

ACT Onco[®] + Report

PATIENT		
Identifier: 吳銘峰		Patient ID: 49383531
Date of Birth: Jun 12, 1981		Gender: Male
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
Name: 沈佳儀醫師		Tel: 886-228712121
Facility: 臺北榮總		
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SPECIMEN		
Specimen ID: S11215111A	Collection site: Cerebellum	Type: FFPE tissue
Date received: Jun 09, 2023	Lab ID: AA-23-03767	D/ID: NA

ABOUT ACT Onco[®]+

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	
TMB-High	Atezolizumab, Cemiplimab-rwlc, Dostarlimab-gxly, Durvalumab, Ipilimumab, Nivolumab, Pembrolizumab, Tremelimumab	-	Avelumab

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
PTPRD Splice donor	-	Bevacizumab
MCL1 Amplification	Regorafenib, Sorafenib	-

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 criteria 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
KEAP1	E582*	27.1%
PTPRD	Splice donor	24.9%
TP53	R273C	25.7%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr17	CD79B, RPTOR	Amplification	6
Chr1	MCL1, NTRK1	Amplification	7

- 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)	14.3 muts/Mb (TMB-High)
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 42% 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 4		
MCL1 Amplification	Regorafenib, Sorafenib	sensitive
PTPRD Splice donor	Bevacizumab	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)

Genomic Alterations	Approved for Patient's Cancer Type	Approved for Other Cancer Type
TMB-High (14.3 muts/Mb)	Atezolizumab, Cemiplimab-rwlc, Dostarlimab-gxly, Durvalumab, Ipilimumab, Nivolumab, Pembrolizumab, Tremelimumab	Avelumab

TMB, Tumor Mutational Burden; Muts/Mb, mutations per megabase

- 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
TP53 R273C	Platinum- and taxane- based regimens	Less sensitive	Clinical	Ovarian cancer

HORMONAL THERAPIES

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

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OTHERS

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AG	Irinotecan-based regimens	Level 1B

Clinical Interpretation:

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 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.

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VARIANT INTERPRETATION

Tumor mutational burden (TMB): High (14.3 mutations / Mb)

High TMB is a potential biomarker that predicts response to immune checkpoint inhibitors, including anti-CTLA-4 and anti-PD-1 in melanoma, anti-PD-1 in non-small cell lung cancer (NSCLC) and colorectal cancer (CRC), cutaneous squamous cell carcinoma (CSCC), and anti-PD-L1 therapy in bladder cancer^{[1][2][3][4][5][6][7][8]}. Of note, the U.S. FDA has approved tumor mutational burden-high (TMB-H) as a predictive biomarker for pembrolizumab in adult and pediatric patients with unresectable or metastatic solid tumor who have progressed following prior treatment and have no satisfactory alternative treatment options. CRCs with defects in mismatch-repair (MMR) are more susceptible to PD-1 blockade^[6]. High mutation load is associated with shorter overall survival in lung cancer and breast cancer patients^{[9][10]}.

KEAP1 E582*

Biological Impact

The Kelch-Like ECH-Associated Protein 1 (KEAP1) gene encodes a subunit of an E3 ubiquitin ligase complex that negatively regulates the nuclear factor erythroid 2-related factor 2 (NRF2) protein stability. Under the unstressed condition, low basal levels of NRF2 protein are maintained via proteasomal degradation by binding to KEAP1. Oxidative stress triggers the oxidation of KEAP1 and releases the NRF2 proteins. Then the NRF2 protein translocates and accumulates in the nucleus, and promoting the expression of genes involved in anti-oxidation responses. The loss of KEAP1 has been demonstrated to promote the accumulation of NRF2^[11].

KEAP1 mutations have been reported in non-small cell lung cancer (NSCLC)^{[12][13]}, biliary cancer^[14], and epithelial ovarian cancer (EOC)^[15]. In particular, mutations have been detected throughout the whole KEAP1 gene sequence in lung adenocarcinoma patients with strong smoking exposure^[16].

E582* mutation results in a premature truncation of the KEAP1 protein at amino acid 582 (UniProtKB). This mutation is predicted to lead to a loss of KEAP1 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

Lung adenocarcinoma (LAC) patients harboring mutations in the KEAP1/NFE2L2 pathway had significantly worse clinical outcomes after chemotherapy, compared to those with wild-type KEAP1/NFE2L2 LAC^[17]. Besides, co-occurring mutations of KRAS and KEAP1/NFE2L2 is an independent prognostic factor associated with shorter duration of response to initial platinum-based chemotherapy and immune checkpoint inhibitors in non-small cell lung cancer^[18].

Tumors with KEAP1 mutations are generally considered as cold tumors and can promote immune evasion^[19].

Preclinical data indicated that loss of KEAP1 may alter cell metabolism with cell proliferation, and modulate the response to vemurafenib, trametinib, erlotinib, and crizotinib in BRAF-, NRAS-, KRAS-, EGFR-, and ALK-mutant lung cancer cell lines^[20].

PTPRD Splice donor

Biological Impact

PTPRD encodes the enzyme Receptor-type tyrosine-protein phosphatase delta (PTPδ), which is involved in various cellular processes and cell-cell adhesion^{[21][22]}. PTPRD is inactivated in a large number of glioblastomas and is mutated, deleted or promoter methylated in multiple other human cancers, ranging from neuroblastomas to endometrial, lung and colon cancers and has a putative tumor suppressor function^{[23][24]}.

PTPRD c.64+1G>C is a variant located at the splice donor region, which may result in the exon skipping.

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Therapeutic and prognostic relevance

Deleterious PTPRD/PTPRT alternations, including PTPRD copy number loss, PTPRD/PTPRT missense variants and truncating variants, have been shown associated with bevacizumab-resistance in metastatic colorectal cancer and lead to shortened survival in bevacizumab-treated patients compared to those without deleterious PTPRT/PTPRD alternations (Median PFS: 8.6 v.s. 13.1 months)^[25]. Reduced expression of PTPRD was shown correlated with poor prognosis in gastric adenocarcinoma^[26]. Moreover, a clinical study suggested that PTPRD/PTPRT mutations were associated with increased TMB and longer OS and PFS in ICI-treated NSCLC patients (doi: 10.1200/JCO.2020.38.15_suppl.e15112).

TP53 R273C

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[27]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[28].

R273C is a hotspot mutation occurred at the DNA-binding domain (DBD) of the p53 protein^[29]. This is a gain-of-function mutation that has been shown to cause aberrant activation of gene expression, increased cell proliferation, migration and increase the HER2 promoter activity and mRNA expression in vitro^{[30][31][32]}.

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)^[33].

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^[34]. 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^[35].

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^{[36][37][38]}. 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)^[39]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[40][41]}. 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^[42].

TP53 oncomorphic mutations, including P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L, and R282W have been shown to predict resistance to platinum- and taxane-based chemotherapy in advanced serous ovarian carcinoma patients^[43].

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CD79B Amplification

Biological Impact

CD79B encodes a surface immunoglobulin that forms a heterodimer with CD79A and non-covalently assembles with membrane-bound IgM to form the B cell receptor (BCR) which plays essential roles in B cell development, activation and survival of mature B cells^{[44][45]}. Activating mutations of CD79B has been demonstrated resulting in chronic BCR signaling and constitutive activation of the NF- κ B pathway. Besides, recurrent mutations of CD79B and MYD88 genes have been suggested as a genetic hallmark in primary central nervous system lymphoma^[46] and diffuse large B-cell lymphoma (DLBCL)^[47].

Therapeutic and prognostic relevance

Polatuzumab vedotin, an antibody-drug conjugate targeting CD79B, in combination with bendamustine and a rituximab product is FDA-approved for treating relapsed or refractory DLBCL, not otherwise specified (NOS), after at least two prior therapies. Also, polatuzumab vedotin in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is FDA-approved for treating previously untreated DLBCL, NOS or high-grade B-cell lymphoma (HGBL) and who have an International Prognostic Index score of 2 or greater.

A preclinical study has demonstrated that CD79B up-regulation associates with limited response to ibrutinib, a selective and reversible inhibitor of BCR, in DLBCL^[48].

MCL1 Amplification

Biological Impact

The myeloid cell leukemia 1 (MCL1) gene encodes a member of the BCL2 pro-survival family^[49]. MCL1 is highly regulated by various oncogenic signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway^[50], the mTOR pathway^[51], and the phosphatidylinositol-3 kinase (PI3K) pathway^[52]. Oncogenic roles for MCL1 have been previously suggested by the report of increased rates of lymphoma in transgenic mice^[53]. Somatic amplification of MCL1 may be a common mechanism in cancer cells to increase cell survival^[54]. MCL1 overexpression was observed from a retrospective analysis of parotid gland carcinomas, including adenoid cystic carcinoma^[55].

Therapeutic and prognostic relevance

Therapies targeting MCL1 and other BCL2 family members with the pan-BCL2 family inhibitors are currently under investigation^[56]. A case report has demonstrated clinical efficacy of sorafenib, when combined with vorinostat, in a metastatic triple-negative breast cancer (TNBC) patient with MCL1-amplified tumor^[57]. Several in vitro studies also showed that sorafenib induces cell death via inhibition of MCL1 expression in multiple cancer types including, hepatocellular carcinoma (HCC), lung cancer, breast cancer, cholangiocarcinoma, endometrial cancer and chronic lymphocytic leukemia^{[58][59][60][61][62][63]}. Preclinical studies have also demonstrated the efficacy of regorafenib in reducing MCL1 expression in human colorectal cancer (CRC) cell lines^{[64][65]}. In vivo models of colon cancer showed that MCL1 expression is inhibited by targeting of the mTOR pathway using everolimus, promoting increased tumor cell killing of cancers with KRAS or BRAF mutations^[66].

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NTRK1 Amplification

Biological Impact

The NTRK1 gene encodes the TRKA (tropomyosin receptor kinase) receptor which plays an important role in the development and function of the nervous system. Gene fusions of NTRK1 lead to constitutive activation of MAP-kinase, PI3-kinase, and PLC-γ pathways, and represent the main molecular alterations with known oncogenic and transforming potential in various malignancies, including soft tissue sarcoma, non-small cell lung cancer (NSCLC), glioblastoma multiforme (GBM), thyroid carcinoma, and pilocytic astrocytomas^{[67][68]}. Apan-cancer study (n=1250) demonstrated that 2.2% of the metastatic cancer patients harbored NTRK amplification and NTRK protein overexpression was observed in 14.8% of NTRK-amplified tumors (doi.org/10.23838/pfm.2017.00142).

Therapeutic and prognostic relevance

Patients with NTRK1 amplification had only limited benefit from larotrectinib treatment according to the few clinical studies. One of them had a partial response with larotrectinib of short duration (3.7 months)^[69], and the other one with metastatic NTRK1-amplified (copy number=8) esophageal carcinoma showed clinical efficacy for six weeks, and then a progressive disease of new lesions were observed^[70].

RPTOR Amplification

Biological Impact

RPTOR (regulatory-associated protein of mTOR, also known as RAPTOR) gene encodes a scaffold protein which is involved in assembly, localization and substrate binding of the mTORC1 complex and plays essential roles in mTOR signaling^{[71][72][73][74]}. Conditional disruption of RAPTOR has been reported to result in a development block of B cell^[75].

Therapeutic and prognostic relevance

RAPTOR overexpression has been reported to associate with acquired resistance to mTOR inhibition in vitro^[76].

A study of breast cancer patients (n=150) indicated that higher expression of RAPTOR was associated with higher tumor grade^[77].

A study of hepatocellular carcinoma patients (n=62) indicated that high Rictor/Raptor ratio was associated with shorter disease-free survival^[78].

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US FDA-APPROVED DRUG(S)

Atezolizumab (TECENTRIQ)

Atezolizumab is a humanized, anti-programmed cell death-ligand 1 (PD-L1) monoclonal antibody of the IgG1 isotype, which can lead to the reactivation of immune cells that might recognize and attack tumor cells. Atezolizumab is developed and marketed by Genentech/Roche under the trade name TECENTRIQ.

- FDA Approval Summary of Atezolizumab (TECENTRIQ)

ML39345 NCT03141684	Alveolar soft part sarcoma (Approved on 2022/12/09)
	- Atezolizumab [ORR(%): 24.0]
IMpower010 NCT02486718	Non-small cell lung carcinoma (Approved on 2021/10/15)
	PD-L1 Atezolizumab vs. Best supportive care (bsc) [DFS (PD-L1 TC≥1%)(M): not reached vs. 35.3]
IMspire150 NCT02908672	Melanoma (Approved on 2020/07/30)
	BRAF V600 mutation Atezolizumab + cobimetinib + vemurafenib vs. Placebo + cobimetinib + vemurafenib [PFS(M): 15.1 vs. 10.6]
IMbrave150 NCT03434379	Hepatocellular carcinoma (Approved on 2020/05/29)
	- Atezolizumab plus bevacizumab vs. Sorafenib [PFS(M): 6.8 vs. 4.3, OS(M): NR vs. 13.2]
IMpower133^[79] NCT02763579	Small cell lung cancer (Approved on 2019/03/18)
	- Atezolizumab plus carboplatin and etoposide vs. Carboplatin and etoposide [PFS(M): 5.2 vs. 4.3, OS(M): 12.3 vs. 10.3]
OAK^[80] NCT02008227	Non-small cell lung carcinoma (Approved on 2016/10/18)
	PD-L1 Atezolizumab vs. Docetaxel [OS(M): 13.8 vs. 9.6]
POPLAR^[81] NCT01903993	Non-small cell lung carcinoma (Approved on 2016/10/18)
	PD-L1 Atezolizumab vs. Docetaxel [OS(M): 12.6 vs. 9.7]
IMvigor210^[82] NCT02951767	Bladder urothelial carcinoma (Approved on 2016/05/18)
	- Atezolizumab [ORR (PD-L1 < 5%)(%): 21.8, ORR (PD-L1 ≥ 5%)(%): 28.1]

Avelumab (BAVENCIO)

Avelumab is fully human monoclonal programmed death ligand-1 (PD-L1) antibody, belonging to the group of immune checkpoint blockade cancer therapies. Avelumab is developed and marketed by Merck KGaA and Pfizer under the trade name BAVENCIO.

- FDA Approval Summary of Avelumab (BAVENCIO)

JAVELIN Renal 101^[83] NCT02684006	Renal cell carcinoma (Approved on 2019/05/14)
	- Avelumab plus axitinib vs. Sunitinib [ORR(%): 51.4 vs. 25.7, PFS(M): 13.8 vs. 8.4]
JAVELIN Solid Tumor NCT01772004	Bladder urothelial carcinoma (Approved on 2017/05/09)
	- Avelumab [ORR(13W)(%): 13.6, ORR(6M)(%): 16.1]

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JAVELIN Merkel 200 ^[84] NCT02155647	Merkel cell carcinoma (Approved on 2017/03/23)
	-
	Avelumab [ORR(%): 33.0, DOR(M): 2.8 to 23.3+]

Cemiplimab-rwlc (LIBTAYO)

Cemiplimab-rwlc is a recombinant human IgG4 monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2. Cemiplimab-rwlc is developed and marketed by Sanofi and Regeneron under the trade name LIBTAYO.

- FDA Approval Summary of Cemiplimab-rwlc (LIBTAYO)

Study 16113 NCT03409614	Lung non-small cell carcinoma (Approved on 2022/11/08)
	-
	Platinum-based chemotherapy [OS(M): 21.9 vs. 13.0]
Study 1624 NCT03088540	Non-small lung cancer (Approved on 2021/02/22)
	PD-L1
	Cemiplimab-rwlc vs. Platinum-based chemotherapy [PFS(M): 6.2 vs. 5.6, OS(M): 22.1 vs. 14.3]
Study 1620 NCT03132636	Locally advanced basal cell carcinoma (labcc) (Approved on 2021/02/09)
	-
	Cemiplimab-rwlc [ORR(%): 29.0, DOR(M): NR]
Study 1620 NCT03132636	Metastatic basal cell carcinoma (mbcc) (Approved on 2021/02/09)
	-
	Cemiplimab-rwlc [ORR(%): 21.0, DOR(M): NR]
Study 1423, Study 1540 ^[7] NCT02383212, NCT02760498	cutaneous squamous cell carcinoma (Approved on 2018/09/28)
	-
	Cemiplimab-rwlc [ORR(%): 47.2]

Dostarlimab-gxly (JEMPERLI)

Dostarlimab-gxly is a programmed death receptor-1 (PD-1)-blocking antibody. Dostarlimab-gxly is developed and marketed by GlaxoSmithKline LLC under the trade name JEMPERLI.

- FDA Approval Summary of Dostarlimab-gxly (JEMPERLI)

GARNET NCT02715284	Cancer (Approved on 2021/08/17)
	dMMR
	Dostarlimab [ORR(%): 41.6, DoR(M): 34.7]
GARNET (Cohort A) NCT02715284	Endometrial carcinoma (Approved on 2021/04/22)
	dMMR
	Dostarlimab-gxly [ORR(%): 42.3, DOR(M): NR]

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Durvalumab (IMFINZI)

Durvalumab is a programmed death ligand-1 (PD-L1)-blocking antibody. Durvalumab is developed and marketed by AstraZeneca under the trade name IMFINZI.

- FDA Approval Summary of Durvalumab (IMFINZI)

HIMALAYA NCT03298451	Hepatocellular carcinoma (Approved on 2022/10/21)
	-
	Durvalumab + tremelimumab vs. Durvalumab + sorafenib [OS(M): 16.4 vs. 13.9]
TOPAZ-1 NCT03875235	Biliary tract cancer (Approved on 2022/09/02)
	-
	Durvalumab [OS(M): 12.8 vs. 11.5]
CASPIAN^[85] NCT03043872	Extensive-stage small cell lung cancer (Approved on 2020/03/27)
	-
	Durvalumab + etoposide + carboplatin or durvalumab + etoposide + cisplatin vs. Etoposide + carboplatin or etoposide + cisplatin [OS(M): 13 vs. 10.3]
PACIFIC^[86] NCT02125461	Non-small cell lung carcinoma (Approved on 2018/02/16)
	-
	Durvalumab vs. Placebo [PFS(M): 16.8 vs. 5.6]

Ipilimumab (YERVOY)

Ipilimumab is a fully human monoclonal antibody against the cytotoxic T-lymphocyte associated protein 4 (CTLA-4), an immune checkpoint protein receptor, to reactivate the immune responses. Ipilimumab is developed by Medarex and Bristol-Myers Squibb, and marketed by the latter under the trade name YERVOY.

- FDA Approval Summary of Ipilimumab (YERVOY)

CHECKMATE-648 NCT03143153	Esophagus squamous cell carcinoma (Approved on 2022/05/27)
	-
	Nivolumab and ipilimumab vs. Chemotherapy [OS(M): 12.8 vs. 10.7]
CHECKMATE-743 NCT02899299	Pleural mesothelioma (Approved on 2020/10/02)
	-
	Nivolumab + ipilimumab vs. Pemetrexed + cisplatin [OS(M): 18.1 vs. 14.1]
CHECKMATE-9LA NCT03215706	Non-small cell lung carcinoma (Approved on 2020/05/26)
	-
	Nivolumab + ipilimumab + platinum-doublet chemotherapy vs. Platinum-doublet chemotherapy [OS(M): 14.1 vs. 10.7]
CHECKMATE-227 NCT02477826	Non-small cell lung carcinoma (Approved on 2020/05/15)
	PD-L1
	Nivolumab + ipilimumab vs. Platinum-doublet chemotherapy [OS(M): 17.1 vs. 14.9]
CHECKMATE-040 NCT01658878	Hepatocellular carcinoma (Approved on 2020/03/10)
	-
	Nivolumab + ipilimumab [ORR(%): 33.0]
CHECKMATE-142^[87] NCT02060188	Colorectal cancer (Approved on 2018/07/10)
	MSI-H or dMMR
	Ipilimumab plus nivolumab vs. Nivolumab [ORR(%): 49.0 vs. 32.0]

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CHECKMATE-214 ^[88] NCT02231749	Renal cell carcinoma (Approved on 2018/04/16)
	-
	Nivolumab plus ipilimumab vs. Sunitinib [OS(M): 67.1 vs. 55.5]
EORTC 18071 ^[89] NCT00636168	Melanoma (Approved on 2015/10/28)
	-
	Ipilimumab vs. Placebo [RFS(M): 26 vs. 17]
MDX010-20 ^[90] NCT00094653	Melanoma (Approved on 2011/03/25)
	-
	Ipilimumab vs. Peptide vaccine with incomplete freund's adjuvant (gp100) [OS(M): 10 vs. 6]

Nivolumab (OPDIVO)

Nivolumab is a programmed death receptor-1 (PD-1)-blocking antibody. Nivolumab is developed and marketed by Bristol-Myers Squibb under the trade name OPDIVO.

- FDA Approval Summary of Nivolumab (OPDIVO)

CHECKMATE-648 NCT03143153	Esophagus squamous cell carcinoma (Approved on 2022/05/27)
	-
	Nivolumab and ipilimumab vs. Chemotherapy [OS(M): 12.8 vs. 10.7]
CHECKMATE-648 NCT03143153	Esophagus squamous cell carcinoma (Approved on 2022/05/27)
	-
	Nivolumab, fluorouracil, and cisplatin vs. Chemotherapy [OS(M): 13.2 vs. 10.7]
CHECKMATE-816 NCT02998528	Non-small cell lung cancer (nslc) (Approved on 2022/03/04)
	-
	Nivolumab plus platinum-doublet chemotherapy vs. Platinum-chemotherapy [EFS(M): 31.6 vs. 20.8]
CHECKMATE-274 NCT02632409	Bladder urothelial carcinoma (Approved on 2021/08/19)
	-
	Nivolumab [DFS (all randomized)(M): 20.8 vs. 10.8, DFS (PD-L1 ≥ 1%)(M): NR vs. 8.4]
CHECKMATE-577 NCT02743494	Gastroesophageal junction adenocarcinoma (Approved on 2021/05/20)
	-
	Nivolumab vs. Placebo every 4 weeks beginning at week 17 for up to one year of treatment [DFS(M): 22.4 vs. 11]
CHECKMATE-649 NCT02872116	Gastroesophageal junction adenocarcinoma, Gastric adenocarcinoma (Approved on 2021/04/16)
	-
	Nivolumab + chemotherapy (xelox or folfox) vs. Chemotherapy (xelox or folfox) [PFS(M): 7.7 vs. 6, OS(M): 14.4 vs. 11.1]
CHECKMATE-9ER NCT03141177	Renal cell carcinoma (Approved on 2021/01/22)
	-
	Nivolumab + cabozantinib vs. Sunitinib [ORR(%): 55.7 vs. 27.1, PFS(M): 16.6 vs. 8.3, OS(M): NR vs. NR]
CHECKMATE-743 NCT02899299	Pleural mesothelioma (Approved on 2020/10/02)
	-
	Nivolumab + ipilimumab vs. Pemetrexed + cisplatin [OS(M): 18.1 vs. 14.1]

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CHECKMATE-9LA NCT03215706	Non-small cell lung carcinoma (Approved on 2020/05/26)
	- Nivolumab + ipilimumab + platinum-doublet chemotherapy vs. Platinum-doublet chemotherapy [OS(M): 14.1 vs. 10.7]
CHECKMATE-227 NCT02477826	Non-small cell lung carcinoma (Approved on 2020/05/15)
	PD-L1 Nivolumab + ipilimumab vs. Platinum-doublet chemotherapy [OS(M): 17.1 vs. 14.9]
CheckMate 040 NCT01658878	Hepatocellular carcinoma (Approved on 2020/03/10)
	- Nivolumab + ipilimumab [ORR(%): 33.0]
CheckMate 142 NCT02060188	Colorectal cancer (Approved on 2017/07/31)
	MSI-H or dMMR Nivolumab [ORR(%): 32.0]
CheckMate 141 ^[91] NCT02105636	Squamous cell carcinoma of the head and neck cancer (Approved on 2016/11/10)
	- Nivolumab vs. Investigator's choice of cetuximab, methotrexate or docetaxel [OS(M): 7.5 vs. 5.1]
CheckMate 205 ^[92] NCT02181738	Hodgkin's lymphoma (Approved on 2016/05/17)
	- Nivolumab [ORR(%): 66.0]
CheckMate 039 ^[93] NCT01592370	Hodgkin's lymphoma (Approved on 2016/05/17)
	- Nivolumab [ORR(%): 66.0]
CheckMate 067 ^[94] NCT01844505	Melanoma (Approved on 2016/01/23)
	- Ipilimumab vs. Placebo [PFS(M): 11.5 vs. 2.9]
CheckMate 066 ^[95] NCT01721772	Melanoma (Approved on 2015/11/24)
	BRAF V600 wild-type Nivolumab vs. Dacarbazine [OS(M): Not Reached vs. 10.8]
CheckMate 025 ^[96] NCT01668784	Renal cell carcinoma (Approved on 2015/11/23)
	- Nivolumab vs. Everolimus [OS(M): 25 vs. 19.6]
CheckMate 057 ^[97] NCT01673867	Non-small cell lung carcinoma (Approved on 2015/10/09)
	- Nivolumab vs. Docetaxel [OS(M): 12.2 vs. 9.4]
CheckMate 017 ^[98] NCT01642004	Non-small cell lung carcinoma (Approved on 2015/03/04)
	- Nivolumab vs. Docetaxel [OS(M): 9.2 vs. 6]
CheckMate 037 ^[99] NCT01721746	Melanoma (Approved on 2014/12/22)
	- Nivolumab vs. Dacarbazine or carboplatin + paclitaxel [ORR(%): 32.0]

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Pembrolizumab (KEYTRUDA)

Pembrolizumab is a programmed death receptor-1 (PD-1)-blocking antibody. Pembrolizumab is developed and marketed by Merck under the trade name KEYTRUDA.

- FDA Approval Summary of Pembrolizumab (KEYTRUDA)

KEYNOTE-091 NCT02504372	Lung non-small cell carcinoma (Approved on 2023/01/26)
	- Pembrolizumab vs. Placebo [DFS(M): 58.7 vs. 34.9]
KEYNOTE-158 NCT02628067	Endometrial carcinoma (Approved on 2022/03/21)
	MSI-H or dMMR Pembrolizumab [ORR(%): 46.0, DoR(M): NR]
KEYNOTE-716 NCT03553836	Melanoma (Approved on 2021/12/03)
	- Pembrolizumab [RFS(M): Not reached vs. Not reached]
KEYNOTE-564 NCT03142334	Renal cell carcinoma (Approved on 2021/11/17)
	- Pembrolizumab vs. Placebo [DFS(M): NR vs. NR, OS(M): NR vs. NR]
KEYNOTE-826 NCT03635567	Cervical cancer (Approved on 2021/10/13)
	PD-L1 Pembrolizumab + paclitaxel + cisplatin with or without bevacizumab vs. Placebo + paclitaxel + cisplatin with or without bevacizumab [OS (PD-L1, CPS ≥1)(M): Not reached vs. 16.3, PFS(M): 10.4 vs. 8.2]
CLEAR (Study 307/KEYNOTE-581) NCT02811861	renal cell carcinoma (Approved on 2021/08/11)
	- Pembrolizumab + lenvatinib vs. Sunitinib [PFS(M): 23.9 vs. 9.2, OS(M): NR vs. NR, ORR(%): 71.0 vs. 36.0]
KEYNOTE-522 NCT03036488	Triple-receptor negative breast cancer (Approved on 2021/07/26)
	- Pembrolizumab + chemotherapy as neoadjuvant treatment vs. Placebo in combination with chemotherapy [pCR(%): 63.0 vs. 56.0, EFS(): 123 vs. 93]
KEYNOTE-775 (Study 309) NCT03517449	Endometrial carcinoma (Approved on 2021/07/22)
	MSS/pMMR Pembrolizumab + lenvatinib vs. Investigator's choice of doxorubicin or paclitaxel [PFS(M): 6.6 vs. 3.8, OS(M): 17.4 vs. 12]
KEYNOTE-811 NCT03615326	Gastroesophageal junction adenocarcinoma (Approved on 2021/05/05)
	HER2+ Pembrolizumab 200 mg every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin vs. Placebo every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin [ORR(%): 74.0 vs. 52.0, DOR(M): 10.6 vs. 9.5]
KEYNOTE-590 NCT03189719	Esophageal cancer, Gastroesophageal junction adenocarcinoma (Approved on 2021/03/22)
	- Pembrolizumab in combination with cisplatin and fluorouracil vs. Placebo with cisplatin and fluorouracil [PFS(M): 6.3 vs. 5.8, OS(M): 12.4 vs. 9.8]

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KEYNOTE-355 NCT02819518	Triple-receptor negative breast cancer (Approved on 2020/11/13)
	PD-L1 Pembrolizumab + paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin vs. Placebo + paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin [PFS(M): 9.7 vs. 5.6]
KEYNOTE-204 NCT02684292	Hodgkin's lymphoma (Approved on 2020/10/14)
	- Pembrolizumab vs. Brentuximab vedotin [PFS(M): 13.2 vs. 8.3]
KEYNOTE-158 NCT02628067	Cancer (Approved on 2020/06/17)
	TMB-H Pembrolizumab (tmb-h) vs. Pembrolizumab (non-tmb-h) [ORR(%): 29.0 vs. 6.0]
KEYNOTE-146 NCT02501096	Endometrial carcinoma (Approved on 2019/09/17)
	MSS/pMMR Pembrolizumab + lenvatinib [ORR(%): 38.3, DOR(M): NR]
KEYNOTE-426 ^[100] NCT02853331	Renal cell carcinoma (Approved on 2019/04/19)
	- Pembrolizumab + axitinib vs. Sunitinib [ORR(%): 59.3 vs. 35.7, PFS(M): 15.1 vs. 11.1]
KEYNOTE-017 ^[101] NCT02267603	Merkel cell carcinoma (Approved on 2018/12/19)
	- Pembrolizumab [ORR(%): 56.0]
KEYNOTE-224 ^[102] NCT02702414	Hepatocellular carcinoma (Approved on 2018/11/09)
	- Pembrolizumab [ORR(%): 17.0]
KEYNOTE-407 ^[103] NCT02775435	Squamous non-small cell lung carcinoma (Approved on 2018/10/30)
	- Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. Carboplatin + paclitaxel/nab-paclitaxel [ORR(%): 58.0 vs. 35.0, PFS(M): 6.4 vs. 4.8]
KEYNOTE-189 ^[103] NCT02578680	Nonsquamous non-small cell lung carcinoma (Approved on 2018/08/20)
	- Pembrolizumab + pemetrexed + platinum vs. Pemetrexed + platinum [PFS(M): 8.8 vs. 4.9, OS(M): NR vs. 11.3]
KEYNOTE-170 NCT02576990	Mediastinal large b-cell lymphoma (Approved on 2018/06/13)
	- Pembrolizumab [ORR(%): 45.0]
KEYNOTE-158 NCT02628067	Cervical cancer (Approved on 2018/06/13)
	- Pembrolizumab [ORR(%): 14.3]
KEYNOTE-059 NCT02335411	Gastric adenocarcinoma, Gastroesophageal junction adenocarcinoma (Approved on 2017/09/22)
	- Pembrolizumab [ORR(%): 13.3]
KEYNOTE-158 NCT02628067	Cancer (Approved on 2017/05/23)
	MSI-H or dMMR Pembrolizumab [ORR(%): 39.6]
KEYNOTE-028 ^{[104][105]} NCT02054806	Cancer (Approved on 2017/05/23)
	MSI-H or dMMR Pembrolizumab [ORR(%): 39.6]

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KEYNOTE-012 ^{[106][107][108][109]} NCT01848834	Cancer (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-164 NCT02460198	Cancer (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-016 ^[6] NCT01876511	Cancer (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-045 ^[110] NCT02256436	Urinary bladder urothelial carcinoma (Approved on 2017/05/18)
	-
	Pembrolizumab vs. Chemotherapy [ORR(%): 21.0 vs. 11.0]
KEYNOTE-052 NCT02335424	Urinary bladder urothelial carcinoma (Approved on 2017/05/18)
	-
	Pembrolizumab [ORR(%): 29.0]
KEYNOTE-087 ^[111] NCT02453594	Hodgkin's lymphoma (Approved on 2017/03/14)
	-
	Pembrolizumab [ORR(%): 69.0]
KEYNOTE-024 ^[112] NCT02142738	Non-small cell lung carcinoma (Approved on 2016/10/24)
	PD-L1
	Pembrolizumab vs. Chemotherapy [PFS(M): 10.3 vs. 6]
KEYNOTE-012 ^[107] NCT01848834	Head and neck squamous cell carcinoma (Approved on 2016/08/05)
	-
	Pembrolizumab [ORR(%): 16.0]
KEYNOTE-006 ^[113] NCT01866319	Melanoma (Approved on 2015/12/18)
	-
	Pembrolizumab vs. Ipilimumab (3mg/kg every 3 weeks) [OS(M): NR vs. 16]
KEYNOTE-010 ^[114] NCT01905657	Non-small cell lung carcinoma (Approved on 2015/10/02)
	PD-L1
	Pembrolizumab [OS(M): 10.4 vs. 8.5]
KEYNOTE-002 ^[115] NCT01704287	Melanoma (Approved on 2014/09/24)
	-
	Pembrolizumab vs. Chemotherapy [PFS(M): 2.9 vs. 2.7]

Regorafenib (STIVARGA)

Regorafenib is a multi-kinase inhibitor which targets angiogenic, stromal and oncogenic receptor tyrosine kinases (RTKs). Regorafenib is developed and marketed by Bayer HealthCare Pharmaceuticals under the trade name STIVARGA.

- FDA Approval Summary of Regorafenib (STIVARGA)

RESORCE ^[116] NCT01774344	Hepatocellular carcinoma, Hepatocellular carcinoma (Approved on 2017/04/27)
	-
	Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]
GRID ^[117] NCT01271712	Gastrointestinal stromal tumor (Approved on 2013/02/25)
	-
	Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]

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CORRECT ^[118] NCT01103323	Colorectal cancer (Approved on 2012/09/27)
	-
	Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

Sorafenib (NEXAVAR)

Sorafenib is a small molecule multi-kinase inhibitor that targets multiple kinase families including VEGFR, PDGFRB, and the RAF family kinases. Sorafenib is co-developed and co-marketed by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals under the trade name NEXAVAR.

- FDA Approval Summary of Sorafenib (NEXAVAR)

DECISION ^[119] NCT00984282	Differentiated thyroid carcinoma (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
SHARP ^[120] NCT00105443	Hepatocellular carcinoma (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]
TARGET ^[121] NCT00073307	Renal cell carcinoma (Approved on 2005/12/20)
	-
	Sorafenib vs. Placebo [PFS(D): 167 vs. 84]

Tremelimumab (IMJUDO)

Tremelimumab a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody. Tremelimumab is developed and marketed by AstraZeneca under the trade name IMJUDO.

- FDA Approval Summary of Tremelimumab (IMJUDO)

POSEIDON NCT03164616	Lung non-small cell carcinoma (Approved on 2022/11/10)
	-
	Durvalumab and platinum-based chemotherapy [PFS(M): 6.2 vs. 4.8, OS(M): 14 vs. 11.7]
HIMALAYA NCT03298451	Hepatocellular carcinoma (Approved on 2022/10/21)
	-
	Tremelimumab + durvalumab vs. Tremelimumab + sorafenib [OS(M): 16.4 vs. 13.9]

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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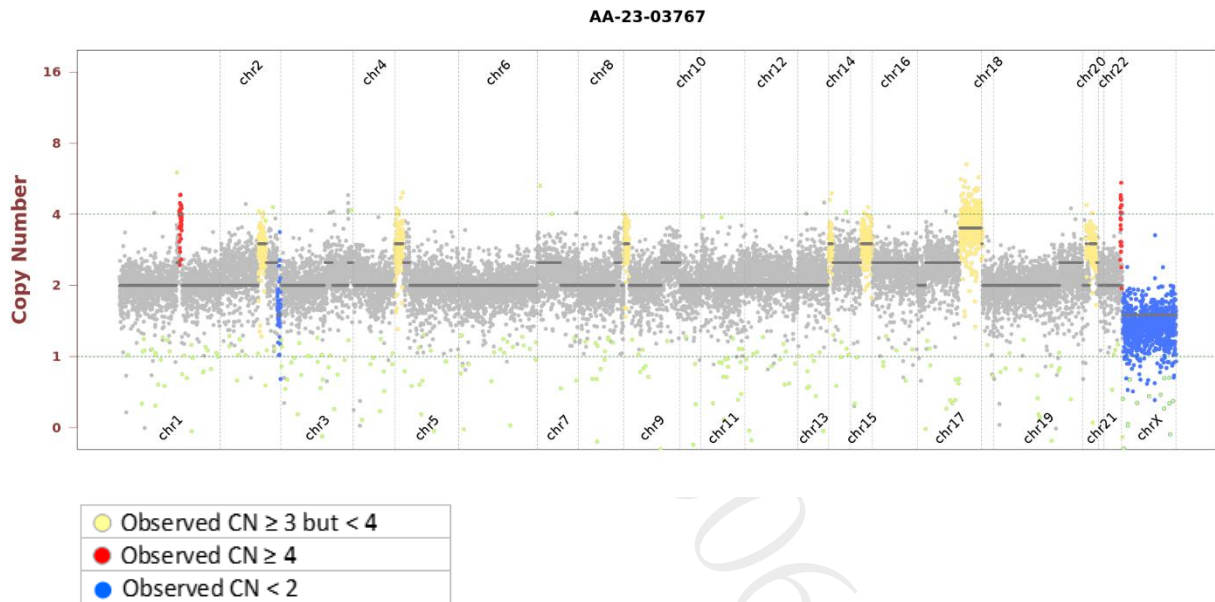
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
KEAP1	E582*	6	c.1744G>T	NM_203500	COSM4277469	27.1%	1319
PTPRD	Splice donor	-	c.64+1G>C	NM_002839	-	24.9%	1013
TP53	R273C	8	c.817C>T	NM_000546	COSM10659	25.7%	1284

- 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
ADAMTS6	W844C	20	c.2532G>T	NM_197941	-	24.4%	1635
ARID1B	Q1448*	17	c.4342C>T	NM_017519	-	25.8%	217
ARID2	D1561H	15	c.4681G>C	NM_152641	-	21.3%	1828
CUL3	G51V	2	c.152G>T	NM_003590	-	11.1%	450
EGFR	L1087H	27	c.3260T>A	NM_005228	-	10.2%	1526
EPHA5	L765F	13	c.2295G>T	NM_001281765	-	18.9%	992
ERBB4	L1145M	27	c.3433C>A	NM_005235	-	11.2%	1721
ERCC3	R589S	11	c.1767G>T	NM_000122	-	23.4%	1133
ETV1	A246S	9	c.735_736delins CT	NM_004956	-	9.4%	1194
FANCD2	Y458H	16	c.1372T>C	NM_001018115	-	39.2%	2279
FGF6	L57P	1	c.170_171delins CT	NM_020996	-	11.2%	1033
HGF	S362L	9	c.1085C>T	NM_000601	-	10.3%	1092
HIST1H1C	A123V	1	c.368C>T	NM_005319	-	40.7%	307
HIST1H1C	K213fs	1	c.637_638insG	NM_005319	-	12.7%	711
IDH2	A307T	7	c.919G>A	NM_002168	-	43.0%	2551
LRP1B	A1533S	28	c.4597G>T	NM_018557	-	22.1%	438
MITF	R508S	10	c.1524G>T	NM_198159	-	25.4%	893
MTOR	K1465N	30	c.4395G>T	NM_004958	-	11.6%	1772
MUC16	L14251M	77	c.42751C>A	NM_024690	-	25.1%	1396
MUC16	L3252V	3	c.9754C>G	NM_024690	-	30.8%	688
MUC16	T8384K	3	c.25151_25152 delinsAA	NM_024690	-	26.7%	1684
NOTCH2	Splice region	-	c.2480-4C>G	NM_024408	-	53.8%	653
NTRK3	R587K	15	c.1760G>A	NM_001012338	COSM3887687	15.3%	3998
PIK3R1	Y150C	4	c.449A>G	NM_181523	-	25.0%	1422
POLE	T449M	13	c.1346C>T	NM_006231	COSM2001775	62.9%	1193
PSMB8	R91Q	2	c.272G>A	NM_148919	-	58.2%	2662
PTCH1	A741V	14	c.2222C>T	NM_000264	-	37.6%	2351
RAD51D	Q229L	8	c.686A>T	NM_002878	-	21.5%	1481
SETD2	M1526I	4	c.4578G>T	NM_014159	COSM6191490	24.0%	434
SYNE1	V200I	9	c.598G>A	NM_182961	-	38.5%	1096
USH2A	Q661L	12	c.1982A>T	NM_206933	-	13.9%	1136
XPO1	E828Q	20	c.2482G>C	NM_003400	-	13.0%	662
ZNF217	A549T	3	c.1645G>A	NM_006526	COSM3939408	63.8%	2149

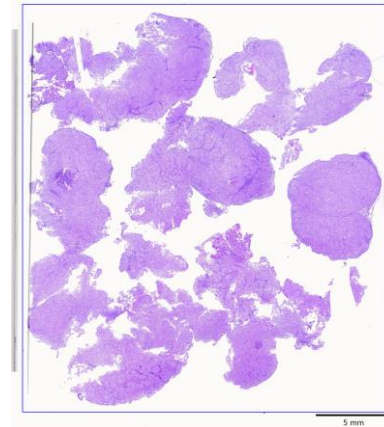
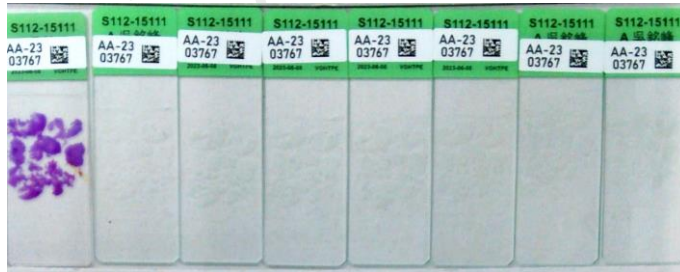
Note:

- 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: Apr 10, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11215111A
- Collection site: Cerebellum
- Examined by: Dr. Yeh-Han Wang
 1. The percentage of viable tumor cells in total cells in the whole slide (%): 80%
 2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 80%
 3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
 4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
 5. Additional comment: NA
- Manual macrodissection: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco[®]+

DNA test

- Mean Depth: 1072x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 154

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 $\geq 5\%$ and actionable variants with allele frequency $\geq 2\%$ were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at $100\times \geq 85\%$ with a mean coverage $\geq 500\times$.

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 $\geq 10\%$; (4) Fusions annotated in Quiver Gene Fusion Database.

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DATABASE USED

- Reference genome: Human genome sequence hg19
- COSMIC v92
- Genome Aggregation database r2.1.1
- ClinVar (version 20210404)
- ACT Genomics in-house database
- Quiver Gene Fusion Database version 5.1.18

Variant Analysis:

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

CT Huang

Sign Off

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

Yeh

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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*	BTB	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	IKBK	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*	SLC18A1*
SLC18A3*	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

Not Applicable.

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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。

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