factor receptor inhibitors in metastatic colorectal cancer.

161. PMID: 24666267; 2014, Acta Oncol;53(7):852-64
The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis.

162. PMID: 19351834; 2009, Cancer Res;69(8):3256-61
PTEN loss contributes to erlotinib resistance in EGFR-mutant lung cancer by activation of Akt and EGFR.

163. PMID: 23133538; 2012, PLoS One;7(10):e48004
Modeling of tumor progression in NSCLC and intrinsic resistance to TKI in loss of PTEN expression.

164. PMID: 23592446; 2013, J Cell Biochem;114(6):1248-56
mTOR inhibitors radiosensitize PTEN-deficient non-small-cell lung cancer cells harboring an EGFR activating mutation by inducing autophagy.

165. PMID: 26645196; 2016, Cancer Discov;6(2):202-16
Loss of PTEN Promotes Resistance to T Cell-Mediated Immunotherapy.

166. PMID: 28228279; 2017, Immunity;46(2):197-204
Loss of PTEN Is Associated with Resistance to Anti-PD-1 Checkpoint Blockade Therapy in Metastatic Uterine Leiomyosarcoma.

167. PMID: 21468130; 2011, Nat Rev Clin Oncol;8(5):302-6
Treatment with olaparib in a patient with PTEN-deficient endometrioid endometrial cancer.

168. PMID: 22293180; 2012, J Clin Invest;122(2):425-34
Understanding pRb: toward the necessary development of targeted treatments for retinoblastoma.

169. PMID: 6320372; 1984, Science;223(4640):1028-33
Retinoblastoma: clues to human oncogenesis.

170. PMID: 27308386; 2015, Mol Cell Oncol;2(1):e968069
Conditional haploinsufficiency of the retinoblastoma tumor suppressor gene.

171. PMID: 23687339; 2013, Cancer Res;73(14):4247-55
Rb1 haploinsufficiency promotes telomere attrition and radiation-induced genomic instability.

172. PMID: 28169375; 2017, Sci Rep;7():42056
The Rb1 tumour suppressor gene modifies telomeric chromatin architecture by regulating TERRA expression.

173. PMID: 15884040; 2005, Hum Mutat;25(6):566-74
Sensitive multistep clinical molecular screening of 180 unrelated individuals with retinoblastoma detects 36 novel mutations in the RB1 gene.

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

175. PMID: 22811582; 2012, Clin Cancer Res;18(18):5110-22
RB-pathway disruption is associated with improved response to neoadjuvant chemotherapy in breast cancer.

176. PMID: 21358261; 2011, Cell Cycle;10(6):956-62
A non-functional retinoblastoma tumor suppressor (RB) pathway in premenopausal breast cancer is associated with resistance to tamoxifen.

177. PMID: 17160137; 2007, J Clin Invest;117(1):218-28
The retinoblastoma tumor suppressor modifies the therapeutic response of breast cancer.

178. PMID: 29236940; 2018, Ann Oncol;29(3):640-645
Polyclonal RB1 mutations and acquired resistance to CDK 4/6 inhibitors in patients with metastatic breast cancer.

179. PMID: 29483214; 2018, Mol Cancer Ther;17(5):897-907
Preclinical Activity of Abemaciclib Alone or in Combination with Antimitotic and Targeted Therapies in Breast Cancer.

180. PMID: 22941188; 2012, Nat Genet;44(10):1104-10
Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer.

181. PMID: 22941189; 2012, Nat Genet;44(10):1111-6
Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer.

182. PMID: 25846096; 2015, Lancet Oncol;16(4):e165-72
Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin.

183. PMID: 19029933; 2008, Oncogene;27(55):6908-19
LKB1; linking cell structure and tumor suppression.

184. PMID: 19584313; 2009, Physiol Rev;89(3):777-98
LKB1 and AMPK family signaling: the intimate link between cell polarity and energy metabolism.

185. PMID: 20142330; 2010, Dis Model Mech;3(3-4):181-93
Lkb1 inactivation is sufficient to drive endometrial cancers that are aggressive yet highly responsive to mTOR inhibitor monotherapy.

186. PMID: 17676035; 2007, Nature;448(7155):807-10
LKB1 modulates lung cancer differentiation and metastasis.

187. PMID: 18245476; 2008, Cancer Res;68(3):759-66
Loss of Lkb1 provokes highly invasive endometrial adenocarcinomas.

188. PMID: 18172296; 2008, Cancer Res;68(1):55-63
LKB1 deficiency sensitizes mice to carcinogen-induced tumorigenesis.

189. PMID: 25244018; 2014, Int J Mol Sci;15(9):16698-718
Recent progress on liver kinase B1 (LKB1): expression, regulation, downstream signaling and cancer suppressive function.

190. PMID: 9425897; 1998, Nat Genet;18(1):38-43
Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase.

191. PMID: 21189378; 2011, J Clin Oncol;29(6):e150-3
mTOR inhibitor treatment of pancreatic cancer in a patient With Peutz-Jeghers syndrome.

192. PMID: 27615706; 2016, CNS Oncol;5(4):203-9
Widely metastatic atypical pituitary adenoma with mTOR pathway STK11(F298L) mutation treated with everolimus therapy.

193. PMID: 27821489; 2017, Cancer Res;77(1):153-163
A Transcriptional Signature Identifies LKB1 Functional Status as a Novel Determinant of MEK Sensitivity in Lung Adenocarcinoma.

194. PMID: 29764856; 2018, Clin Cancer Res;24(22):5710-5723
TP53, STK11, and EGFR Mutations Predict Tumor Immune Profile and the Response to Anti-PD-1 in Lung Adenocarcinoma.

195. PMID: 29773717; 2018, Cancer Discov;8(7):822-835
STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma.

196. PMID: 29337640; 2018, J Clin Oncol;36(7):633-641
Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non-Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing.

197. PMID: 26833127; 2016, Cancer Res;76(5):999-1008
STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment.

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

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

200. PMID: 20525995; 2010, N Engl J Med;362(24):2260-70
Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.

201. PMID: 18541900; 2008, J Clin Oncol;26(19):3204-12
Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia.

202. PMID: 17496201; 2007, Blood;110(7):2309-15
Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study.

203. PMID: 26703889; 2016, Lancet;387(10022):968-977
Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study.

204. PMID: 22149876; 2012, N Engl J Med;366(6):520-9
Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.

205. PMID: 23158522; 2013, Lancet;381(9861):125-32
Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial.

206. PMID: 18653228; 2008, Lancet;372(9637):449-56
Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial.

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

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

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

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

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

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

213. PMID: 25981810; 2015, Lancet Oncol;16(6):716-28
Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial.

214. PMID: 17538086; 2007, N Engl J Med;356(22):2271-81
Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma.

215. PMID: 29072975; 2018, J Clin Oncol;36(1):7-13
Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer.

216. PMID: 27080216; 2016, Lancet Oncol;17(5):642-50
Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial.

217. PMID: 25265492; 2014, N Engl J Med;371(20):1877-88
Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma.

218. PMID: 22663011; 2012, N Engl J Med;367(2):107-14
Improved survival with MEK inhibition in BRAF-mutated melanoma.

219. PMID: 22670903; 2012, N Engl J Med;366(23):2171-9
Efficacy and safety of vismodegib in advanced basal-cell carcinoma.

ACT GENOMICS®

CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS

ACTFusion™ Report

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_FUS
Date Reported: Nov 09, 2021

PATIENT	SPECIMEN	ORDERING PHYSICIAN
Name: 賴鼎曜	Type: FFPE tissue	Name: 陳三奇醫師
Gender: Male	Date received: Oct 27, 2021	Facility: 臺北榮總
Date of Birth: Jan 20, 1967	Collection site: Bone	Tel: 886-228712121
Patient ID: 47708009	Specimen ID: S11030849	Address: 臺北市北投區石牌路二段 201 號
Diagnosis: Cholangiocarcinoma	Lab ID: AA-21-04817	
	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.*

VARIANT(S) WITH CLINICAL RELEVANCE

FUSION RESULTS

No fusion gene detected in this sample.

Variant Analysis:
醫檢師黃靖婷 博士
Ching-Ting Huang Ph.D.
檢字第 016511 號

CT Huang

Sign Off
解剖病理專科醫師王業翰
Yeh-Han Wang M.D.
病解字第 000545 號

Yeh

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_FUS
Date Reported: Nov 09, 2021

THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Not Applicable.

VARIANT INTERPRETATION

Not Applicable.

US FDA-APPROVED DRUG(S)

Not Applicable.

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_FUS
Date Reported: Nov 09, 2021

ONGOING CLINICAL TRIAL(S)

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.

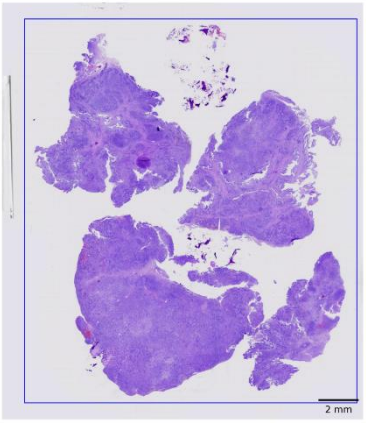
No trial has been found.

ACTFusion™ GENE LIST

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

TEST DETAILS

SPECIMEN RECEIVED



- H&E-stained section No.: S11030849
- Collection date: Oct 2021
- Collection site: Bone
- Facility retrieved: 臺北榮總
- Examined by: Dr. Yeh-Han Wang
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 50%
  The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 50%
  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.

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_FUS
Date Reported: Nov 09, 2021

NEXT-GENERATION SEQUENCING (NGS) METHODS

The extracted RNA was reverse-transcribed and subjected to library construction. The quality and quantity of the amplified library was determined using the fragment analyzer (AATI) and Qubit (Invitrogen). Sequencing was performed on the Ion 540™ Chip/ Ion 550™ Chip / Ion P1™ Chip and Ion GeneStudio™ S5 Prime System / Ion Proton™ System (Life Technologies). All assays were performed in accordance with ACT Genomics testing SOPs.

Data processing and statistical analysis for the identification of relevant fusions was performed using in-house fusion calling pipeline with default parameter setting. The four internal controls for the purpose of monitoring the overall sequencing quality of the sample were built into the assay, including CHMP2A, RABA7A, GPI, and VCP. Amplification of these genes using gene specific primers was performed, and the sequencing results were applied to the analysis pipeline to assess RNA quality. The inability of the software to detect these genes was considered a run failure. To ensure optimal sequencing quality for variant analysis, all samples had to meet the following sample quality control (QC) criteria: 1) Average unique RNA Start Sites (SS) per control Gene Specific Primer 2 (GSP 2) ≥ 10 (default), and 2) Total reads after sequencing ≥ 500,000 (recommended).

Samples passed the sample QC would be subjected to the fusion analysis pipeline for fusion transcript calling. Briefly, the analysis pipeline aligned sequenced reads to a reference genome, identified regions that map to noncontiguous regions of the genome, and applied filters to exclude probable false-positive events and annotate previously characterized fusion events. A minimum of 5 reads with 3 unique sequencing start sites that cross the breakpoints was set as the cutoff value to indicate strong evidence of fusions. RNA fusions would need to be in frame in order to generate productive transcripts. In addition, databases with details for documented fusions were used to authenticate the fusion sequence identified. Known fusions were queried using Quiver Gene Fusion Database, a curated database owned and maintained by ArcherDX. In summary, samples with detectable fusions had to meet the following criteria: 1) Number of unique start sites (SS) for the GSP2 ≥ 3. 2) Number of supporting reads spanning the fusion junction ≥ 5. 3) Percentage of supporting reads spanning the fusion junction ≥ 10%. 4) Fusions annotated in Quiver Gene Fusion Database.

DATABASE USED

Quiver Gene Fusion Database version 5.1.18

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.

STANDARD OPERATING PROCEDURES (SOPs)

Standard operating procedures (SOPs) are shown below:

- 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)

RUN QC

- Panel: ACTFusion™
- Total reads: 1010221
- Average unique RNA Start Sites per control GSP2: 171

DISCLAIMER

Legal Statement

This test was developed by ACT Genomics and its performing characteristics were determined by ACT Genomics. This test result is to be used for clinical consultative purposes only and is not intended as a substitute for a clinical guidance of your doctor or another qualified medical practitioner. It should not be regarded as investigational or used for research.

The detection of genomic alterations does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; the detection of no genomic alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Treatment Decisions are the Responsibility of the Physician

Decisions on clinical care and treatment should be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, including physical examinations, information from other diagnostics tests and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test, or the information contained in this report.

In terms of consulting a different treating physician, the patient must file an application and fulfill the listed criteria for ACT Genomics to provide the patient's report to the assigned physician. The report may not be copied or reproduced except in its totality.

Genetic Alterations and Drugs Not Presented in Ranked Order

In this report, neither any biomarker alteration nor any drug associated with a potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

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.

No Guarantee of Clinical Benefit

This report makes no promises or guarantees about the effectiveness of a particular drug or any treatment procedure in any disease or in any patient. This report also makes no promises or guarantees that a drug without an association of reportable genomic alteration will, in fact, provide no clinical benefit.

Liability

ACT Genomics is not affiliated with any medical facility or medical practitioner. We provide information for informational purposes only, therefore, ACT Genomics and their employees cannot be held responsible for any direct, indirect, special, incidental or consequential damages that may arise from the use of information provided in the report.

賴鼎曜
Project ID: C21-M001-01050
Report No.: AA-21-04817_FUS
Date Reported: Nov 09, 2021

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。

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。

REFERENCES

Not Applicable.