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PATIENT AND SAMPLE INFORMATION

PATIENT

Name: 林碧雲
Gender: Female
Date of Birth: Apr 20, 1949
Patient ID: 29103966
Diagnosis: Neuroendocrine carcinoma

SPECIMEN

Type: FFPE tissue
Date received: Nov 25, 2021
Collection site: Liver
Specimen ID: S11062167A
Lab ID: AA-21-05770
D/ID: NA

ORDERING PHYSICIAN

Name: 陳明晃醫師
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VARIANT(S) WITH CLINICAL RELEVANCE

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

SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
APC	Q1517*	1567	37.8%	COSM6842412
BLM	Splice donor	842	91.1%	-
BRAF	V600E	2118	59.4%	COSM476
FBXW7	R505C	2160	43.0%	COSM22975
NBN	R714*	1226	56.5%	COSM6982725
TP53	R273P	1136	84.8%	COSM43896

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 **84%** tumor purity.

Amplification (Copy number ≥ 8)

Chr	Gene	Copy Number
ND	ND	ND

Homozygous deletion (Copy number=0)

Chr	Gene
ND	ND

Heterozygous deletion (Copy number=1)

Chr	Gene
chr5	RAD50
chr16	PALB2

ND, Not Detected

TUMOR MUTATIONAL BURDEN (TMB)

1.9 muts/Mb

Muts/Mb, mutations per megabase

Note:

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

MICROSATELLITE INSTABILITY (MSI)

Microsatellite stable (MSS)

Variant Analysis:

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Sign Off

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3A		
BRAF V600E	Cobimetinib, Binimetinib, Encorafenib, Trametinib, Dabrafenib, Vemurafenib	sensitive
BRAF V600E	Cetuximab, Panitumumab	resistant
Level 3B		
BRAF V600E	Selumetinib	sensitive
NBN R714*	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
BLM Splice donor	Niraparib, Olaparib, Talazoparib	sensitive
PALB2 Heterozygous deletion	Niraparib, Rucaparib	sensitive
Level 4		
FBXW7 R505C	Everolimus, Temsirolimus	sensitive
PALB2 Heterozygous deletion	Olaparib	sensitive
RAD50 Heterozygous deletion	Olaparib, Rucaparib	sensitive
FBXW7 R505C	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

IMMUNE CHECKPOINT INHIBITORS (ICI) THERAPIES

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

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

MMR, mismatch repair; ND, not detected

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

CHEMOTHERAPIES

Therapies	Genomic Alterations	Effect	Gene / Variant Level Evidence	Cancer Type
Platinum-based regimens	NBN R714*	sensitive	Clinical	Ovarian cancer

HORMONAL THERAPIES

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

OTHERS

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Clinical Interpretation	Level of Evidence*
UGT1A1	rs4148323	AG	Irinotecan-based regimens	Patients with the AG genotype and cancer who are treated with irinotecan-based regimens may have an increased risk of diarrhea and neutropenia as compared to patients with the GG genotype, or a decreased risk of diarrhea and neutropenia compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk of diarrhea and neutropenia.	Level 1B

* Level of evidence was defined by PharmGKB (<https://www.pharmgkb.org/page/clinAnnLevels>)

Level 1A: Clinical annotations describe variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation.

Level 1B: Clinical annotations describe variant-drug combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label.

Level 2A: Variants in Level 2A clinical annotations are found in PharmGKB's Tier 1 Very Important Pharmacogenes (VIPs). These variants are in known pharmacogenes, implying causation of drug phenotype is more likely.

Note:

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

VARIANT INTERPRETATION

APC Q1517*

Biological Impact

APC (adenomatous polyposis coli) gene encodes a negative regulator of the WNT/ β -catenin signaling pathway. It binds to β -catenin, leading to its degradation and subsequently inhibits transcriptional activation^[1]. APC is also associated with cell migration and adhesion, apoptosis, and DNA repair^{[2][3]}. APC mutations are commonly observed in colorectal cancer and are also reported in lung, breast, prostate, uterine, skin, bladder, stomach and head and neck cancers (cBioPortal, MSKCC, April 2015).

Q1517* mutation results in a premature truncation of the APC protein at amino acid 1517 (UniProtKB). This mutation is predicted to lead to a loss of APC function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

A study of colorectal cancer patients (n= 468) indicated that MSS tumors without any APC mutation carry a worse prognosis than single APC mutation tumors. However, tumors with two APC, KRAS, and TP53 mutations confer the poorest survival among all the subgroups examined^[4].

BLM Splice donor

Biological Impact

The BLM (Bloom syndrome RecQ like helicase) gene encodes the BLM RecQ helicase protein, one of the five members of the human RECQ helicase family^[5], whose germline loss has been associated with the Bloom syndrome^[6]. BLM 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^[7].

BLM c.98+1G>A is a variant located at the splice donor region, which may result in the exon skipping.

Therapeutic and prognostic relevance

BLM loss of function mutations or homozygous deletion have been selected as an inclusion criteria for the trial examining olaparib in ovarian cancer^[8] and metastatic urothelial cancer (NCT03448718), niraparib in solid tumors (except prostate cancer) (NCT03207347), and talazoparib in unresectable or metastatic melanoma (NCT04187833).

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^{[9][10]}. 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)^{[11][12]}. 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^{[13][14]}.

Therapeutic and prognostic relevance

In melanoma, several BRAF inhibitors like vemurafenib, dabrafenib, and encorafenib combined with binimetinib are approved by the U.S. FDA for the treatment of patients with V600 E/K-mutant advanced melanoma^{[15][16][17][18]}. Notably, to prevent or delay the resistance to BRAF inhibitors which has been occurred in nearly all patients, combined regimens containing BRAF inhibitors and MEK inhibitors such as trametinib, cobimetinib, and binimetinib were investigated in the patients with BRAF V600-mutated melanoma. Compared with BRAF inhibitor monotherapy, combined therapy significantly prolonged the progression-free survival (PFS) and overall survival (OS)^{[19][20][21][18][22]}. Therefore, in 2018 April, the U.S. FDA granted approval for dabrafenib plus trametinib for adjuvant treatment of patients with BRAF V600E/K-mutated melanoma. Furthermore, there are ongoing early clinical studies of triple-combined therapy containing BRAF and MEK inhibition combined with immune checkpoint blockades such as dabrafenib plus trametinib and pembrolizumab^[23] or vemurafenib plus cobimetinib and atezolizumab^[24] in patients with BRAF-mutated melanoma. Long lasting anti-tumor activity was observed in a subset of patients.

Unlike melanoma, BRAF inhibitor monotherapy has historically shown disappointing results in patients with BRAF-mutated CRC^{[25][26]}. However, clinical trials evaluating the combinations of BRAF, EGFR and/or MEK inhibitors have revealed promising results in BRAF-mutated CRCs^{[27][28][29][30]}. The BEACON CRC trial (NCT02928224) demonstrated that both triplet-therapy (encorafenib + cetuximab + binimetinib) and doublet-therapy (encorafenib + cetuximab) had better overall survival and higher response rate than standard therapy (cetuximab + irinotecan or FOLFIRI) in patients with BRAF V600E mutated mCRC^[31]. However, the addition of binimetinib did not increase the overall efficacy and was associated with additional MEK inhibitor-related adverse events. Based on these results, encorafenib plus cetuximab had been approved by U.S. FDA for BRAF V600E-mutated mCRC^[32].

Meanwhile, most studies demonstrated that patients harboring BRAF V600E mutation might not benefit from anti-EGFR-containing therapies. The National Comprehensive Cancer Network (NCCN) guidelines recommended BRAF mutation testing for metastatic CRC and stated that anti-EGFR therapies should not be utilized for CRC patients with RAS or BRAF mutations^[33]. Notably, there is currently no evidence exists that these mutations significantly impact treatment outcomes for the approved anti-angiogenic agents such as bevacizumab, aflibercept, ramucirumab, and regorafenib.

In non-small cell lung carcinoma (NSCLC), BRAF V600E was demonstrated to predict clinical response to BRAF-inhibitors such as vemurafenib^{[34][35][36]} or dabrafenib^[37], as well as combined BRAF-MEK inhibition with dabrafenib and trametinib^{[38][39][40]}. In 2017, the U.S. Food and Drug Administration (FDA) approved the combination of

dabrafenib and trametinib for patients with advanced or metastatic NSCLC harboring BRAF V600E mutations as detected by an FDA-approved test^[41], and BRAF testing is recommended for all patients with advanced adenocarcinoma in clinical practice^[42]. The NCCN guidelines recommended vemurafenib as first-line treatment for metastatic NSCLC with BRAF V600E mutation if the combination of dabrafenib and trametinib is not tolerated. It should be noted that BRAF mutations are usually found in tumors wild type for EGFR, ALK, and other driver mutations. BRAF mutations (e.g., G469A and V600E) were suggested as one of the mechanisms of resistance to EGFR tyrosine kinases inhibitors (TKIs) that has been reported in 1-2% of cases^{[43][44]}. The association between BRAF mutations and acquired resistance to EGFR TKIs was confirmed by ectopic expression of mutated BRAF in drug-sensitive EGFR-mutant cells, and the phenomenon was overcome by the addition of a MEK inhibitor^[43].

In papillary thyroid cancers (PTC), accumulating evidence showed a strong association of BRAF mutation with lymph node metastasis, advanced stages of the disease, and disease recurrence^{[45][46][47][48]}. And in 2018 U.S. FDA approved dabrafenib plus trametinib for the treatment of patients with advanced anaplastic thyroid cancer with BRAF V600E mutation and with no satisfactory locoregional treatment options.

In brain tumors, the VE-BASKET study also indicated that vemurafenib showed durable antitumor activity in some patients with BRAF V600-mutant gliomas, although efficacy seemed to vary qualitatively by histologic subtype^[49]. Besides, there are cases reports of patients whose tumor carried BRAF V600E showed a complete or nearly complete response to dabrafenib monotherapy^{[50][51]} and vemurafenib monotherapy^{[52][53]}. Furthermore, sustained response to dabrafenib and trametinib combination therapy was observed in patients with BRAF V600E mutated high-grade gliomas^{[54][55]}.

In NCCN guidelines for hepatobiliary cancers (version 5, 2021), dabrafenib combined with trametinib treatment has been suggested for patients with BRAF V600E mutated biliary tract cancers^{[56][57]}. On the other hand, it has also been evaluated in patients with BRAF V600E mutated endometrial adenocarcinoma^[58] and salivary duct carcinoma^[59]. BRAF activating mutations have been determined as an inclusion criterion for the trials evaluating selumetinib efficacies in cancers (NCT01089101, NCT00888134, NCT00866177, and NCT00936221).

FBXW7 R505C

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^{[60][61]}, c-Jun^[62], cyclin E^[63], Notch family members^{[64][65]}, Aurora-A^[66], mTOR^[67], KLF5^[68], and MCL-1^[69]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation^[70]. 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^{[68][69][71]}.

R505C mutation is located in the WD40 repeat region of the FBXW7 protein (UniProtKB). This is a loss-of-function mutation that has been reported to disrupt FBXW7 binding to its substrates, such as MYC and glucocorticoid receptor α ^{[72][73]}.

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)^{[74][75]}. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor^[67].

Preclinical studies suggested that mutations or loss of FBXW7 were associated with regorafenib and oxaliplatin resistance in CRC cell lines^{[76][77]} and gefitinib resistance in lung cancer cells^{[78][79]}.

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^{[80][78]}.

Results of an in vitro study indicated that FBXW7 R505C mutation was associated with regorafenib resistance in colorectal cancer (CRC)^[76].

NBN R714*

Biological Impact

The NBN gene encodes a component of the MRE11-RAD50-NBN (MRN) complex, which involves in DNA double-strand break sensing and repair^[81]. NBN mutation is related to Nijmegen breakage syndrome, increased cancer incidence and ionizing radiation sensitivity^{[81][82]}. NBN mutations have been found in various cancers, including cholangiocarcinoma, hepatocellular carcinoma^[83], prostate cancer^[84], leukemia, lymphoma^[85], and triple-negative breast cancer^[86].

R714* mutation results in a premature truncation of the NBN protein at amino acid 714 (UniProtKB). This mutation is predicted to lead to a loss of NBN function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

NBN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer^[8]; the trials evaluating rucaparib efficacy in ovarian cancer^[87] or prostate cancer^[88]; the trials evaluating talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556), and the trials evaluating niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate) cancer (NCT03207347).

Germline and somatic mutations in homologous recombination genes, including NBN, have been suggested to be prognostic biomarkers for platinum-based treatment response and superior survival in patients with ovarian, fallopian tube, peritoneal carcinomas and pancreatic cancer^{[89][90]}.

TP53 R273P

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[91]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[92].

TP53 R273P is a missense mutation located in the DNA-binding domain of the p53 protein (UniProtKB). It was demonstrated as a loss-of-function mutant with attenuated p21 response when overexpressed in vitro. Besides, it exerts dominant-negative effect when expressed in p53-proficient cells^[93].

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)^[94].

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^[95]. 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^[96].

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^{[97][98][99]}. 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)^[100]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[101][102]}. 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^[103].

PALB2 Heterozygous deletion

Biological Impact

The partner and localizer of BRCA2 (PALB2) gene encodes a protein that plays a critical role in homologous recombination repair (HRR) through its ability to interact with BRCA2 in nuclear foci, promoting its localization and stability in key nuclear structures^[104]. The Fanconi anemia complementation group (FANC) which includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCI (also called BRIP1), FANCL, FANCM and FANCN (also called PALB2) are involved in the repair of DNA double-strand breaks (DSBs) by homologous recombination (HR)^{[105][106][107]}. PALB2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function^[108]. Biallelic germline loss-of-function mutations in PALB2 cause Fanconi anemia, whereas monoallelic loss-of-function mutations are associated with an increased risk of breast cancer and pancreatic cancer^[109]. Fanconi Anemia is an autosomal recessive disease characterized by hematological abnormalities, bone marrow failure, limb deformities, skin hyperpigmentation, and susceptibility to hematologic and solid malignancies, such as acute myeloid leukemia and head and neck carcinoma^{[110][111]}.

Therapeutic and prognostic relevance

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate^[112].

PALB2 loss of function mutation has been determined as an inclusion criterion for the trial evaluating rucaparib efficacy in ovarian cancer^[87] or prostate cancer^[88]; talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556); niraparib efficacy in pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), or any malignancy (except prostate) cancer (NCT03207347).

A case report demonstrated an exceptional response to mitomycin C and cisplatin treatment in a gemcitabine-resistant pancreatic cancer patient with biallelic inactivation of PALB2^[113].

RAD50 Heterozygous deletion

Biological Impact

The RAD50 gene encodes a highly-conserved DNA double-strand break (DSB) repair factor. It forms MRN complex with NBS1 and MRE11 protein and is involved in sensing and early processing of DSB, cell cycle checkpoints, DNA recombination and maintenance of telomeres^{[114][115]}. Mutations in the components of the MRN complex could increase susceptibility to familial breast cancer^{[116][117]}, gastric cancer^[118] colorectal cancer^[119], and urothelial cancer^[120]. RAD50 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^[121]. Besides, RAD50 deletion was also suggested as a marker of BRCAness, a phenotype shared between non-BRCA1/2-mutated ovarian cancers and BRCA1/2-mutated ovarian cancers^[122].

Therapeutic and prognostic relevance

Preclinical data showed that knockdown of the RAD50 gene in ovarian cancer cell lines was significantly associated with better responses to two PARP inhibitors, olaparib and rucaparib^[122].

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^[18] 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^[123] 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^[124] NCT02034110	Anaplastic thyroid cancer (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib
	[ORR(%): 61.0]
BRF113928^[38] 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^[125] NCT01584648	Melanoma (Approved on 2014/01/10)
	BRAF V600E
	Dabrafenib + trametinib vs. Dabrafenib + placebo [PFS(M): 9.8 vs. 8.8]
COMBI-v^[126] NCT01597908	Melanoma (Approved on 2014/01/10)
	BRAF V600E
	Dabrafenib + trametinib vs. Vemurafenib [OS(M): 11.4 vs. 7.3]
BREAK-3^[127] 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^[32] 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^[18] 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^[128] NCT01524783	Lung or gastrointestinal neuroendocrine tumor (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]

BOLERO-2^[129] NCT00863655	Breast cancer (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
RADIANT-3^[130] NCT00510068	Pancreatic neuroendocrine tumor (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1^[131] NCT00789828	Subependymal giant cell astrocytoma (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1^[132] 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^[133] 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^[134] 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^[134] 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]

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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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 ^[112] 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 ^[135] 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 ^[136] 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 ^[137] 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 ^[138] 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 ^[139] NCT01874353	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	gBRCA+
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]

Study19^[140] 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^[141] 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^[87] 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^[142] NCT01482715, NCT01891344	Ovarian cancer (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation
	Rucaparib [ORR(%): 54.0]

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]

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^[143] NCT01945775	Breast cancer (Approved on 2018/10/16)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

Temsirolimus (TORISEL)

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

FDA Approval Summary of Temsirolimus (TORISEL)

[144] 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 ^[124] NCT02034110	Anaplastic thyroid cancer (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928 ^[37] 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 ^[145] NCT01584648	Melanoma (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC ^[146] 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 ^[147] NCT01524978	Erdheim-chester disease (Approved on 2017/11/06)
	BRAF V600
	Vemurafenib [ORR(%): 54.5]
BRIM 3 ^[15] 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

ONGOING CLINICAL TRIALS

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

No trial has been found.

DETAILED TEST RESULTS

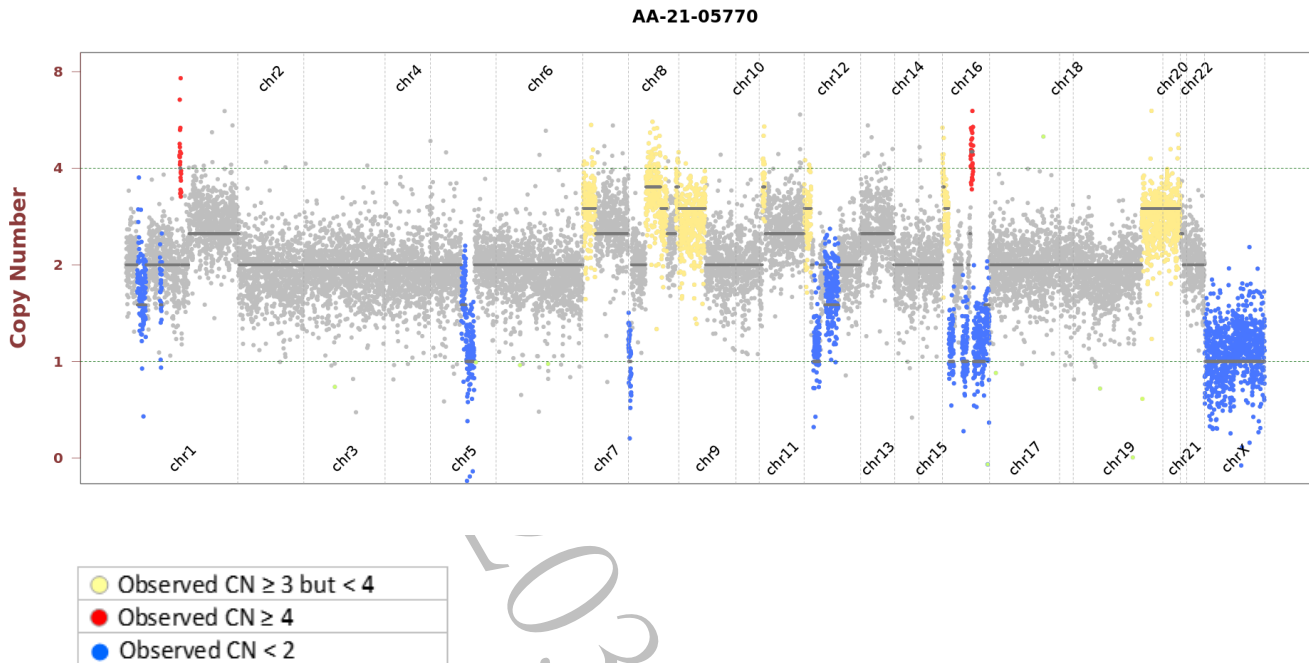
SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Chr	Exon	Accession Number	cDNA Change	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
ABL1	9	8	NM_005157	c.1301C>T	T434I	931	41.0%	-
ADAMTS9	3	20	NM_182920	c.2901G>C	R967S	1930	50.4%	-
APC	5	16	NM_000038	c.4549C>T	Q1517*	1567	37.8%	COSM6842412
AXIN1	16	6	NM_003502	c.1540G>A	G514R	964	74.4%	COSM143873
BLM	15	-	NM_000057	c.98+1G>A	Splice donor	842	91.1%	-
BRAF	7	15	NM_004333	c.1799T>A	V600E	2118	59.4%	COSM476
FAT1	4	3	NM_005245	c.3423G>C	E1141D	1696	50.1%	COSM6476272
FBXW7	4	10	NM_033632	c.1513C>T	R505C	2160	43.0%	COSM22975
FGFR3	4	-	NM_000142	c.615+6C>A	Splice region	313	55.3%	-
IRS2	13	1	NM_003749	c.3660G>T	W1220C	242	69.8%	-
JAK1	1	-	NM_002227	c.1900-6C>T	Splice region	1375	89.2%	-
KDR	4	30	NM_002253	c.3998G>T	G1333V	1518	45.5%	-
NBN	8	14	NM_002485	c.2140C>T	R714*	1226	56.5%	COSM6982725
PIK3CA	3	21	NM_006218	c.3073A>G	T1025A	902	42.0%	COSM771
PRKN	6	10	NM_004562	c.1096C>T	R366W	1500	40.0%	-
PSMB8	6	4	NM_148919	c.433C>T	R145C	825	49.5%	-
TP53	17	8	NM_000546	c.818G>C	R273P	1136	84.8%	COSM43896

Mutations with clinical relevance are highlighted in red.

COPY NUMBER VARIANTS (CNVs)

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



HOTSPOT GENOTYPES

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

Gene	Variant	Genotype Detected
<i>BRAF</i>	V600X	V600E
<i>EGFR</i>	A763_Y764insFQEA, E709K, E709_T710delinsD, Exon 19 deletion, Exon 19 insertion, Exon 20 insertion, G719A/C/D/S, L747P, L833V, L858R, L861Q/R, S768I, T790M	Not detected
<i>IDH2</i>	R140Q, R172G/K/M/S	Not detected
<i>KIT</i>	A502_Y503dup, D419del, D579del, D816F/V/Y, D820A/E/G/Y, E554_I571del, E554_K558del, E554_V559del, Exon 11 mutation, F522C, H697Y, I563_L576del, I653T, K550_W557del, K558N, K558_E562del, K558_V559del, K558delinsNP, K642E, M552_W557del, N505I, N564_Y578del, N822H/I/K/Y, P551_M552del, P573_D579del, P577_D579del, P577_W582delinsPYD, P838L, Q556_K558del, T417_D419delinsI, T417_D419delinsRG, T574_Q575insTQLPYD, V530I, V555_L576del, V555_V559del, V559A/C/D/G, V559_V560del, V559del, V560D/G, V560del, V569_L576del, V654A, W557G/R, W557_K558del, Y553N, Y553_K558del, Y570H, Y578C	Not detected
<i>KRAS</i>	A146T/V/P, G12X, G13X, Q61X	Not detected
<i>MET</i>	D1028H/N/Y	Not detected
<i>NRAS</i>	G12X, G13X, Q61X	Not detected
<i>PDGFRA</i>	A633T, C450_K451insMIEWMI, C456_N468del, C456_R481del, D568N, D842I/V, D842_H845del, D842_M844del, D846Y, E311_K312del, G853D, H650Q, H845Y, H845_N848delinsP, I843del, N659K/R/S, N848K, P577S, Q579R, R560_V561insER, R748G, R841K, S566_E571delinsR, S584L, V469A, V536E, V544_L545insAVLVLLVIVISLI, V561A/D, V561_I562insER, V658A, W559_R560del, Y375_K455del, Y555C, Y849C/S	Not detected
<i>PIK3CA</i>	C420R, E542K/V, E545A/D/G/K, H1047X, Q546E/R	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
<i>CDK4</i>	2
<i>EGFR</i>	3
<i>ERBB2</i>	2
<i>MET</i>	3

Copy number ≥ 8 is considered amplification

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	2
MDM2	2
MDM4	3

Copy number ≥ 8 is considered amplification

TEST DETAILS

ABOUT ACTOnco®+

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

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

DATABASE USED

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

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

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

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

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

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

The copy number variations (CNVs) were predicted as described below:

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

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

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

STANDARD OPERATING PROCEDURES (SOPS)

Standard operating procedures (SOPs) are shown below:

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

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

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

LIMITATIONS

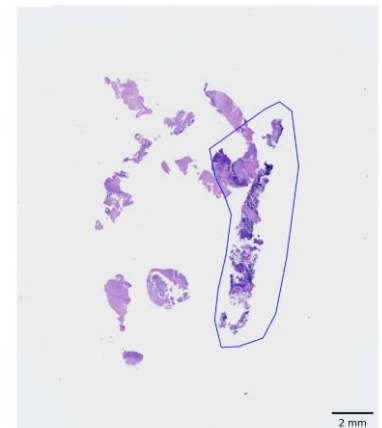
This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject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

NOTES

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

PATHOLOGY EVALUATION

- H&E-stained section No.: S11062167A
- Collection site: Liver
- Examined by: Dr. Yeh-Han Wang
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 40%
The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 70%
The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 40%
The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 10%
Additional comment: NA
- Manual macrodissection: Performed on the highlighted region



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

SPECIMEN PHOTO(S)



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

RUN QC

- Panel: ACTOnco®+
- Mean Depth: 1062x
- Target Base Coverage at 100x: 95%

ACTOnco® + GENE LIST

ABCB1*	AURKB	CBL	CDKN2B	E2F3	FAT1	GRIN2A	JAK2	MED12	NOTCH4	PMS1	RAD51D	SLCO1B3*	TNFRSF14
ABCC2*	AXIN1	CCNA1	CDKN2C	EGFR	FBXW7	GSK3B	JAK3	MEF2B	NPM1	PMS2	RAD52	SMAD2	TNFSF11
ABCG2*	AXIN2	CCNA2	CEBPA*	EP300	FCGR2B	GSTP1*	JUN*	MEN1	NQO1*	POLB	RAD54L	SMAD3	TOP1
ABL1	AXL	CCNB1	CHEK1	EPCAM	FGF1*	GSTT1*	KAT6A	MET	NRAS	POLD1	RAF1	SMAD4	TP53
ABL2	B2M	CCNB2	CHEK2	EPHA2	FGF10	HGF	KDM5A	MITF	NSD1	POLE	RARA	SMARCA4	TPMT*
ADAMTS1	BAP1	CCNB3	CIC	EPHA3	FGF14	HIF1A	KDM5C	MLH1	NTRK1	PPARG	RB1	SMARCB1	TSC1
ADAMTS13	BARD1	CCND1	CREBBP	EPHA5	FGF19*	HIST1H1C*	KDM6A	MPL	NTRK2	PPP2R1A	RBM10	SMO	TSC2
ADAMTS15	BCL10	CCND2	CRKL	EPHA7	FGF23	HIST1H1E*	KDR	MRE11	NTRK3	PRDM1	RECQL4	SOC1*	TSHR
ADAMTS16	BCL2*	CCND3	CRLF2	EPHB1	FGF3	HNF1A	KEAP1	MSH2	PAK3	PRKAR1A	REL	SOX2*	TYMS
ADAMTS18	BCL2L1	CCNE1	CSF1R	ERBB2	FGF4*	HR	KIT	MSH6	PALB2	PRKCA	RET	SOX9	U2AF1
ADAMTS6	BCL2L2*	CCNE2	CTCF	ERBB3	FGF6	HRAS*	KMT2A	MTHFR*	PARP1	PRKCB	RHOA	SPEN	UBE2A*
ADAMTS9	BCL6	CCNH	CTLA4	ERBB4	FGFR1	HSP90AA1	KMT2C	MTOR	PAX5	PRKCG	RICTOR	SPOP	UBE2K
ADAMTSL1	BCL9	CD19	CTNNA1	ERCC1	FGFR2	HSP90AB1	KMT2D	MUC16	PAX8	PRKCI	RNF43	SRC	UBR5
ADGRA2	BCOR	CD274	CTNNB1	ERCC2	FGFR3	HSPA4	KRAS	MUC4	PBRM1	PRKCQ	ROS1	STAG2	UGT1A1*
ADH1C*	BIRC2	CD58	CUL3	ERCC3	FGFR4	HSPA5	LCK	MUC6	PDCD1	PRKDC	RPPH1	STAT3	USH2A
AKT1	BIRC3	CD70*	CYLD	ERCC4	FH	IDH1	LIG1	MUTYH	PDCD1LG2	PRKN	RPTOR	STK11	VDR*
AKT2	BLM	CD79A	CYP1A1*	ERCC5	FLCN	IDH2	LIG3	MYC	PDGFRA	PSMB8	RUNX1	SUFU	VEGFA
AKT3	BMPR1A	CD79B	CYP2B6*	ERG	FLT1	IFNL3*	LMO1	MYCL	PDGFRB	PSMB9	RUNX1T1	SYK	VEGFB
ALDH1A1*	BRAF	CDC73	CYP2C19*	ESR1	FLT3	IGF1	LRP1B	MYCN	PDIA3	PSME1	RXRA	SYNE1	VHL
ALK	BRCA1	CDH1	CYP2C8*	ESR2	FLT4	IGF1R	LYN	MYD88	PGF	PSME2	SDHA	TAF1	WT1
AMER1	BRCA2	CDK1	CYP2D6	ETV1	FOXL2*	IGF2	MALT1	NAT2*	PHOX2B*	PSME3	SDHB	TAP1	XIAP
APC	BRD4	CDK12	CYP2E1*	ETV4	FOXP1	IKBKB	MAP2K1	NBN	PIK3C2B	PTCH1	SDHC	TAP2	XPO1
AR	BRIP1	CDK2	CYP3A4*	EZH2	FRG1	IKBKE	MAP2K2	NEFH	PIK3C2G	PTEN	SDHD	TAPBP	XRCC2
ARAF	BTG1*	CDK4	CYP3A5*	FAM46C	FUBP1	IKZF1	MAP2K4	NF1	PIK3C3	PTGS2	SERPINB3	TBX3	ZNF217
ARID1A	BTG2*	CDK5	DAXX	FANCA	GATA1	IL6	MAP3K1	NF2	PIK3CA	PTPN11	SERPINB4	TEK	
ARID1B	BTK	CDK6	DCUN1D1	FANCC	GATA2	IL7R	MAP3K7	NFE2L2	PIK3CB	PTPRD	SETD2	TERT	
ARID2	BUB1B	CDK7	DDR2	FANCD2	GATA3	INPP4B	MAPK1	NFKB1	PIK3CD	PTPRT	SF3B1	TET1	
ASXL1	CALR	CDK8	DICER1	FANCE	GNA11	INSR	MAPK3	NFKBIA	PIK3CG	RAC1	SGK1	TET2	
ATM	CANX	CDK9	DNMT3A	FANCF	GNA13	IRF4	MAX	NKX2-1*	PIK3R1	RAD50	SH2D1A*	TGFBR2	
ATR	CARD11	CDKN1A	DOT1L	FANCG	GNAQ	IRS1	MCL1	NOTCH1	PIK3R2	RAD51	SLC19A1*	TMSB4X*	
ATRX	CASP8	CDKN1B	DPYD	FANCL	GNAS	IRS2*	MDM2	NOTCH2	PIK3R3	RAD51B	SLC22A2*	TNF	
AURKA	CBFB	CDKN2A	DTX1	FAS	GREM1	JAK1	MDM4	NOTCH3	PIM1	RAD51C	SLCO1B1*	TNFAIP3	

*Analysis of copy number alteration not available.

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

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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。

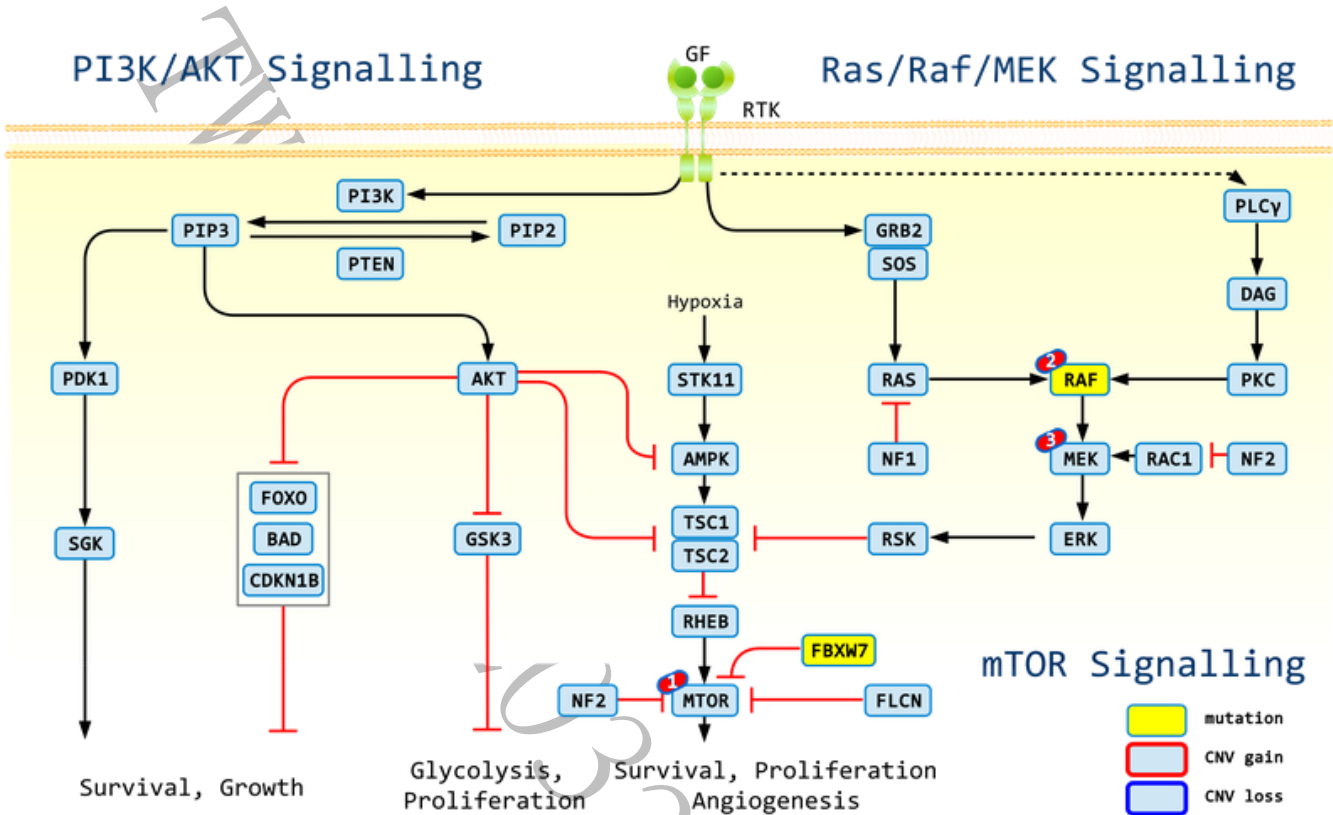
證據等級

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。

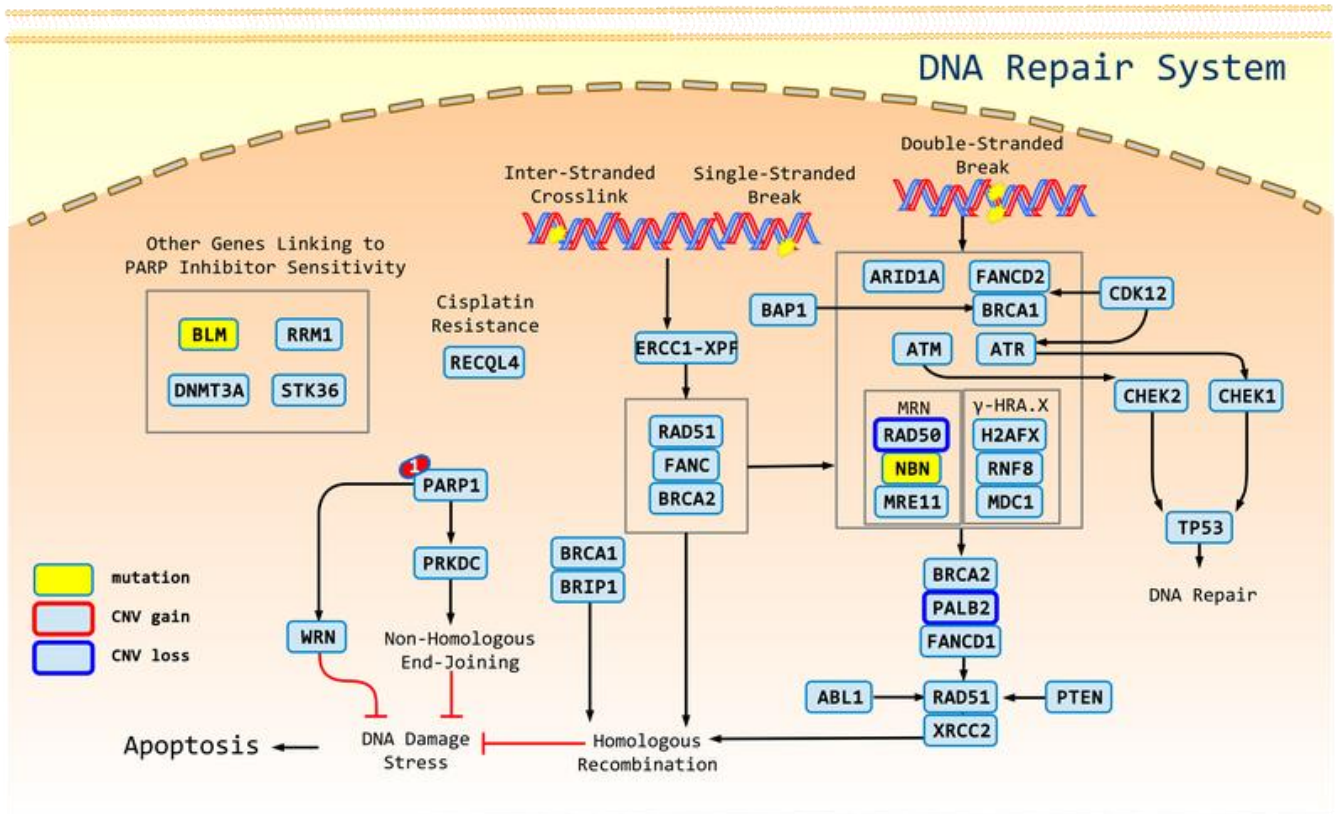
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SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



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



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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