ACTOnco® + Report

TW202032021207163608

REPORT SUMMARY

REPORT DETAILS

APPENDIX

PATIENT AND SAMPLE INFORMATION

PATIENT	SPECIMEN	ORDERING PHYSICIAN
Name: 蘇綠菲	Type: FFPE tissue	Name: 陳三奇醫師
Gender: Female	Date received: Nov 24, 2021	Facility: 臺北榮總
Date of Birth: Jan 16, 1947	Collection site: Lymph node	Tel: 886-228712121
Patient ID: 45285981	Specimen ID: S10933597A	Address: 臺北市北投區石牌路二段 201 號
Diagnosis: Melanoma	Lab ID: AA-21-05696	
	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
NRAS	Q61R	1297	42.8%	COSM584

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 **74%** tumor purity.

Amplification (Copy number ≥ 8)

Chr	Gene	Copy Number
chr6	*E2F3*	7¥

Homozygous deletion (Copy number=0)

Chr	Gene
ND	ND

Heterozygous deletion (Copy number=1)

Chr	Gene
chr4	*FBXW7*
chr10	*PTEN*
chr15	*RAD51*

¥ Increased gene copy number was observed.

ND, Not Detected

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:
醫藥資訊研究員
楊杭哲 博士
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Sign Off
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Yeh-Han Wang M.D.
病解字第 000545 號

TW21-00-115-16308

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 2		
NRAS Q61R	Binimetinib	**sensitive**
Level 3A		
NRAS Q61R	Cetuximab, Panitumumab	**resistant**
Level 3B		
NRAS Q61R	Cobimetinib, Selumetinib, Trametinib	**sensitive**
PTEN Heterozygous deletion	Everolimus, Olaparib, Temsirolimus	**sensitive**
RAD51 Heterozygous deletion	Niraparib, Rucaparib	**sensitive**
Level 4		
FBXW7 Heterozygous deletion	Everolimus, Temsirolimus	**sensitive**
RAD51 Heterozygous deletion	Olaparib	**sensitive**
PTEN Heterozygous deletion	Cetuximab, Erlotinib, Gefitinib, Panitumumab, Trastuzumab	**resistant**
FBXW7 Heterozygous deletion	Gefitinib, Regorafenib	**resistant**

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

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICI) THERAPIES

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

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

MMR, mismatch repair; ND, not detected

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

CHEMOTHERAPIES

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.

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VARIANT INTERPRETATION

NRAS Q61R

Biological Impact

The neuroblastoma RAS viral oncogene homolog (NRAS) gene encodes a membrane-associated RAS protein which belongs to the large family of small GTPases. RAS proteins cycle between an active (GTP-bound) and an inactive (GDP-bound) state, to regulate intracellular oncogenic MAPK and PI3K signaling pathways[1]. Activated RAS proteins mediate the regulation of cellular proliferation and other cellular functions through the activation of distinct intracellular signaling pathways, including the RAF/MEK/ERK and PI3K/AKT/mTOR pathways. Mutations in NRAS are present in thyroid cancer, ovarian cancers, melanoma and hematological cancers[2][3][4].

Q61R is a hotspot within a GTP-binding region of the Nras protein, resulting in the constitutive activation of RAS/RAF/MAPK and PI3K/AKT/mTOR pathways[5].

Therapeutic and prognostic relevance

Two Phase I clinical studies showed that melanoma and biliary tract cancer patients whose tumor harbored an NRAS mutation were sensitive to MEK1/2 inhibitor trametinib and binimetinib[6][7]. In another clinical study, a melanoma patient harboring an ATM mutation and NRAS Q61R demonstrated a partial response and 16-month progression free survival (PFS) when treated with MEK1/2 inhibitor binimetinib[8]. Additional in vitro preclinical studies showed that NRAS-mutant lung cancer, liver cancer, ovarian cancer, melanoma and autonomic ganglia cancer cell lines were sensitive to MEK inhibitors, including selumetinib (AZD6244; ARRY-142886) and trametinib[9][10][11][12]. In an inducible NRAS Q61K genetically engineered mouse model of melanoma, the combination of MEK and CDK4/6 inhibitors caused tumor regression that paralleled extinction of mutant NRAS[13]. An additional preclinical evidence has shown efficacy of MEK1/2 inhibitor selumetinib in KRAS-mutant thyroid cancer model with NF2 loss[14].

Both clinical and preclinical studies demonstrated a limited response to monotherapy using MEK inhibitors like selumetinib and trametinib in RAS/RAF mutant colorectal cancer (CRC) patients[15][16]. Several clinical trials are in progress to evaluate the combination of MEK and mTOR inhibition as a new potential therapeutic strategy in CRC[17], and in patient-derived xenografts of RAS-mutant CRC, inhibition of MEK and mTOR suppressed tumor growth, but not tumor regression[18]. Preclinically, cetuximab synergistically triggers apoptotic cell death with MEK1/2 inhibitors in NRAS mutant metastatic colorectal cancer cells[19].

Results from the PRIME and FIRE-3 trials indicated that panitumumab and cetuximab did not benefit patients with KRAS or NRAS mutations and may even have a detrimental effect on these patients[20]. Taken together, the National Comprehensive Cancer Network (NCCN) recommended that, cetuximab and panitumumab should only be used if both KRAS and NRAS genes are normal (NCCN guidelines)[21][22].

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NRAS mutations have been determined as an inclusion criterion for the trial evaluating cobimetinib or selumetinib efficacy in patients with multiple myeloma, melanoma, thyroid carcinoma, lung cancer, and solid tumor (NCT04109456, NCT03732703, NCT03181100, NCT02639546, NCT02664935)[23].

NCCN guidelines for cutaneous melanoma (Version 2. 2021) suggested that NRAS-mutated tumors may produce response to binimetinib based on the results from NEMO phase III trial (NCT01763164). In the NEMO trial, treating immune therapy-pretreated melanoma patients harboring NRAS Q61R/K/L with binimetinib improved median PFS compared to dacarbazine (2.8 v.s. 1.5 months)[24].

E2F3 Amplification

Biological Impact

The E2F3 gene encodes a transcription factor that interacts directly with the retinoblastoma protein (pRB) to regulate the expression of genes involved in the cell cycle and DNA replication[25][26][27].

Amplification or overexpression of E2F3 has been reported in various types of cancers, including bladder cancer, hepatocellular carcinoma, retinoblastomas, and melanoma[28][29][30][31][32].

Therapeutic and prognostic relevance

A tissue microarray analysis indicated that amplification of the E2F3 gene is associated with increased E2F3 protein overexpression, accelerated cell proliferation, and poor prognosis in bladder cancer[29]. Besides, elevated E2F genes and E2F transcriptional targets in tumors have been linked with poor prognosis in the liver and pancreatic cancers[27].

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[33][34], c-Jun[35], cyclin E[36], Notch family members[37][38], Aurora-A[39], mTOR[40], KLF5[41], and MCL-1[42]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation[43]. 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[41][42][44].

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)[45][46]. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor[40].

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Preclinical studies suggested that mutations or loss of FBXW7 were associated with regorafenib and oxaliplatin resistance in CRC cell lines[47][48] and gefitinib resistance in lung cancer cells[49][50].

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[51][49].

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[52][53]. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway[54]. 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[55][56][57]. 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[58][59][60]. 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[61][62][63][64][65].

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[66][67]. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes[68][69][70][71][72][73]. Moreover, early clinical data also indicated that PTEN loss was associated with improved response and longer PFS in patients with advanced breast cancer[74], advanced pancreatic neuroendocrine tumors[75]and metastatic castration-resistant prostate cancer[76] 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[77][78][79][80][81].

Loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab[82][83][84][85][86][87]. 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.

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Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib[88][89]. 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[90].

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[91][92][93].

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[94].

RAD51 **Heterozygous deletion**

Biological Impact

The RAD51 gene encodes a recombinase that is crucial for homologous recombination (HR)-mediated repair of double-strand DNA breaks (DSBs) by forming complexes with known tumor suppressors including BRCA1, BRCA2, and PALB2[95][96][97]. RAD51 has been characterized as a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[98]. Overexpression of RAD51 has been observed in many cancer cells, including pancreatic cancer and breast cancer and its hyperexpression is implicated in drug resistance[99][100][101][102][103][104][105]. Germline mutations in RAD51 are associated with increased susceptibility to breast cancer[106][107][108][109].

Therapeutic and prognostic relevance

RAD51 loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer[110]; rucaparib efficacy in solid tumor (NCT04171700); talazoparib efficacy in lung cancer (NCT03377556); niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate cancer) (NCT03207347).

Preclinical studies showed that decreased RAD51 expression could sensitize cells to olaparib-induced tumor cell cytotoxicity[111][112].

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US FDA-APPROVED DRUG(S)

Binimetinib (MEKTOVI)

Binimetinib is an oral kinase inhibitor that targets MEK. Binimetinib is developed and marketed by Array BioPharma under the trade name MEKTOVI.

FDA Approval Summary of Binimetinib (MEKTOVI)

MEKTOVI[113] NCT01909453	**Melanoma** (Approved on 2018/06/27)
	BRAF V600E/K
	Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3]

Cobimetinib (COTELLIC)

Cobimetinib is a reversible inhibitor which targets MEK1 and MEK2. Cobimetinib is developed by Exelixis and Genentech, and marketed by Genentech under the trade name COTELLIC.

FDA Approval Summary of Cobimetinib (COTELLIC)

coBRIM[114] NCT01689519	**Melanoma** (Approved on 2015/11/10)
	BRAF V600E/K
	Cobimetinib + vemurafenib vs. Placebo + vemurafenib [PFS(M): 12.3 vs. 7.2]

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[115] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[116] NCT00863655	**Breast cancer** (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]

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RADIANT-3[75] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[117] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[118] 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[119] 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[120] 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[120] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27)
	gBRCA- CR/PR to platinum-based chemotherapy
	Niraparib vs. Placebo [PFS(M): 9.3 vs. 3.9]

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Olaparib (LYNPARZA)

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

FDA Approval Summary of Olaparib (LYNPARZA)

PROfound[121] 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[122] 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[123] 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[124] 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[125] 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[126] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA+
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]

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Study19[127] 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[128] NCT01078662	**Ovarian cancer** (Approved on 2014/12/19)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

Rucaparib (RUBRACA)

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

FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA+, sBRCA
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[129] 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[130] NCT01482715, NCT01891344	**Ovarian cancer** (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation
	Rucaparib [ORR(%): 54.0]

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Selumetinib (KOSELUGO)

Selumetinib is a kinase inhibitor. Selumetinib is developed and marketed by AstraZeneca under the trade name KOSELUGO.

FDA Approval Summary of Selumetinib (KOSELUGO)

SPRINT NCT01362803	**Plexiform neurofibromas** (Approved on 2020/04/10)
	Neurofibromatosis type 1
	Selumetinib [ORR(%): 66.0]

Temsirolimus (TORISEL)

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

FDA Approval Summary of Temsirolimus (TORISEL)

[131] 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[132] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[133] 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]

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COMBI-d[134] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[135] NCT01245062	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

d=day; w=week; m=month

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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.

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DETAILED TEST RESULTS

SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Chr	Exon	Accession Number	cDNA Change	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
ATM	11	4	NM_000051	c.283C>A	Q95K	375	50.4%	COSM7346277
CD19	16	3	NM_001178098	c.445G>A	G149R	230	48.7%	-
CDH1	16	3	NM_004360	c.263C>G	P88R	772	49.4%	-
CYP2B6	19	4	NM_000767	c.499C>G	P167A	131	59.5%	-
ETV1	7	4	NM_004956	c.55G>A	G19R	1027	47.8%	-
KEAP1	19	2	NM_203500	c.25G>A	G9R	923	38.0%	COSM2812662
MSH6	2	4	NM_000179	c.2615T>C	I872T	1193	51.9%	-
NRAS	**1**	**3**	**NM_002524**	**c.182A>G**	**Q61R**	**1297**	**42.8%**	**COSM584**
PIK3CB	3	19	NM_006219	c.2687G>T	R896L	1738	50.9%	-
PPP2R1A	19	5	NM_014225	c.547C>T	R183W	3401	68.2%	COSM51211
PTCH1	9	16	NM_000264	c.2692G>A	D898N	646	53.3%	COSM1111473
PTPRD	9	25	NM_002839	c.2763C>A	F921L	1954	46.6%	COSM7735382
RECQL4	8	15	NM_004260	c.2420G>A	R807H	95	60.0%	COSN15633630
TET1	10	9	NM_030625	c.4889A>T	Y1630F	637	14.1%	-
TET1	10	9	NM_030625	c.4829A>G	K1610R	258	8.1%	COSM5777117

Mutations with clinical relevance are highlighted in red.

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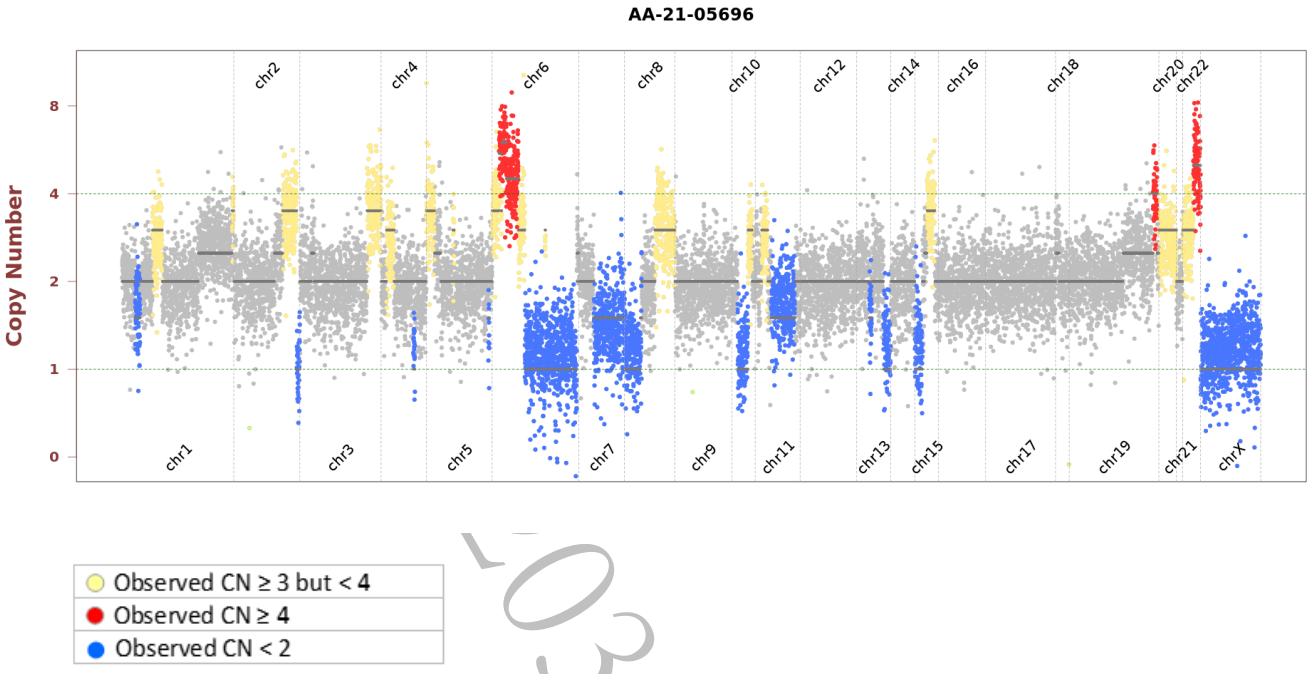
COPY NUMBER VARIANTS (CNVS)

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.



Observed CN ≥ 3 but < 4
Observed CN ≥ 4
Observed CN < 2

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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	**Q61R**
PDGFRA	A633T, C450_K451insMIEWMI, C456_N468del, C456_R481del, D568N, D842I/V, D842_H845del, D842_M844del, D846Y, E311_K312del, G853D, H650Q, H845Y, H845_N848delinsP, I843del, N659K/R/S, N848K, P577S, Q579R, R560_V561insER, R748G, R841K, S566_E571delinsR, S584L, V469A, V536E, V544_L545insAVLVLLVIVIISLI, V561A/D, V561_I562insER, V658A, W559_R560del, Y375_K455del, Y555C, Y849C/S	Not detected
PIK3CA	C420R, E542K/V, E545A/D/G/K, H1047X, Q546E/R	Not detected

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

Gene	Copy Number Detected
CDK4	2
EGFR	2
ERBB2	2
MET	1

Copy number ≥ 8 is considered amplification

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

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

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

Gene	Copy Number Detected
FGFR1	1
MDM2	2
MDM4	2

Copy number ≥ 8 is considered amplification

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TEST DETAILS

ABOUT ACTOnco®+

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

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

DATABASE USED

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

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

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite (version 5.10). Coverage depth was calculated using Torrent Coverage Analysis plug-in. Single nucleotide variants (SNVs) and short insertions/deletions (INDELs) were identified using the Torrent Variant Caller plug-in (version 5.10). The coverage was down-sampled to 4000. VEP (Variant Effect Predictor) (version 100) was used to annotate every variant using databases from Clinvar (version 20210208), COSMIC v.92 and Genome Aggregation database r2.1.1. Variants with coverage ≥ 25, allele frequency ≥ 5% and actionable variants with allele frequency ≥ 2% were retained.

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

Variants reported in Genome Aggregation database r2.1.1 with > 1% minor allele frequency (MAF) were

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

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

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

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

STANDARD OPERATING PROCEDURES (SOPS)

Standard operating procedures (SOPs) are shown below:

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

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

LIMITATIONS

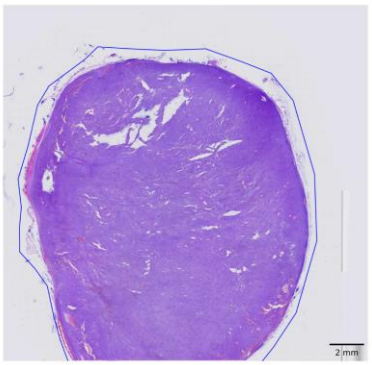
This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject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

NOTES

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

PATHOLOGY EVALUATION

- H&E-stained section No.: S10933597A
- Collection site: Lymph node
- Examined by: Dr. Pei-Yi Chu
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 90%
  The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 90%
  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.

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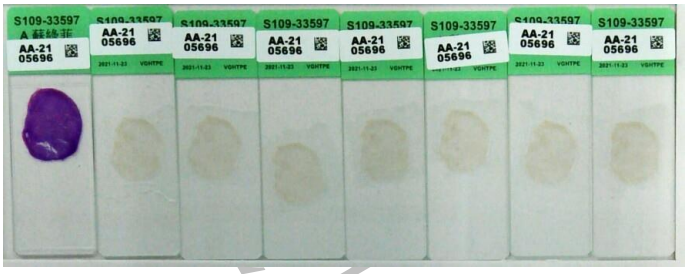
SPECIMEN PHOTO(S)



- Collection date: Oct 2020
- Facility retrieved: 臺北榮總

RUN QC

- Panel: ACTOnco®+
- Mean Depth: 906x
- Target Base Coverage at 100x: 94%

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ACTOnco®+ GENE LIST

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

*Analysis of copy number alteration not available.

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

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

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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。

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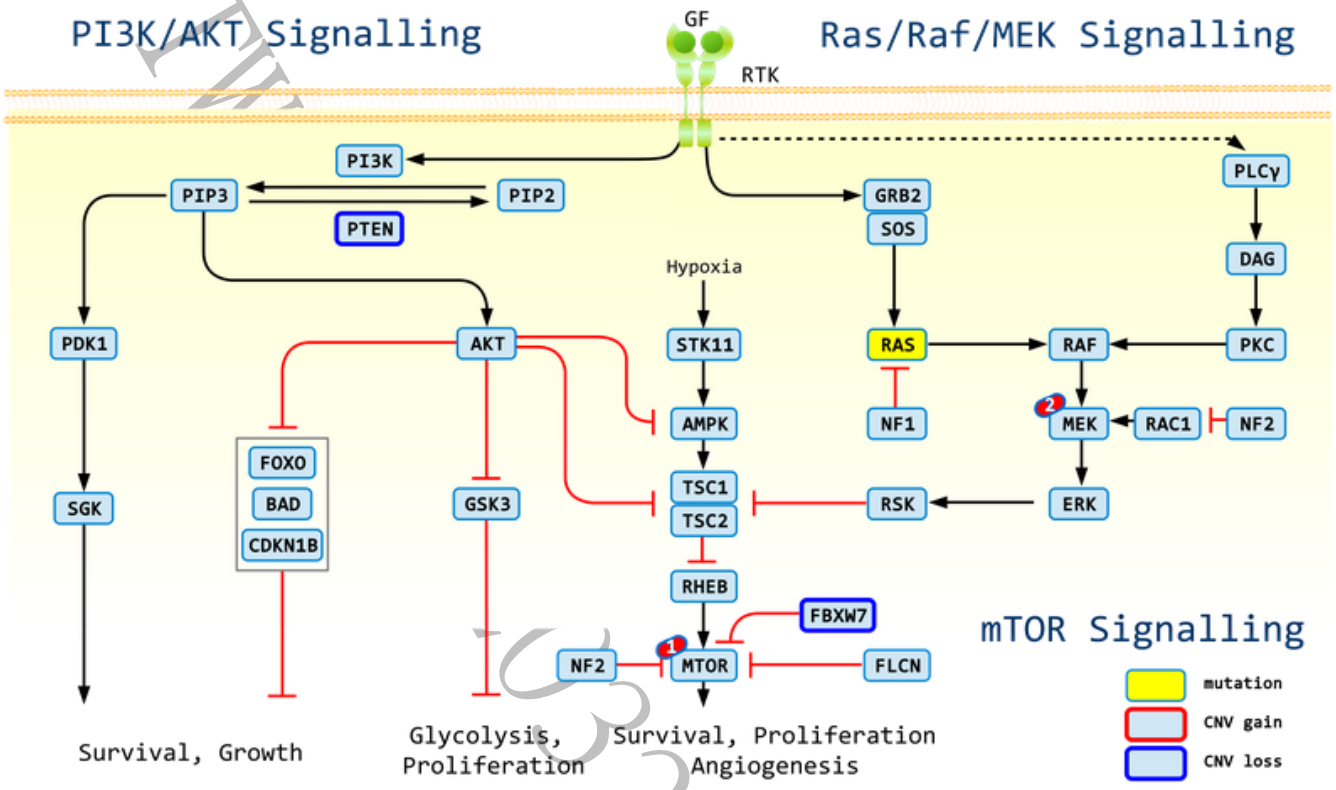
SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Everolimus, Temsirolimus; 2: Trametinib, Cobimetinib, Binimetinib, Selumetinib

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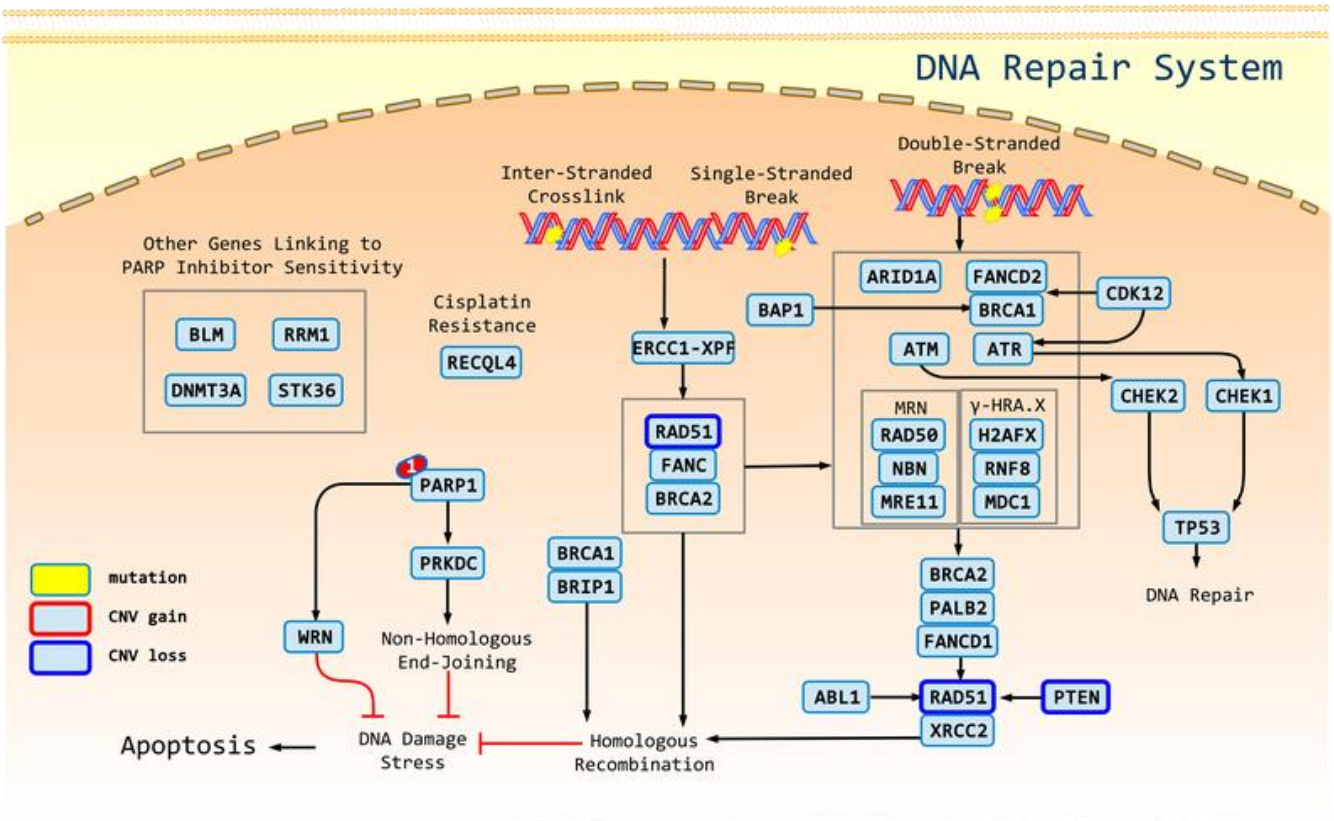

1: Olaparib, Niraparib, Rucaparib

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REFERENCES

1. PMID: 22189424; 2011, Nat Rev Mol Cell Biol;13(1):39-51
Regulating the regulator: post-translational modification of RAS.

2. PMID: 21993244; 2011, Nat Rev Cancer;11(11):761-74
RAS oncogenes: weaving a tumorigenic web.

3. PMID: 22589270; 2012, Cancer Res;72(10):2457-67
A comprehensive survey of Ras mutations in cancer.

4. PMID: 24651010; 2014, Cancer Cell;25(3):272-81
Dragging ras back in the ring.

5. PMID: 18814281; 2009, Int J Cancer;124(1):16-26
Oncogenic NRAS has multiple effects on the malignant phenotype of human melanoma cells cultured in vitro.

6. PMID: 22805292; 2012, Lancet Oncol;13(8):782-9
Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial.

7. PMID: 28152546; 2017, Br J Cancer;116(5):575-583
A phase 1 dose-escalation and expansion study of binimetinib (MEK162), a potent and selective oral MEK1/2 inhibitor.

8. PMID: 28514312; 2017, Medicine (Baltimore);96(20):e6931
Treatment inferred from mutations identified using massive parallel sequencing leads to clinical benefit in some heavily pretreated cancer patients.

9. PMID: 23515407; 2013, Clin Cancer Res;19(9):2584-91
Characteristics of lung cancers harboring NRAS mutations.

10. PMID: 26343583; 2015, Cancer Cell;28(3):384-98
Inhibition of RAF Isoforms and Active Dimers by LY3009120 Leads to Anti-tumor Activities in RAS or BRAF Mutant Cancers.

11. PMID: 25110411; 2014, World J Gastroenterol;20(29):9732-43
Beyond KRAS: Predictive factors of the efficacy of anti-EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer.

12. PMID: 24024839; 2013, N Engl J Med;369(11):1023-34
Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer.

13. PMID: 22983396; 2012, Nat Med;18(10):1503-10
Oncogenic NRAS signaling differentially regulates survival and proliferation in melanoma.

14. PMID: 26359368; 2015, Cancer Discov;5(11):1178-93
NF2 Loss Promotes Oncogenic RAS-Induced Thyroid Cancers via YAP-Dependent Transactivation of RAS Proteins and Sensitizes Them to MEK Inhibition.

15. PMID: 20127139; 2011, Invest New Drugs;29(5):1021-8
A Phase II, open-label, randomised study to assess the efficacy and safety of the MEK1/2 inhibitor AZD6244 (ARRY-142886) versus capecitabine monotherapy in patients with colorectal cancer who have failed one or two prior chemotherapeutic regimens.

16. PMID: 24947927; 2014, Clin Cancer Res;20(16):4251-61
Phase I expansion and pharmacodynamic study of the oral MEK inhibitor RO4987655 (CH4987655) in selected patients

with advanced cancer with RAS-RAF mutations.

17. PMID: 27340376; 2016, Curr Colorectal Cancer Rep;12():141-150
Molecular Subtypes and Personalized Therapy in Metastatic Colorectal Cancer.

18. PMID: 22392911; 2012, Clin Cancer Res;18(9):2515-25
Inhibition of MEK and PI3K/mTOR suppresses tumor growth but does not cause tumor regression in patient-derived xenografts of RAS-mutant colorectal carcinomas.

19. PMID: 27636997; 2016, Oncotarget;7(50):82185-82199
Synthetic lethal interaction of cetuximab with MEK1/2 inhibition in NRAS-mutant metastatic colorectal cancer.

20. PMID: 25937522; 2015, Eur J Cancer;51(10):1243-52
FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer.

21. PMID: 19188670; 2009, J Clin Oncol;27(12):2091-6
American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy.

22. PMID: 18802721; 2008, Virchows Arch;453(5):417-31
KRAS mutation testing for predicting response to anti-EGFR therapy for colorectal carcinoma: proposal for an European quality assurance program.

23. PMID: 32669708; 2020, Nature;583(7818):807-812
The National Lung Matrix Trial of personalized therapy in lung cancer.

24. PMID: 28284557; 2017, Lancet Oncol;18(4):435-445
Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial.

25. PMID: 10733529; 2000, Genes Dev;14(6):690-703
E2f3 is critical for normal cellular proliferation.

26. PMID: 24901045; 2014, Cell Death Dis;5():e1274
Retinoblastoma protein (RB) interacts with E2F3 to control terminal differentiation of Sertoli cells.

27. PMID: 31053804; 2019, Nat Rev Cancer;19(6):326-338
The broken cycle: E2F dysfunction in cancer.

28. PMID: 12782593; 2003, Cancer Res;63(11):2872-80
Array-based comparative genomic hybridization for genome-wide screening of DNA copy number in bladder tumors.

29. PMID: 15122326; 2004, Oncogene;23(33):5616-23
E2F3 amplification and overexpression is associated with invasive tumor growth and rapid tumor cell proliferation in urinary bladder cancer.

30. PMID: 28134624; 2017, J Clin Invest;127(3):830-842
Dosage-dependent copy number gains in E2f1 and E2f3 drive hepatocellular carcinoma.

31. PMID: 16007192; 2005, Oncogene;24(42):6441-9
Gains and overexpression identify DEK and E2F3 as targets of chromosome 6p gains in retinoblastoma.

32. PMID: 30214236; 2018, Onco Targets Ther;11():5303-5313
E2F3 promotes cancer growth and is overexpressed through copy number variation in human melanoma.

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

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

35. 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.

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

37. 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.

38. 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.

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

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

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

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

43. 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.

44. 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.

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

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

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

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

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

50. 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.

51. 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.

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

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

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

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

56. 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.

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

58. 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.

59. 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.

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

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

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

63. 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.

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

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

66. 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.

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

68. 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.

69. 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.

70. 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.

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

72. 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.

73. 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.

74. 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.

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

76. 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).

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

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

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

84. 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.

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

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

87. 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.

88. 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.

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

90. 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.

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

92. 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.

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

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

95. PMID: 20930833; 2010, Nature;467(7316):667-8
DNA repair: A protein giant in its entirety.

96. PMID: 20729858; 2010, Nat Struct Mol Biol;17(10):1263-5
The breast cancer tumor suppressor BRCA2 promotes the specific targeting of RAD51 to single-stranded DNA.

97. PMID: 20729832; 2010, Nature;467(7316):678-83
Purified human BRCA2 stimulates RAD51-mediated recombination.

98. PMID: 22305526; 2012, Am J Hum Genet;90(2):301-7
RAD51 haploinsufficiency causes congenital mirror movements in humans.

99. PMID: 18243065; 2008, DNA Repair (Amst);7(5):686-93
The consequences of Rad51 overexpression for normal and tumor cells.

100. PMID: 24811120; 2014, Oncotarget;5(10):3261-72
Rad51 supports triple negative breast cancer metastasis.

101. PMID: 26317153; 2015, Cell Cycle;14(19):3190-202
High levels of RAD51 perturb DNA replication elongation and cause unscheduled origin firing due to impaired CHK1

activation.

102. PMID: 21807066; 2011, Biochim Biophys Acta;1816(2):209-18
RAD51 as a potential biomarker and therapeutic target for pancreatic cancer.

103. PMID: 10851081; 2000, Oncogene;19(23):2791-5
DNA repair and recombination factor Rad51 is over-expressed in human pancreatic adenocarcinoma.

104. PMID: 24741789; 2014, Rev Med Chir Soc Med Nat Iasi;118(1):133-40
Rad51 overexpression and resistance to genotoxic agents. A study in the fission yeast Schizosaccharomyces pombe.

105. PMID: 18618591; 2009, Mol Carcinog;48(2):105-9
Rad51 overexpression rescues radiation resistance in BRCA2-defective cancer cells.

106. PMID: 10807537; 2000, J Hum Genet;45(3):133-7
Identification of Rad51 alteration in patients with bilateral breast cancer.

107. PMID: 26108708; 2015, Sci Rep;5():11588
RAD51 135G>C substitution increases breast cancer risk in an ethnic-specific manner: a meta-analysis on 21,236 cases and 19,407 controls.

108. PMID: 11248061; 2001, Proc Natl Acad Sci U S A;98(6):3232-6
A single nucleotide polymorphism in the RAD51 gene modifies cancer risk in BRCA2 but not BRCA1 carriers.

109. PMID: 17999359; 2007, Am J Hum Genet;81(6):1186-200
RAD51 135G-->C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies.

110. PMID: 30353044; 2018, Br J Cancer;119(11):1401-1409
Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes.

111. PMID: 24577941; 2014, Mol Cancer Ther;13(5):1170-80
The use of Olaparib (AZD2281) potentiates SN-38 cytotoxicity in colon cancer cells by indirect inhibition of Rad51-mediated repair of DNA double-strand breaks.

112. PMID: 28759753; 2017, Biomed Pharmacother;94():165-168
Inhibition of Rad51 sensitizes breast cancer cells with wild-type PTEN to olaparib.

113. PMID: 29573941; 2018, Lancet Oncol;19(5):603-615
Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial.

114. PMID: 27480103; 2016, Lancet Oncol;17(9):1248-60
Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial.

115. 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.

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

117. 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.

118. 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.

119. 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.

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

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

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

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

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

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

126. 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.

127. 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.

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

129. 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.

130. 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.

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

132. 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.

133. 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.

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

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

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ACTFusion™ Report

TW10020211207 1636

PATIENT		
Name: 蘇綠菲		Patient ID: 45285981
Date of Birth: Jan 16, 1947		Gender: Female
Diagnosis: Melanoma		
ORDERING PHYSICIAN		
Name: 陳三奇醫師		Tel: 886-228712121
Facility: 臺北榮總		
Address: 臺北市北投區石牌路二段201號		
SPECIMEN		
Specimen ID: S10933597A	Collection site: Lymph node	Date received: Nov 24, 2021
Lab ID: AA-21-05696	Type: FFPE tissue	D/ID: NA

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

TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Fusions

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

ACTFusion™ Report

TW21070020321207 1636

THERAPEUTIC IMPLICATION

Not Applicable.

VARIANT INTERPRETATION

Not Applicable.

US FDA-APPROVED DRUG(S)

Not Applicable.

ACTFusion™ Report

TW21070020211207 1636

ONGOING CLINICAL TRIALS

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

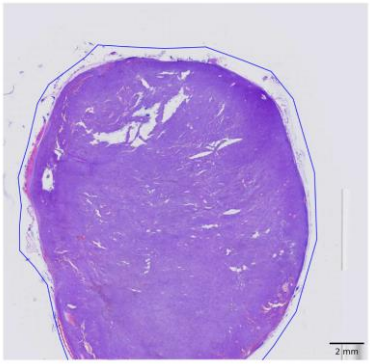
No trial has been found.

ACTFusion™ Report

TW-002-20211207-1636

TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Oct 2020
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S10933597A
- Collection site: Lymph node
- Examined by: Dr. Pei-Yi Chu
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 90%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 90%
    3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
    4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
    5. Additional comment: NA
- Manual macrodissection: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTFusion™
- Total reads: 1174830
- Average unique RNA Start Sites per control GSP2: 165

LIMITATIONS

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

ACTFusion™ Report

TW21700082021120716

NEXT-GENERATION SEQUENCING (NGS) METHODS

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

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

STANDARD OPERATING PROCEDURES (SOPs)

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

DATABAES USED

- Quiver Gene Fusion Database version 5.1.18

GENE LIST

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

Variant Analysis:
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ACT Fusion™ Report

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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。

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REFERENCE

Not Applicable.