ACT Onco® + Report

PATIENT		
Identifier: 楊國勝		Patient ID: 8654453
Date of Birth: Dec 17, 1939		Gender: Male
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
Name: 趙恒勝醫師		Tel: 886-228712121
Facility: 臺北榮總		
Address: 臺北市北投區石牌路二段 201 號		
SPECIMEN		
Specimen ID: S11144782A	Collection site: Lung	Type: FFPE tissue
Date received: Nov 10, 2022	Lab ID: AA-22-06838	D/ID: NA

ABOUT ACTOnco®+

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

SUMMARY FOR ACTIONABLE VARIANTS

VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Probable Effects in Patient's Cancer Type		Probable Sensitive in Other Cancer Types
	Sensitive	Resistant	
SMARCB1 G33fs	-	-	Tazemetostat
TMB-High	Atezolizumab, Cemiplimab-rwlc, Dostarlimab-gxly, Durvalumab, Ipilimumab, Nivolumab, Pembrolizumab	-	Avelumab, Tremelimumab

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
BRAF G466V	Cetuximab, Panitumumab, Dabrafenib, Dasatinib	Trametinib
CCNE1 Amplification	-	Palbociclib, Trastuzumab

Note:

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

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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
APC	E1345*	19.3%
BRAF	G466V	15.2%
SMARCB1	G33fs	9.9%
TP53	Q331H	18.3%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr5	*APC*	Heterozygous deletion	1
Chr19	*CCNE1*	Amplification	10

- 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)	10 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 30% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- 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 3A		
SMARCB1 G33fs	Tazemetostat	**sensitive**
Level 4		
BRAF G466V	Cetuximab, Panitumumab, Dabrafenib, Dasatinib	**sensitive**
BRAF G466V	Trametinib	**resistant**
CCNE1 Amplification	Palbociclib, Trastuzumab	**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 (10 muts/Mb)	Atezolizumab, Cemiplimab-rwlc, Dostarlimab-gxly, Durvalumab, Ipilimumab, Nivolumab, Pembrolizumab	Avelumab, Tremelimumab

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

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

HORMONAL THERAPIES

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

OTHERS

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

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

VARIANT INTERPRETATION

Tumor mutational burden (TMB): High (10 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][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].

APC E1345*, Heterozygous deletion

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[11]. APC is also associated with cell migration and adhesion, apoptosis, and DNA repair[12][13]. 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). E1345* mutation results in a premature truncation of the APC protein at amino acid 1345 (UniProtKB). This mutation is predicted to lead to a loss of APC function, despite not having characterized in the literature. Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

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[14].

BRAF G466V

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[15][16]. 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)[17][18]. 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[19][20].

The G466V mutation results in an amino acid substitution from a glycine to a valine at position 466 in exon11 of BRAF protein. This mutation impairs BRAF kinase activity but activates MEK and ERK through transactivation of c-RAF[21].

Therapeutic and prognostic relevance

In a clinical study, a patient with metastatic colorectal cancer harboring BRAF G466V was treated with a panitumumab combined with irinotecan and resulted in tumor regression[22].

In a preclinical study, treatment of trametinib, dabrafenib, or combination resulted in decreased cell proliferation in a NSCLC cell line harboring BRAF G466V[23]. However, in the phase II NCI-MATCH trial (NCT02465060), a NSCLC

patient harboring BRAF G466V resulted in progressive disease after the treatment with trametinib[24]. Other preclinical studies showed that lung cancer cell lines harboring BRAF G466V were sensitive to dasatinib and cetuximab but had decreased response to vemurafenib in vitro[21][22][25][26].

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

SMARCB1 G33fs

Biological Impact

SMARCB1, also known as INI1 and SNF5, encodes a core subunit of SWI/SNF chromatin remodeling complex which plays essential roles in transcription regulation and cell differentiation[27][28][29]. In cancer, SMARCB1 acts as a strong tumor suppressor, inactivation of SMARCB1 by mutation or deletion are frequently found in various types of cancer. SMARCB1 biallelic inactivation has been reported in the majority of atypical teratoid/rhabdoid tumors (AT/RT)[30][31][32]while gene deletions are observed in poorly differentiated chordomas[33], epithelioid schwannoma[34][35], hepatoblastoma[36], soft tissue sarcoma[37][38], epithelioid sarcoma[39], and sinonasal carcinoma[40].

G33fs mutation results in a change in the amino acid sequence beginning at 33, likely to cause premature truncation of the functional SMARCB1 protein (UniProtKB). This mutation is predicted to lead to a loss of SMARCB1 protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

On January, 2020 FDA has approved tazemetostat, an EZH2 inhibitor in patients with histologically confirmed, metastatic or locally advanced epithelioid sarcoma with INI1 (SMARCB1) loss (Study EZH-202, NCT02601950)[41]. The preclinical investigation has mainly focused on the specific interrogation of SMARCB1-related biology[42]. For example, inhibition of EZH2 has been reported to induce apoptosis and differentiation in SMARCB1-deleted malignant rhabdoid tumor (MRT) cells[43][44]. Of note, a patient with SMARCB1-deleted, metastatic, poorly differentiated chordoma displayed an exceptional and durable response after treated with tazemetostat, an EZH2 inhibitor[45]. Downregulation of SMARCB1 has been correlated with poor prognosis in patients with melanoma and knocking down of SMARCB1 in melanoma cell lines resulted in chemoresistance[46]. Furthermore, there are case reports demonstrated that patients with squamous cell carcinoma or myoepithelial carcinoma harboring copy number loss of SMARCB1 showed rapid disease progression after chemotherapy treatments[47][48].

TP53 Q331H

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[49]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[50].

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)[51].

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[52]. 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[53].

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[54][55][56]. 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)[57]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[58][59]. 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[60].

CCNE1 Amplification

Biological Impact

The CCNE1 gene encodes the cyclin E1 protein, a regulator of the cell cycle that activates the cyclin-dependent protein kinase 2 (CDK2) and plays a role in regulating cells' transition from G1 to S phase and the maintenance of genomic stability[61]. Increasing in cyclin E1 level, either by gene amplification or overexpression, is found in a diverse range of cancers and can be indicative of poor prognosis[62].

Therapeutic and prognostic relevance

There are no FDA-approved therapies targeting cyclin E1 currently available[63]. Dinaciclib, a CDK1/2 specific inhibitor, is currently under clinical evaluation[64]. A combination of dinaciclib, a small molecule CDK2 inhibitor, and AKT inhibitors that may selectively target patients with CCNE1-amplified high-grade serous ovarian cancer (HGSC) in preclinical setting[65]. A preclinical study in breast cancer cell lines showed that amplification of CCNE1 is associated with acquired resistance to CDK4/6 inhibition by palbociclib[66]. A study of HER2-amplified breast cancer patients indicated that amplification of CCNE1 was associated with trastuzumab resistance and shorter progression-free survival[67].

There are retrospective study and meta-analysis demonstrated that amplification and overexpression of CCNE1 are associated with poor survival in cancer patients[68][69]. From the result of PALOMA-3 phase III trial, pre-treated hormone receptor-positive/HER2-negative metastatic breast cancer patients were resistant to palbociclib treatment when CCNE1 was highly expressed (median PFS: CCNE1 high, 7.6 months; CCNE1 low, 14.1 months)[70]. CCNE1 amplification has been selected as an inclusion criteria for the trial examining palbociclib in malignant solid tumor (NCT02896335, NCT03155620, NCT01037790, NCT03526250).

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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)

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]
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[71] 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[72] NCT02008227	**Non-small cell lung carcinoma** (Approved on 2016/10/18)
	PD-L1
	Atezolizumab vs. Docetaxel [OS(M): 13.8 vs. 9.6]
POPLAR[73] NCT01903993	**Non-small cell lung carcinoma** (Approved on 2016/10/18)
	PD-L1
	Atezolizumab vs. Docetaxel [OS(M): 12.6 vs. 9.7]
IMvigor210[74] 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[75] 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]
JAVELIN Merkel 200[76] NCT02155647	**Merkel cell carcinoma** (Approved on 2017/03/23)
	-
	Avelumab [ORR(%): 33.0, DOR(M): 2.8 to 23.3+]

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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 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]

Cetuximab (ERBITUX)

Cetuximab is a recombinant, chimeric (human/mouse) monoclonal antibody that binds to the extracellular domain and inhibits epidermal growth factor receptor (EGFR). Cetuximab is developed by ImClone and marketed by Eli Lilly under the trade name ERBITUX.

- FDA Approval Summary of Cetuximab (ERBITUX)

BEACON CRC[77] 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]
CRYSTAL[78] NCT00154102	**Colorectal cancer** (Approved on 2012/07/06)
	KRAS Wild-type/EGFR-expressing
	Cetuximab + 5-fluorouracil + folinic acid + irinotecan vs. 5-fluorouracil + folinic acid + irinotecan [PFS(M): 8.9 vs. 8.1]
EXTREME[79] NCT00122460	**Head and neck cancer** (Approved on 2011/11/07)
	-
	Cetuximab + cisplatin/carboplatin + 5-fu vs. Cisplatin/carboplatin + 5-fu [OS(M): 10.1 vs. 7.4]
[80] NCT00004227	**Head and neck cancer** (Approved on 2006/03/01)
	-
	Cetuximab + radiation vs. Radiation [OS(M): 49 vs. 29.3]
[81] NCT00063141	**Colorectal cancer** (Approved on 2004/02/12)
	KRAS Wild-type/EGFR-expressing
	Cetuximab + irinotecan vs. Irinotecan [DOR(M): 5.7 vs. 4.2]

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Dabrafenib (TAFINLAR)

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

- FDA Approval Summary of Dabrafenib (TAFINLAR)

BRF117019, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060, NCT02124772	**Cancer** (Approved on 2022/06/22)
	BRAF V600E
	Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0]
BRF117019[82] NCT02034110	**Thyroid gland anaplastic carcinoma** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[83] 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[84] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E
	Dabrafenib + trametinib vs. Dabrafenib + placebo [PFS(M): 9.8 vs. 8.8]
COMBI-v[85] NCT01597908	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E
	Dabrafenib + trametinib vs. Vemurafenib [OS(M): 11.4 vs. 7.3]
BREAK-3[86] NCT01227889	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E
	Dabrafenib vs. Dacarbazine [PFS(M): 5.1 vs. 2.7]

Dasatinib (SPRYCEL)

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

- FDA Approval Summary of Dasatinib (SPRYCEL)

DASISION[87] NCT00481247	**Chronic myeloid leukemia** (Approved on 2010/10/28)
	-
	Dasatinib vs. Imatinib [ORR(%): 76.8 vs. 66.2]
[88] NCT00123474	**Chronic myeloid leukemia** (Approved on 2007/11/08)
	-
	Dasatinib [ORR(%): 63.0]
[89] NCT00123487	**Acute lymphocytic leukemia** (Approved on 2006/06/28)
	-
	Dasatinib [ORR(%): 38.0]

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]

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[90] 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[91] 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[92] NCT02060188	**Colorectal cancer** (Approved on 2018/07/10)
	MSI-H or dMMR
	Ipilimumab plus nivolumab vs. Nivolumab [ORR(%): 49.0 vs. 32.0]
CHECKMATE-214[93] NCT02231749	**Renal cell carcinoma** (Approved on 2018/04/16)
	-
	Nivolumab plus ipilimumab vs. Sunitinib [OS(M): 67.1 vs. 55.5]
EORTC 18071[94] NCT00636168	**Melanoma** (Approved on 2015/10/28)
	-
	Ipilimumab vs. Placebo [RFS(M): 26 vs. 17]
MDX010-20[95] 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 (nsclc)** (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]
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[96] 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[97] NCT02181738	**Hodgkin's lymphoma** (Approved on 2016/05/17)
	-
	Nivolumab [ORR(%): 66.0]
CheckMate 039[98] NCT01592370	**Hodgkin's lymphoma** (Approved on 2016/05/17)
	-
	Nivolumab [ORR(%): 66.0]
CheckMate 067[99] NCT01844505	**Melanoma** (Approved on 2016/01/23)
	-
	Ipilimumab vs. Placebo [PFS(M): 11.5 vs. 2.9]
CheckMate 066[100] NCT01721772	**Melanoma** (Approved on 2015/11/24)
	BRAF V600 wild-type
	Nivolumab vs. Dacarbazine [OS(M): Not Reached vs. 10.8]
CheckMate 025[101] NCT01668784	**Renal cell carcinoma** (Approved on 2015/11/23)
	-
	Nivolumab vs. Everolimus [OS(M): 25 vs. 19.6]
CheckMate 057[102] NCT01673867	**Non-small cell lung carcinoma** (Approved on 2015/10/09)
	-
	Nivolumab vs. Docetaxel [OS(M): 12.2 vs. 9.4]

CheckMate 017[103] NCT01642004	**Non-small cell lung carcinoma** (Approved on 2015/03/04)
	-
	Nivolumab vs. Docetaxel [OS(M): 9.2 vs. 6]
CheckMate 037[104] NCT01721746	**Melanoma** (Approved on 2014/12/22)
	-
	Nivolumab vs. Dacarbazine or carboplatin + paclitaxel [ORR(%): 32.0]

Panitumumab (VECTIBIX)

Panitumumab is a fully human monoclonal antibody against the human epidermal growth factor receptor (EGFR) and binds to the extracellular domain to prevent its activation. Panitumumab is developed by Abgenix and Amgen, and marketed by the latter under the trade name VECTIBIX.

- FDA Approval Summary of Panitumumab (VECTIBIX)

Study 20050203[105] NCT01412957	**Colorectal cancer** (Approved on 2017/06/29)
	KRAS Wild-type
	Panitumumab + bsc vs. Bsc [OS(M): 10 vs. 6.9]
PRIME[106] NCT00364013	**Colorectal cancer** (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab + folfox vs. Folfox [PFS(M): 9.6 vs. 8]
ASPECCT[107] NCT01001377	**Colorectal cancer** (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab vs. Cetuximab [OS(M): 10.4 vs. 10]
Study 20080763[108] NCT00113763	**Colorectal cancer** (Approved on 2006/09/27)
	KRAS Wild-type
	Panitumumab + bsc vs. Bsc [PFS(M): 3.2 vs. 2]

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-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]

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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]
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[109] 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[110] NCT02267603	**Merkel cell carcinoma** (Approved on 2018/12/19)
	-
	Pembrolizumab [ORR(%): 56.0]

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KEYNOTE-224[111] NCT02702414	**Hepatocellular carcinoma** (Approved on 2018/11/09)
	-
	Pembrolizumab [ORR(%): 17.0]
KEYNOTE-407[112] 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[112] 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-158 NCT02628067	**Cervical cancer** (Approved on 2018/06/13)
	-
	Pembrolizumab [ORR(%): 14.3]
KEYNOTE-170 NCT02576990	**Mediastinal large b-cell lymphoma** (Approved on 2018/06/13)
	-
	Pembrolizumab [ORR(%): 45.0]
KEYNOTE-059 NCT02335411	**Gastric adenocarcinoma, Gastroesophageal junction adenocarcinoma** (Approved on 2017/09/22)
	-
	Pembrolizumab [ORR(%): 13.3]
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-158 NCT02628067	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-028[113][114] NCT02054806	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-012[115][116][117][118] NCT01848834	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-045[119] 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[120] NCT02453594	**Hodgkin's lymphoma** (Approved on 2017/03/14)
	-
	Pembrolizumab [ORR(%): 69.0]
KEYNOTE-024[121] NCT02142738	**Non-small cell lung carcinoma** (Approved on 2016/10/24)
	PD-L1
	Pembrolizumab vs. Chemotherapy [PFS(M): 10.3 vs. 6]

KEYNOTE-012[116] NCT01848834	**Head and neck squamous cell carcinoma** (Approved on 2016/08/05)
	-
	Pembrolizumab [ORR(%): 16.0]
KEYNOTE-006[122] NCT01866319	**Melanoma** (Approved on 2015/12/18)
	-
	Pembrolizumab vs. Ipilimumab (3mg/kg every 3 weeks) [OS(M): NR vs. 16]
KEYNOTE-010[123] NCT01905657	**Non-small cell lung carcinoma** (Approved on 2015/10/02)
	PD-L1
	Pembrolizumab [OS(M): 10.4 vs. 8.5]
KEYNOTE-002[124] NCT01704287	**Melanoma** (Approved on 2014/09/24)
	-
	Pembrolizumab vs. Chemotherapy [PFS(M): 2.9 vs. 2.7]

Tazemetostat (TAZVERIK)

Tazemetostat is an inhibitor of the methyltransferase, EZH2, and some EZH2 gain-of-function mutations including Y646X, A682G, and A692V. Tazemetostat is developed and marketed by Epizyme under the trade name TAZVERIK.

- FDA Approval Summary of Tazemetostat (TAZVERIK)

E7438-G000-101 NCT01897571	**Follicular lymphoma** (Approved on 2020/06/18)
	EZH2 mutation
	Tazemetostat (ezh2 mutant) vs. Tazemetostat (ezh2 wild-type) [ORR(%): 69.0 vs. 34.0, DOR(M): 10.9 vs. 13]
EZH-202 NCT02601950	**Epithelioid sarcoma** (Approved on 2020/01/23)
	INI1 loss
	Tazemetostat [ORR(%): 15.0]

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)

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.

IMMUNE CHECKPOINT INHIBITORS

Atezolizumab

(NCT04589845, Phase 2)

TAPISTRY is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in participants with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations or who are tumor mutational burden (TMB)-high as identified by a validated next-generation sequencing (NGS) assay. Participants with solid tumors will be treated with a drug or drug regimen tailored to their NGS assay results at screening. Participants will be assigned to the appropriate cohort based on their genetic alteration(s). Treatment will be assigned on the basis of relevant oncogenotype, will have cohort-specific inclusion/exclusion criteria, and, unless otherwise specified, will continue until disease progression, loss of clinical benefit, unacceptable toxicity, participant or physician decision to discontinue, or death, whichever occurs first.

- Contact

Name: Reference Study ID Number: BO41932 https://forpatients.roche.com/
Phone: 888-662-6728 (U.S. and Canada)
Email: Global-Roche-Genentech-Trials@gene.com

- Location

Status: Recruiting Country: Taiwan City: Tainan Name: National Cheng Kung University Hospital; Oncology	Status: Recruiting Country: Taiwan City: Taipei City Name: Taipei Veterans General Hospital; Department of Oncology
Status: Recruiting Country: Taiwan City: Taoyuan County Name: Chang Gung Memorial Hospital-Linkou; Dept of Oncology	Status: Active, not recruiting Country: Taiwan City: Zhongzheng Dist. Name: National Taiwan University Hospital; Oncology

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

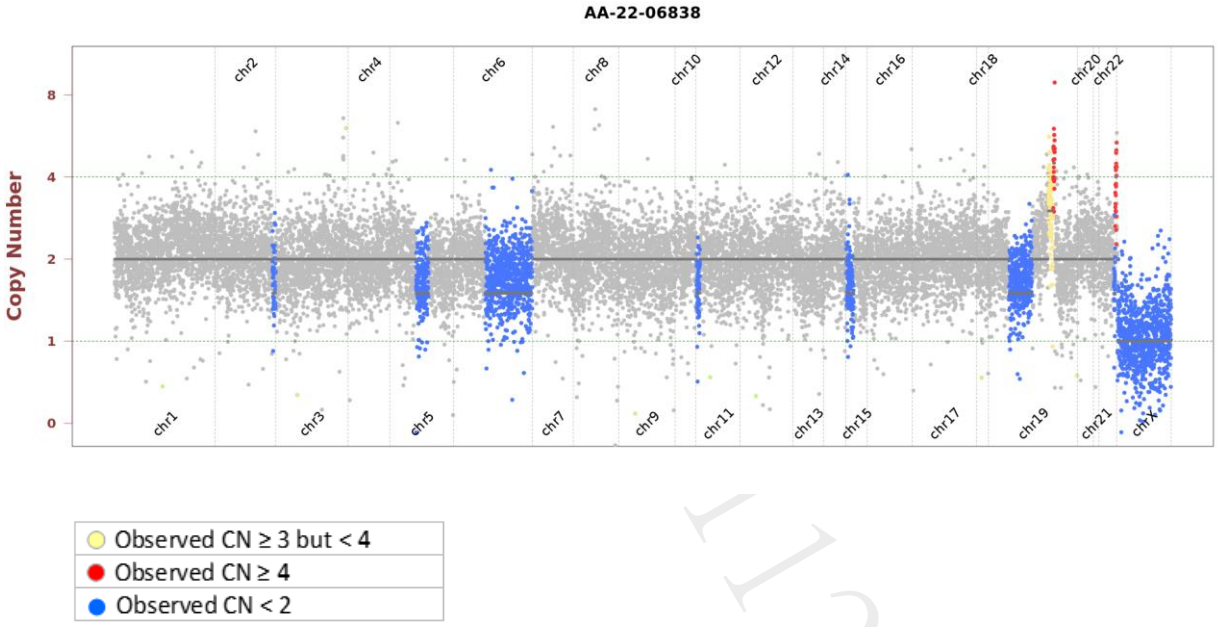
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
APC	E1345*	16	c.4033G>T	NM_000038	COSM18759	19.3%	742
BRAF	G466V	11	c.1397G>T	NM_004333	COSM451	15.2%	1742
SMARCB1	G33fs	2	c.98del	NM_003073	COSM6922621	9.9%	553
TP53	Q331H	9	c.993G>T	NM_000546	COSM96339	18.3%	988

- 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
ADAMTS16	P966L	19	c.2897C>T	NM_139056	-	6.2%	417
AKT3	P469fs	13	c.1406del	NM_005465	-	10.3%	880
ATR	A1488V	25	c.4463C>T	NM_001184	-	48.7%	872
B2M	A11E	1	c.32C>A	NM_004048	-	16.0%	381
BUB1B	Splice acceptor	-	c.2285del	NM_001211	-	10.0%	957
CTCF	R533L	9	c.1598G>T	NM_006565	COSM3957719	16.7%	1077
FGFR2	V28F	2	c.82G>T	NM_000141	-	14.8%	1397
IGF1R	P842S	12	c.2524C>T	NM_000875	COSM2141393	54.7%	1095
MUC16	D6322F	3	c.18964_18965delinsTT	NM_024690	-	58.1%	1493
NOTCH3	G1012V	19	c.3035G>T	NM_000435	-	26.0%	1037
PARP1	G93E	2	c.278G>A	NM_001618	-	7.4%	1140
PIK3CB	V284A	5	c.851T>C	NM_006219	-	15.6%	1782
PTCH1	T416S	9	c.1247C>G	NM_000264	COSM27114	37.8%	1158
PTPRT	I441M	8	c.1323C>G	NM_007050	-	53.8%	1330
RECQL4	R780W	15	c.2338C>T	NM_004260	-	36.9%	358
SMO	Splice acceptor	-	c.1802-1G>T	NM_005631	-	16.8%	934
STAT3	A766T	24	c.2296G>A	NM_139276	-	48.0%	1202
TNF	P215A	4	c.643C>G	NM_000594	-	16.4%	1295
TSHR	S305R	10	c.915T>A	NM_000369	-	48.6%	1314
USH2A	V1702L	25	c.5104G>T	NM_206933	COSM3977010	14.3%	546
WT1	Q437K	8	c.1309C>A	NM_024426	-	16.8%	1105

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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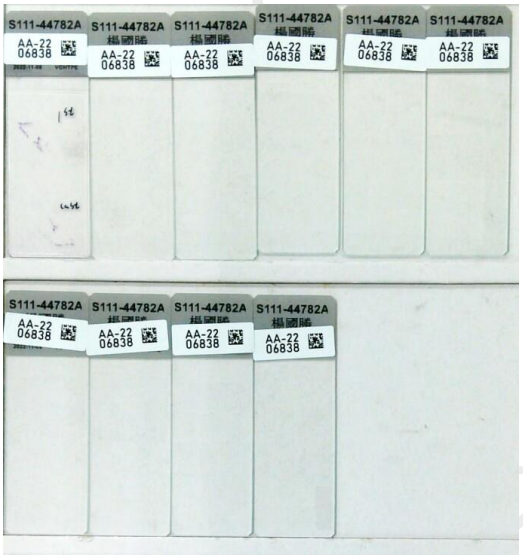
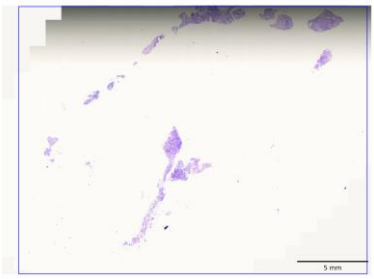
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: Nov 01, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11144782A
- Collection site: Lung
- Examined by: Dr. Chien-Ta Chiang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 30%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 30%
    3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 5%
    4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 5%
    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: 975x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 119

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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.

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

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RNA test

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

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

DATABASE USED

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

Variant Analysis:
醫檢師張筑芃 博士
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GENE LIST

SNV & CNV

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

*Analysis of copy number alterations NOT available.

FUSION

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

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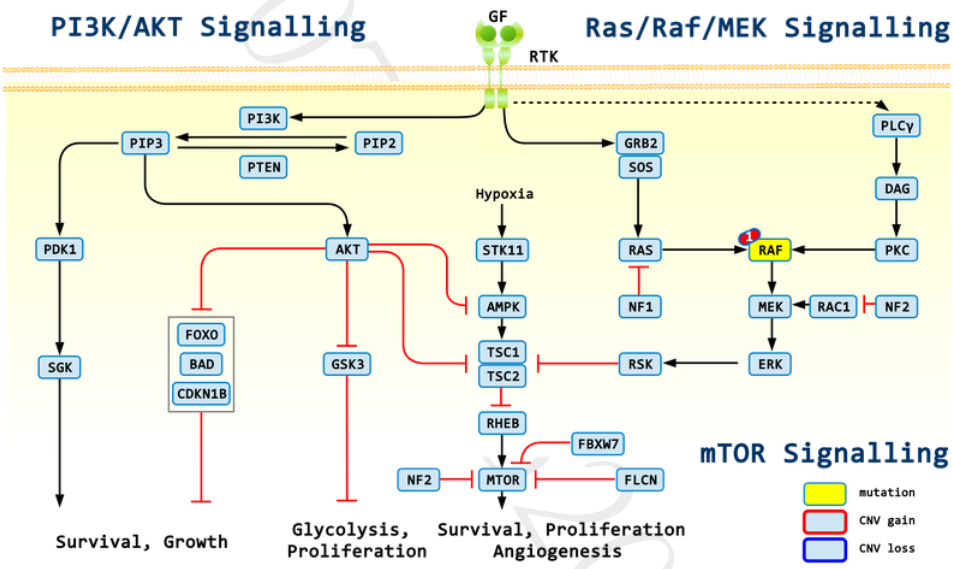
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Not Applicable.

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Dabrafenib

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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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