ACT Onco® + Report

PATIENT		
Identifier: 王淑娟		Patient ID: 30233126
Date of Birth: Apr 17, 1965		Gender: Female
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
Name: 許文虎醫師/蔡俊明醫師		Tel: 886-228712121
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SPECIMEN		
Specimen ID: S11205784C	Collection site: Lung	Type: FFPE tissue
Date received: Mar 02, 2023	Lab ID: AA-23-01241	D/ID: NA

ABOUT ACTOnco®+

The test is a next-generation sequencing (NGS)-based assay developed for efficient and comprehensive genomic profiling of cancers. This test interrogates coding regions of 440 genes associated with cancer treatment, prognosis and diagnosis. Genetic mutations detected by this test include small-scale mutations like single nucleotide variants (SNVs), small insertions and deletions (InDels) (≤ 15 nucleotides) and large-scale genomic alterations like copy number alterations (CNAs). The test also includes an RNA test, detecting fusion transcripts of 13 genes.

SUMMARY FOR ACTIONABLE VARIANTS

VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Probable Effects in Patient's Cancer Type		Probable Sensitive in Other Cancer Types
	Sensitive	Resistant	
BRAF V600E	Dabrafenib, Trametinib, Vemurafenib	-	Binimetinib, Cobimetinib, Encorafenib, Selumetinib
PIK3CA E545K	-	-	Alpelisib, Everolimus

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
ATRX S25*	Olaparib, Talazoparib	-
BRAF V600E	-	Cetuximab, Panitumumab
PIK3CA E545K	Temsirolimus, Trametinib, Lapatinib†, Trastuzumab†	-
SMAD4 D537fs	-	Cetuximab

†Based on published evidence, this alteration may confer less benefit from the indicated drug.

Note:

- The above summary tables present genomic variants and biomarkers based on the three-tiered approach proposed by US FDA for reporting tumor profiling NGS testing. "Variants/biomarkers with evidence of clinical significance" refers to mutations that are widely recognized as standard-of-care biomarkers (FDA level 2/AMP tier 1). "Variants/biomarkers with potential clinical significance" refers to mutations that are not included in the standard of care but are informational for clinicians, which are commonly biomarkers used as inclusion criterial for clinical trials (FDA level 3/AMP tier 2).
- The therapeutic agents and possible effects to a given drug are based on mapping the variants/biomarkers with ACT Genomics clinical knowledge database. The mapping results only provide information for reference, but not medical recommendation.
- Please refer to corresponding sections for more detailed information about genomic alteration and clinical relevance listed above.

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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
ATRX	S25*	20.1%
BRAF	V600E	20.8%
PIK3CA	E545K	28.3%
SETD2	Q2207*	16.0%
SMAD4	D537fs	25.4%
TP53	P98T	33.8%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Not detected			

- Fusions

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

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	5.7 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:
- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 35% tumor purity.
- TMB was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is < 30%.

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 1		
BRAF V600E	Dabrafenib, Trametinib	**sensitive**
Level 2		
BRAF V600E	Vemurafenib	**sensitive**
Level 3A		
BRAF V600E	Binimetinib, Cobimetinib, Encorafenib, Selumetinib	**sensitive**
PIK3CA E545K	Alpelisib, Everolimus	**sensitive**
BRAF V600E	Cetuximab, Panitumumab	**resistant**
Level 3B		
ATRX S25*	Olaparib	**sensitive**
PIK3CA E545K	Temsirolimus	**sensitive**
Level 4		
ATRX S25*	Talazoparib	**sensitive**
PIK3CA E545K	Trametinib	**sensitive**
PIK3CA E545K	Lapatinib, Trastuzumab	**less sensitive**
SMAD4 D537fs	Cetuximab	**resistant**

Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence in professional guidelines or peer-reviewed journals.

Level	Description
1	FDA-recognized biomarkers predictive of response or resistance to FDA approved drugs in this indication
2	Standard care biomarkers (recommended by the NCCN guideline) predictive of response or resistance to FDA approved drugs in this indication
3A	Biomarkers predictive of response or resistance to therapies approved by the FDA or NCCN guideline in a different cancer type
3B	Biomarkers that serve as inclusion criteria for clinical trials (minimal supportive data required)
4	Biomarkers that show plausible therapeutic significance based on small studies, few case reports, or preclinical studies

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

No genomic alterations detected to confer sensitivity or lack of benefit to immune checkpoint therapies.

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
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

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
SMAD4 D537fs	Fluorouracil	**Resistant**	Clinical	Colorectal cancer

HORMONAL THERAPIES

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

OTHERS

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

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

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VARIANT INTERPRETATION

ATRX S25*

Biological Impact

The alpha thalassemia/mental retardation syndrome X-linked (ATRX) gene encodes a tumor suppressor and member of the SWI1/SNF2 family of helicase/adenosine triphosphatase (ATPase) involved in chromatin remodeling[1][2]. ATRX mutations are associated with chromosomal instability and are hence implicated in oncogenesis[3]. Mutations in the ATRX gene cause alpha thalassemia/ mental retardation X-linked syndrome[4].

S25* mutation results in a premature truncation of the ATRX protein at amino acid 25 (UniProtKB). This mutation is predicted to lead to a loss of ATRX function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

ATRX has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in metastatic/advanced urothelial carcinoma (NCT03375307) and ovarian cancer[5], niraparib efficacy in melanoma (NCT03925350), and rucaparib efficacy in ovarian cancer[6]. In a preclinical study, immortalized astrocytes with loss of ATRX were sensitive to olaparib and talazoparib treatment in vitro[7].

A retrospective study of patients with glioma showed that those with loss of ATRX expression showed increased overall survival compared to those with retained ATRX expression ($p < 0.0001$)[8]. However, loss of ATRX or DAXX expression in uterine leiomyosarcoma and mutations in the DAXX/ATRX genes in Chinese patients with pancreatic neuroendocrine tumors are correlated with poor overall survival[9][10], and progression-free survival[10].

BRAF V600E

Biological Impact

BRAF is a serine/threonine kinase that belongs to the RAF family. The protein plays an essential role in the regulation of mitogen-activated protein kinase (MAPK) cascade, which affects a range of cellular response including cell division, differentiation, and secretion[11][12]. Mutations in the BRAF gene, most commonly the V600 residue, are the most frequently identified oncogenic mutations in melanomas, and have been identified in several types of cancers including non-Hodgkin lymphoma, thyroid cancers, non-small cell lung carcinoma, hairy cell leukemia, glioma, gastrointestinal stromal tumor, and colorectal cancers (CRCs)[13][14]. Of note, in the vast majority of cases, BRAF mutations are non-overlapping with other oncogenic mutations (e.g., NRAS mutations, KIT mutations, etc.) found in melanoma. V600E has been determined to be an activating mutation, which results in enhanced BRAF kinase activity and constitutive activation of downstream MEK/ERK signaling cascade[15][16].

Therapeutic and prognostic relevance

Dabrafenib in combination with trametinib is FDA-approved for treating adult and pediatric patients with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative options. The combination therapy is also approved for BRAF V600E/K-mutated melanoma, advanced or metastatic NSCLC, advanced anaplastic thyroid, and metastatic CRC harboring BRAF V600E.

The NCCN guidelines recommend BRAF mutation testing for metastatic CRC and stated that anti-EGFR therapies should not be utilized for CRC patients with RAS or BRAF mutations[17]. The NCCN guidelines also recommend vemurafenib or dabrafenib for advanced thyroid carcinoma, vemurafenib for metastatic NSCLC, and vemurafenib with cobimetinib for WHO grade 1 gliomas and glioblastomas, dabrafenib with trametinib for biliary tract cancers, all with BRAF V600E mutation.

BRAF mutations (e.g., G469A and V600E) can cause resistance to EGFR TKIs in 1-2% of cases. This resistance was confirmed by ectopic expression of mutated BRAF in drug-sensitive EGFR-mutant cells and can be overcome with a

MEK inhibitor[18][19][18]. Targeting with BRAF V600E mutations have also been evaluated in endometrial adenocarcinoma and salivary duct carcinoma patients[20][21].

The NCCN guidelines for central nervous system cancers recommended selumetinib for pilocytic astrocytoma patients with BRAF fusion or BRAF V600E activating mutation. BRAF activating mutations have been determined as an inclusion criterion for the trials evaluating selumetinib efficacies in cancers (NCT01089101, NCT00888134, NCT00866177, and NCT00936221).

PIK3CA E545K

Biological Impact

The PIK3CA gene encodes the catalytic subunit (p110α) of phosphatidylinositol 3-kinase (PI3K) that plays a key role in the PI3K/AKT signaling pathway and is involved in the regulation of cellular functions such as proliferation, metabolism and protein synthesis, angiogenesis and apoptosis. PIK3CA has long been described as an oncogene and the PIK3CA gene amplification, deletion, and mutations have been reported in a wide range of cancers, including colorectal, breast, brain, liver, ovarian, stomach and lung cancers[22][23][24][25]. Mutations located in the exon 9 that encodes the PI3K helical (like E542K, E545K) and the exon 20 that encodes the catalytic/kinase domain (like H1047R, H1047L, H1047Y) have been shown to result in the constitutively activated mutant, which could enhance downstream signaling and oncogenic transformation in vitro and in vivo[23][26][27][28].

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

Therapeutic and prognostic relevance

In a Phase II trial, a patient with head and neck squamous cell carcinoma harboring PIK3CA E545K demonstrated a partial response when treated with the combination of temsirolimus, carboplatin, and paclitaxel[29].

In a preclinical study, cells harbored different activating PIK3CA mutations (H1047R, E545K, G1049R, Q546K, N345K, H1047L, E542K) were significantly more sensitive to PIK3 pathway inhibitors (dactolisib, MK2206, alpelisib), and MEK1/2 inhibitor trametinib, compared to wild-type[30]. According to ExteNET trial, PIK3CA activating mutation was not an appropriate predictive biomarker of response to neratinib in HER2-positive early breast cancer[31].

Alpelisib in combination with fulvestrant is FDA-approved for treating HR+, HER2-, PIK3CA-mutated, advanced breast cancer following progression on or after an endocrine-based regimen.

In NCCN guidelines for breast cancer, alpelisib plus fulvestrant has been recommended for HR-positive/HER2-negative breast cancer patients with PIK3CA activating mutation. Also, the NCCN guidelines for histiocytic neoplasms has recommended everolimus for patients with PIK3CA mutation.

PIK3CA mutation has been determined as an inclusion criterion for the trials evaluating everolimus, temsirolimus, and alpelisib efficacies in various types of solid tumors (NCT03805399, NCT03203525, NCT04251533).

Everolimus has shown clinical benefit when added to trastuzumab for patients with HER2-overexpressing metastatic breast cancer, particularly in those with PIK3CA mutations, PTEN loss, or hyperactive PI3K pathway[32]. The addition of everolimus to trastuzumab plus vinorelbine has also prolonged PFS in patients with trastuzumab-resistant and taxane-pretreated, HER2-positive, advanced breast cancer. However, adverse events should be taken into consideration[33]. Patients with PIK3CA mutations have shown a favorable response to mTOR inhibitors-containing monotherapy or in combination with doxorubicin and bevacizumab. Combining PI3K-targeted agents with endocrine therapy is suggested[34][35][36][37].

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Hyperactivation of the PI3K signaling pathway is associated with resistance to endocrine and HER2-targeting therapies in advanced breast cancer patients[38][39][40][41]. PIK3CA mutations also occur in 5% of EGFR-mutated lung cancers that developed resistance to EGFR TKI therapy[42][43].

In CRC patients, PIK3CA mutation and wild-type KRAS/BRAF showed fair responses to anti-EGFR therapies[44]. PIK3CA mutations are significantly correlated with better recurrence-free survival in unsorted breast cancer patients, according to two meta-analyses involving five studies[45][46][47]. However, in patients with advanced EGFR- or KRAS-mutant lung adenocarcinoma, a concurrent PIK3CA mutation is a poor prognostic factor[48].

SETD2 Q2207*

Biological Impact

SET Domain Containing 2 (SETD2) gene encodes a chromatin modulating enzyme that functions by site specific trimethylation of histone H3K36 and plays essential roles in gene regulation[49][50]and DNA mismatch repair. Inactivation of SETD2 leads to genetic instability, enrichment of nonsense and frameshift mutations and ultimately tumorigenesis[51][50][52][53]. Importantly, SETD2-mutant renal tumors failed to activate the p53 tumor suppressor, thus providing an alternative pathway for the inactivation of p53 that leads to defects in DNA damage repair[54]. Loss-of-function mutations of SETD2 has been reported in leukemia[55], renal carcinomas[52], and high-grade gliomas[56].

Q2207* mutation results in a premature truncation of the SETD2 protein at amino acid 2207 (UniProtKB). This mutation is predicted to lead to a loss of SETD2 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

A study of metastatic renal cell carcinoma patients (n=111) treated with sunitinib or sorafenib indicated that Low SETD2 expression was associated with poorer overall survival and progression-free survival[57]. In chronic lymphocytic leukemia, patients harboring SETD2 abnormalities along with wild-type of TP53 and ATM genes from clinical trials employing chemotherapy or chemoimmunotherapy had shorter progression-free survival and overall survival compared with cases harboring wild-type for all three genes[58].

Low expression of SETD2 was associated with large tumor size, advanced pT stage, poor overall survival and recurrence-free survival in non-metastatic clear-cell renal cell carcinoma[59].

SMAD4 D537fs

Biological Impact

The SMAD family member 4 (SMAD4) gene encodes a transcription factor that acts as a downstream effector in the TGF-β signaling pathway. Upon phosphorylated and activated by serine-threonine receptor kinase, Smad4 is the Co-Smad which recruits other activated R-Smad proteins to the Smad transcriptional complex and regulate TGF-β-targeted genes[60]. Smad4 has been identified as a haploinsufficient gene with one copy loss may lead to a weak protein expression and is insufficient to execute its original physiological function[61]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)[62][63][64][65]. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer[66], colorectal cancer (CRC)[64][67][68], and less frequently seen in other cancers such as lung adenocarcinoma[69], head and neck cancer[70][71], and cutaneous squamous cell carcinoma[72].

D537fs mutation results in a change in the amino acid sequence beginning at 537, likely to cause premature truncation of the functional SMAD4 protein (UniProtKB). This mutation is predicted to lead to a loss of SMAD4 protein function, despite not being characterized in the literature.

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Therapeutic and prognostic relevance

In Chinese patients with metastatic colorectal cancer, SMAD4 or NF1 mutations are suggested as a potential biomarker for poor prognosis to cetuximab-based therapy[73]. Preclinical data demonstrated that depletion of SMAD4 by shRNA knockdown increased clonogenic survival and cetuximab resistance in HPV-negative head and neck squamous cell carcinoma cells[74].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)[75][76]. CRC patients with normal SMAD4 diploidy exhibited three-fold higher benefit of 5-FU/mitomycin-based adjuvant therapy when compared with those with SMAD4 deletion[77].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis[78][79][80][81][82][83][84][85]. In cervical cancer patients, weak cytoplasmic SMAD4 expression and absent nuclear SMAD4 expression were shown to be significantly associated with poor disease-free and overall 5-year survival[86].

TP53 P98T

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[87]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[88].

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)[89].

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[90]. 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[91].

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[92][93][94]. 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)[95]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[96][97]. 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[98].

US FDA-APPROVED DRUG(S)

Alpelisib (PIQRAY)

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models. Alpelisib is developed and marketed by Novartis under the trade name PIQRAY.

- FDA Approval Summary of Alpelisib (PIQRAY)

SOLAR-1[99] NCT02437318	**Hr-positive, her2-negative breast cancer** (Approved on 2019/05/24)
	PIK3CA mutation
	Alpelisib plus fulvestrant vs. Placebo plus fulvestrant [PFS(M): 11 vs. 5.7]

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[100] 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[101] NCT01689519	**Melanoma** (Approved on 2015/11/10)
	BRAF V600E/K
	Cobimetinib + vemurafenib vs. Placebo + vemurafenib [PFS(M): 12.3 vs. 7.2]

Dabrafenib (TAFINLAR)

Dabrafenib is a reversible ATP-competitive kinase inhibitor of the enzyme B-Raf, which plays a role in the regulation of cell growth via the ERK signaling cascade. Dabrafenib is developed and marketed by GlaxoSmithKline under the trade name TAFINLAR.

- FDA Approval Summary of Dabrafenib (TAFINLAR)

BRF117019, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060, NCT02124772	**Cancer** (Approved on 2022/06/22)
	BRAF V600E
	Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0]

BRF117019[102] NCT02034110	**Thyroid gland anaplastic carcinoma** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[103] NCT01336634	**Non-small cell lung cancer** (Approved on 2017/06/22)
	BRAF V600E
	Dabrafenib + trametinib vs. Dabrafenib [ORR(%): 64.0 vs. 52.0]
COMBI-d[104] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E
	Dabrafenib + trametinib vs. Dabrafenib + placebo [PFS(M): 9.8 vs. 8.8]
COMBI-v[105] NCT01597908	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E
	Dabrafenib + trametinib vs. Vemurafenib [OS(M): 11.4 vs. 7.3]
BREAK-3[106] NCT01227889	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E
	Dabrafenib vs. Dacarbazine [PFS(M): 5.1 vs. 2.7]

Encorafenib (BRAFTOVI)

Encorafenib is an oral kinase inhibitor that targets BRAF. Encorafenib is developed and marketed by Array BioPharma under the trade name BRAFTOVI.

- FDA Approval Summary of Encorafenib (BRAFTOVI)

BEACON CRC[107] NCT02928224	**Colorectal cancer** (Approved on 2020/04/08)
	BRAF V600E
	Encorafenib in combination with cetuximab vs. Irinotecan or folfiri with cetuximab [OS(M): 8.4 vs. 5.4]
COLUMBUS[100] NCT01909453	**Melanoma** (Approved on 2018/06/27)
	BRAF V600E/K
	Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3]

Everolimus (AFINITOR)

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

- FDA Approval Summary of Everolimus (AFINITOR)

RADIANT-4[108] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[109] NCT00863655	**Breast cancer** (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]

EXIST-2 NCT00790400	**Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma** (Approved on 2012/04/26)
	-
	Everolimus vs. Placebo [ORR(%): 41.8 vs. 0]
RADIANT-3[110] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[111] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[112] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

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)

OlympiA NCT02032823	**Her2-negative high-risk early breast cancer** (Approved on 2022/03/11)
	HER2-/gBRCA mutation
	Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound[113] NCT02987543	**Prostate cancer** (Approved on 2020/05/19)
	HRR genes mutation
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1[114] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[115] NCT02184195	**Pancreatic adenocarcinoma** (Approved on 2019/12/27)
	gBRCA mutation
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1[116] NCT01844986	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19)
	gBRCA mutation or sBRCA mutation
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD[117] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[118] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA mutation
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19[119] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

ACT Onco® + Report

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)
	-
	Selumetinib [ORR(%): 66.0]

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[120] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	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)

[121] 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, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060, NCT02124772	**Cancer** (Approved on 2022/06/22)
	BRAF V600E
	Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0]
BRF117019[102] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]

BRF113928[122] 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[123] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[124] NCT01245062	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

Vemurafenib (ZELBORAF)

Vemurafenib is an anti-cancer inhibitor which targets B-Raf. Vemurafenib is developed and marketed by Genentech under the trade name ZELBORAF.

- FDA Approval Summary of Vemurafenib (ZELBORAF)

VE-BASKET [125] NCT01524978	**Erdheim-chester disease** (Approved on 2017/11/06)
	BRAF V600X
	Vemurafenib [ORR(%): 54.5]
BRIM 3[126] NCT01006980	**Melanoma** (Approved on 2011/08/17)
	BRAF V600E
	Vemurafenib vs. Dacarbazine [PFS(M): 5.3 vs. 1.6, OS(M): 13.6 vs. 10.3]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

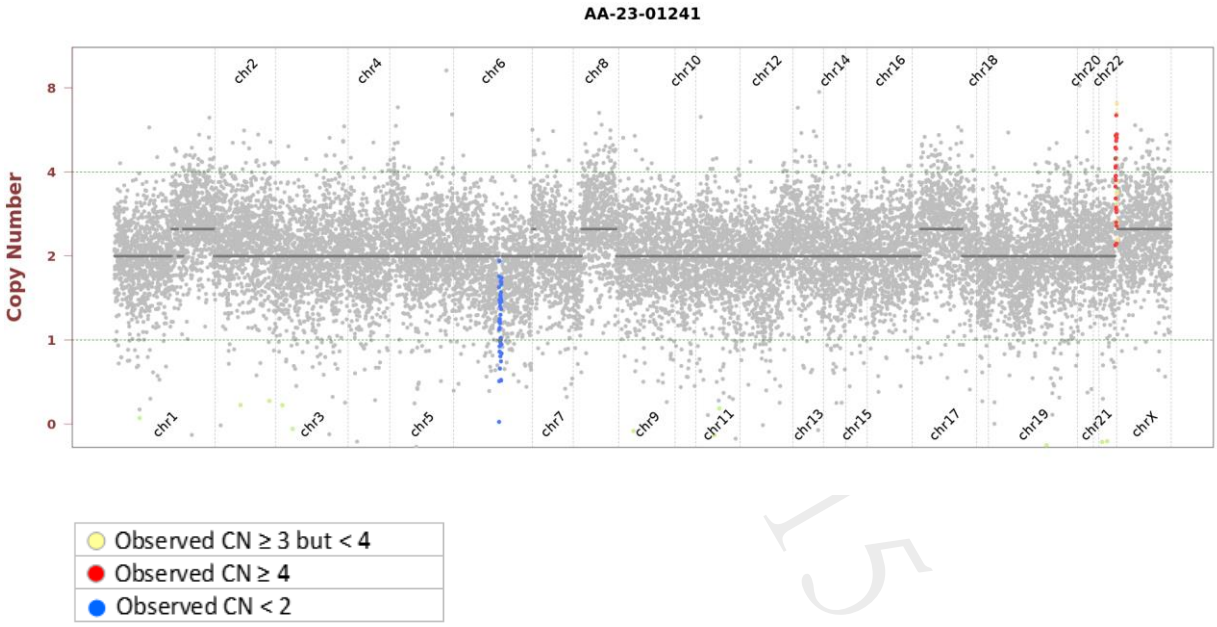
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ATRX	S25*	2	c.74C>G	NM_000489	-	20.1%	1478
BRAF	V600E	15	c.1799T>A	NM_004333	COSM476	20.8%	1987
PIK3CA	E545K	10	c.1633G>A	NM_006218	COSM763	28.3%	1316
SETD2	Q2207*	15	c.6619C>T	NM_014159	-	16.0%	940
SMAD4	D537fs	12	c.1610_1633delinsCTCCTAGACGAACATGCCGT	NM_005359	-	25.4%	350
TP53	P98T	4	c.292C>A	NM_000546	COSM6907550	33.8%	157

- Copy Number Alterations

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



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OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
BRCA2	C315S	10	c.943T>A	NM_000059	-	61.6%	331
CALR	D335N	8	c.1003G>A	NM_004343	COSM3528934	44.8%	1342
ERBB2	Splice region	-	c.2872+4C>T	NM_004448	-	45.1%	861
FOXP1	Q340H	13	c.1020A>T	NM_032682	-	22.9%	730
HIF1A	T163I	5	c.488C>T	NM_001530	-	44.3%	817
KMT2D	E292K	7	c.874G>A	NM_003482	COSM7157648	15.7%	612
LRP1B	Q3140E	59	c.9418C>G	NM_018557	-	48.0%	732
MET	Splice region	-	c.2637+6A>G	NM_001127500	-	46.4%	1822
MUC16	L3252V	3	c.9754C>G	NM_024690	-	52.0%	914
NBN	E584K	11	c.1750G>A	NM_002485	-	8.1%	1981
RAD51D	A293V	9	c.878C>T	NM_002878	COSM6961681	39.6%	2141
RXRA	I345M	7	c.1035C>G	NM_002957	COSM7644738	23.2%	125

Note:

- This table enlists variants detected by the panel other than those with clinical relevance (reported in Testing Result section). The clinical impact of a genetic variant is determined according to ACT Genomics in-house clinical knowledge database. A negative result does not necessarily indicate absence of biological effect on the tumor. Some variants listed here may possibly have preclinical data or may show potential clinical relevance in the future.

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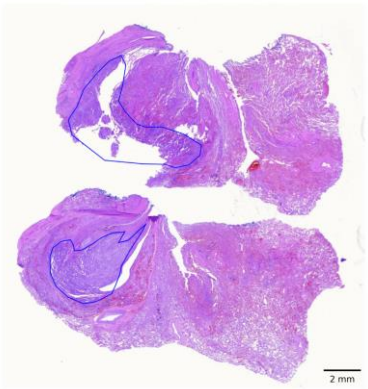
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Feb 14, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11205784C
- Collection site: Lung
- Examined by: Dr. Yun-An Chen
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 10%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 35%
  3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
  4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
  5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 924x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 210

LIMITATIONS

1. This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject to validation by Sanger or other technologies.
2. The possibility cannot be excluded that certain pathogenic variants detected by other sequencing tools may not be reported in the test because of technical limitation of bioinformatics algorithm or the NGS sequencing platform, e.g. low coverage.
3. This test has been designed to detect fusions in 13 genes sequenced. Therefore, fusion in genes not covered by this test would not be reported. For novel fusions detected in this test, Sanger sequencing confirmation is recommended if residue specimen is available.

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NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

Extracted genomic DNA was amplified using primers targeting coding exons of analyzed genes and subjected to library construction. Barcoded libraries were subsequently conjugated with sequencing beads by emulsion PCR and enriched using Ion Chef system. Sequencing was performed according to Ion Proton or Ion S5 sequencer protocol (Thermo Fisher Scientific).

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite. Coverage depth was calculated using Torrent Coverage Analysis plug-in. Single nucleotide variants (SNVs) and short insertions/deletions (InDels) were identified using the Torrent Variant Caller plug-in. VEP (Variant Effect Predictor) was used to annotate every variant using databases from Clinvar, COSMIC and Genome Aggregation database. Variants with coverage ≥ 20, allele frequency ≥ 5% and actionable variants with allele frequency ≥ 2% were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at 100x ≥ 85% with a mean coverage ≥ 500x.

Variants reported in Genome Aggregation database with > 1% minor allele frequency (MAF) were considered as polymorphisms. ACT Genomics in-house database was used to determine technical errors. Clinically actionable and biologically significant variants were determined based on the published medical literature.

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

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

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

RNA test

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

The fusion analysis pipeline aligned sequenced reads to the human reference genome, identified regions that map to noncontiguous regions of the genome, applied filters to exclude probable false-positive events and, annotated previously characterized fusion events according to Quiver Gene Fusion Database, a curated database owned and maintained by ArcherDX. In general, samples with detectable fusions need to meet the following criteria: (1) Number of unique start sites (SS) for the GSP2 ≥ 3; (2) Number of supporting reads spanning the fusion junction ≥ 5; (3) Percentage of supporting reads spanning the fusion junction ≥ 10%; (4) Fusions annotated in Quiver Gene Fusion Database.

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DATABASE USED

- Reference genome: Human genome sequence hg19
- COSMIC v.92
- Genome Aggregation database r2.1.1
- ClinVar (version 20210404)
- ACT Genomics in-house database
- Quiver Gene Fusion Database version 5.1.18

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

Yun Yu Chen

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

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GENE LIST

SNV & CNV

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

*Analysis of copy number alterations NOT available.

FUSION

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

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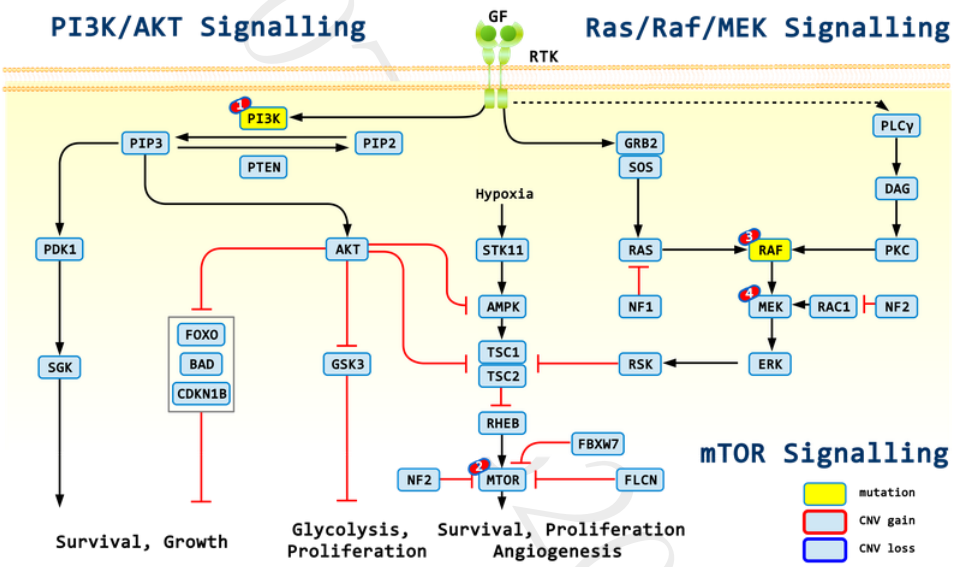
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Not Applicable.

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Alpelisib; 2: Everolimus, Temsirolimus; 3: Dabrafenib, Vemurafenib, Encorafenib; 4: Binimetinib, Cobimetinib, Trametinib, Selumetinib

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DISCLAIMER

法律聲明

本檢驗報告僅提供專業醫療參考，結果需經專業醫師解釋及判讀。基因突變資訊非必具備藥物或治療有效性指標，反之亦然。本檢驗報告提供之用藥指引不聲明或保證其臨床有效性，反之亦然。本基因檢測方法係由本公司研究開發，已經過有效性測試。
本檢驗報告非經本公司許可，不得私自變造、塗改，或以任何方式作為廣告及其他宣傳之用途。
本公司於提供檢驗報告後，即已完成本次契約義務，後續之報告解釋、判讀及用藥、治療，應自行尋求相關專業醫師協助，若需將報告移件其他醫師，本人應取得該醫師同意並填寫移件申請書，主動告知行動基因，行動基因僅能配合該醫師意願與時間提供醫師解說。

醫療決策需由醫師決定

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

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

責任

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