ACT Onco®+ Report

PATIENT		
Identifier: 陳玉秀		Patient ID: 7759844
Date of Birth: Jun 13, 1946		Gender: Female
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
Name: 趙恒勝醫師		Tel: 886-228712121
Facility: 臺北榮總		
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SPECIMEN		
Specimen ID: S11139470A/B	Collection site: Lung	Type: FFPE tissue
Date received: Oct 17, 2022	Lab ID: AA-22-06246	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	
KRAS G12V	-	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-
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
KRAS G12V	-	Cetuximab, Panitumumab

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
KRAS	G12V	21.5%
RBM10	Splice donor	21.1%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr17	*FLCN*	Heterozygous deletion	1

- 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)	9.4 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 50% 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 2		
KRAS G12V	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	**resistant**
Level 3A		
KRAS G12V	Cetuximab, Panitumumab	**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 (9.4 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.

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VARIANT INTERPRETATION

Tumor mutational burden (TMB): High (9.4 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].

KRAS G12V

Biological Impact

The V-Ki-Ras2 Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (KRAS) gene encodes a small GTPase protein, a member of the RAS family of small GTPases, which catalyze the hydrolysis of GTP to GDP. RAS proteins cycle between an active (GTP-bound) and an inactive (GDP-bound) state, to activate the downstream oncogenic pathways, including the PI3K/AKT/mTOR and MAPK pathways[11]. KRAS mutations occur primarily in three hotspots G12, G13 and Q61, and less frequently in codon A146[11][12]. These are activating mutations that lead to constitutive activation and persistent stimulation of the downstream signaling pathways[13][14]. Mutations in KRAS have been reported in a diverse spectrum of human malignancies, including pancreatic carcinomas (>80%)[11][15], colon carcinomas (40-50%)[16][17], and lung carcinomas (30-50%)[18][19], but are also present in biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer, liver cancer, myeloid leukemia and breast cancer[12].

KRAS G12V is a hotspot mutation that has been shown to result in the increased activation of downstream signaling pathways[20].

Therapeutic and prognostic relevance

Except for KRAS G12C, other KRAS mutants are not currently targetable, but the downstream MEK serves as a potential target[21]. MEK inhibitors trametinib, cobimetinib, and binimetinib were approved by the U.S. FDA for patients with advanced metastatic melanoma whose tumors harbor BRAF V600 mutations[22][23][24][25].

There are case reports indicated that patients harboring a KRAS mutation may benefit from MEK inhibitor treatment. A patient with small cell neuroendocrine carcinoma (SCNEC) of the cervix harboring a KRAS G12D mutation showed significant response with trametinib[26]. Another low-grade serous carcinoma case with KRAS G12D also has sustained response to trametinib (Am J Clin Exp Obstet Gynecol 2015;2(3):140-143). In addition, a low-grade serous ovarian cancer patient harboring KRAS G12V mutation showed stable disease after 8 weeks of binimetinib treatment, and demonstrated a partial response after another 26 weeks of treatment[27]. However, trametinib did not demonstrate superiority to docetaxel in KRAS-mutant non-small cell lung cancer (NSCLC) patients, based on results from a randomized Phase II study[28].

Both clinical and preclinical studies demonstrated a limited response to monotherapy using MEK inhibitors[29]. Moreover, several clinical trials are in progress to evaluate the combination of MEK and mTOR inhibition as a new potential therapeutic strategy in CRC[30], and in patient-derived xenografts of RAS-mutant CRC, inhibition of MEK and mTOR suppressed tumor growth, but not tumor regression[31]. A study using the CRC patient-derived xenograft (PDX) model showed that the combination of trametinib, a MEK inhibitor, and palbociclib, a CDK4/6 inhibitor, was well tolerated and resulted in objective responses in all KRAS mutant models[32].

KRAS mutation has been determined as an inclusion criterion for the trials evaluating MEK inhibitors efficacies in various types of solid tumors (NCT03704688, NCT02399943, NCT02285439, NCT03637491, NCT04214418).

Cetuximab and panitumumab are two EGFR-specific antibodies approved by the U.S. FDA for patients with KRAS wild-type metastatic colorectal cancer (NCT00154102, NCT00079066, NCT01412957, NCT00364013). Results from the PRIME and FIRE-3 trials indicated that panitumumab and cetuximab did not benefit patients with KRAS or NRAS mutations and may even have a detrimental effect in these patients[33]. Taken together, the National Comprehensive Cancer Network (NCCN) recommended that, cetuximab and panitumumab should only be used if both KRAS and NRAS genes are normal (NCCN guidelines)[34][35]. Numerous studies have demonstrated the presence of KRAS or NRAS mutations at exon 2, 3 or 4 as a predictor of resistance to anti-EGFR therapies[36][37][38][39][40][41][42].

Sorafenib, a multi-kinase inhibitor, has been shown to be beneficial in KRAS-mutant CRC[43], KRAS-mutant NSCLC[44], and KRAS-amplified melanoma[45].

There has been conflicting data on the effect of KRAS mutation on the efficacy of bevacizumab in metastatic CRC patients(J Clin Oncol 34, 2016 (suppl; abstr 3525))[46][47].

In NCCN guidelines for NSCLC, KRAS mutations have been suggested as an emerging biomarker for EGFR TKIs in NSCLC patients. KRAS mutations are associated with a lack of efficacy of EGFR TKIs, including erlotinib, gefitinib, afatinib, and osimertinib, in NSCLC patients[48][49][50].

Studies have shown that KRAS mutation, especially those occurs in exon 2 (codon 12 or 13) and codon 61 indicated a poor prognosis for patients with CRC[51].

In low-grade serous carcinoma of the ovary or peritoneum, patients with KRAS or BRAF mutations (n=21) had a significantly better OS than those with wild-type KRAS or BRAF (n=58) (106.7 months vs 66.8 months), respectively[52]. In ovarian serous borderline tumor with recurrent low-grade serous carcinoma, patient harboring KRAS G12V mutation appeared to have shorter survival time[53].

In patients with metastatic colorectal cancer treated with bevacizumab, the shortest survival was observed in patients with tumors harboring G12V or G12A KRAS mutation, and the PFS and OS for patients with G12V/A KRAS mutation was 6.6 and 16.8 compared to 11.6 and 23.6 months for patients with tumors harboring other KRAS mutation type[54]. In another retrospective study, Patients with KRAS G12V exhibited worse OS and higher recurrence incidences compared with the entire cohort (OS: 26 months vs 60 months; DFS: 15 months vs 24 months) in lung adenocarcinoma[55].

RBM10 Splice donor

Biological Impact

RBM10 (RNA binding motif protein 10) gene encodes a nuclear protein of the RNA-binding motif gene family which plays essential roles in alternative splicing[56][57]. Loss-of-function of RBM10 has been reported as the causes of TARP syndrome which results in pre- or postnatal death in affected males[58][59][60]. Mutations of RBM10 have been reported in lung adenocarcinoma[61][62][63], bladder and colorectal cancer[64].

RBM10 c.502+1G>T is a variant located at the splice donor region, which may result in the exon skipping.

Therapeutic and prognostic relevance

Low expression of RBM10 was associated with shorter overall survival in lung adenocarcinoma patients[65].

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FLCN Heterozygous deletion

Biological Impact

The FLCN gene encodes the tumor suppressor, Folliculin, a GTPase activating protein (GAP) for RagC/D GTPase proteins involved in amino acid sensing and signaling to mTORC1[66]. FLCN has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[67][68]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[69][70]. Germline mutation of the FLCN gene causes the Birt-Hogg-Dubé syndrome, a rare disorder that is characterized by benign hamartomatous skin lesions and an increased risk of pneumothorax and renal tumors[71].

Therapeutic and prognostic relevance

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTC) patients who had PI3K/mTOR/AKT alterations, including TSC2, FLCN or NF1, showed impressive progression-free survival (PFS) of 15.2 months after receiving everolimus[72]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[73].

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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[74] 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[75] NCT02008227	**Non-small cell lung carcinoma** (Approved on 2016/10/18)
	PD-L1
	Atezolizumab vs. Docetaxel [OS(M): 13.8 vs. 9.6]
POPLAR[76] NCT01903993	**Non-small cell lung carcinoma** (Approved on 2016/10/18)
	PD-L1
	Atezolizumab vs. Docetaxel [OS(M): 12.6 vs. 9.7]
IMvigor210[77] 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[78] 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[79] 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 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]

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[80] 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[81] NCT02125461	**Non-small cell lung carcinoma** (Approved on 2018/02/16)
	-
	Durvalumab vs. Placebo [PFS(M): 16.8 vs. 5.6]

Everolimus (AFINITOR)

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

- FDA Approval Summary of Everolimus (AFINITOR)

RADIANT-4[82] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[83] NCT00863655	**Breast cancer** (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
EXIST-2 NCT00790400	**Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma** (Approved on 2012/04/26)
	-
	Everolimus vs. Placebo [ORR(%): 41.8 vs. 0]
RADIANT-3[84] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[85] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[86] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

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]
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 (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]

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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[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]

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]
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[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-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[104][105] NCT02054806	**Cancer** (Approved on 2017/05/23) **MSI-H or dMMR** Pembrolizumab [ORR(%): 39.6]
KEYNOTE-012[106][107][108][109] NCT01848834	**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]

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Temsirolimus (TORISEL)

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

- FDA Approval Summary of Temsirolimus (TORISEL)

[116] NCT00065468	**Renal cell carcinoma** (Approved on 2007/05/30)
	-
	Temsirolimus vs. Ifn-α [OS(M): 10.9 vs. 7.3]

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

ACT Onco® + Report

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

ACT Onco® + Report

SUPPLEMENTARY INFORMATION OF TESTING RESULTS

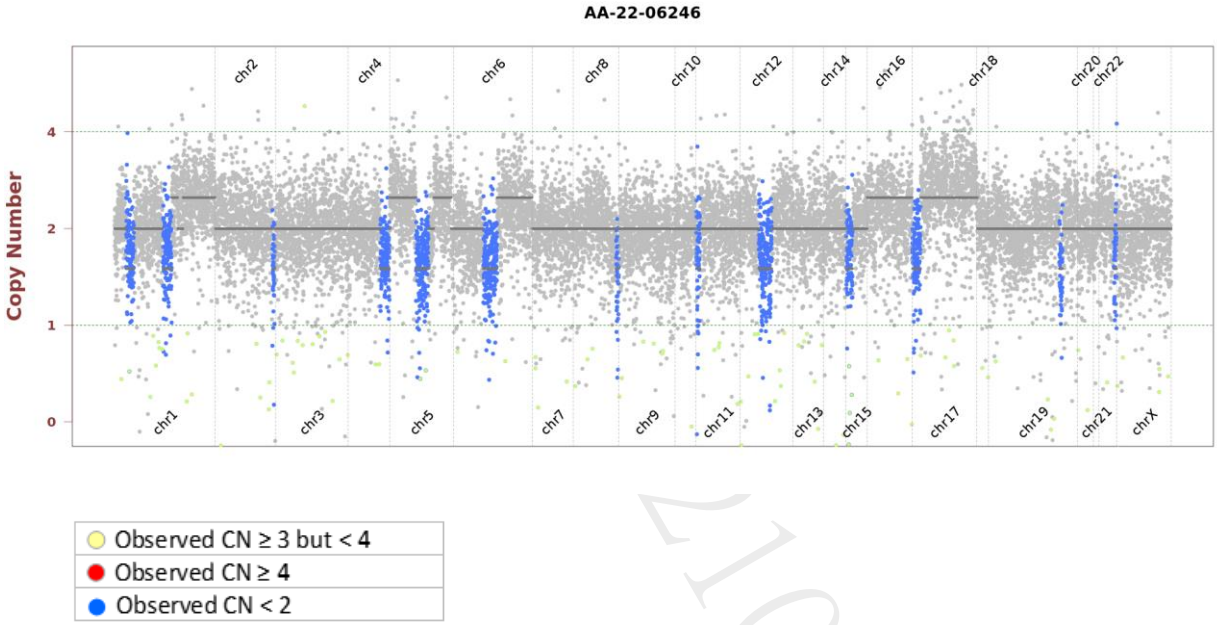
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
KRAS	G12V	2	c.35G>T	NM_004985	COSM520	21.5%	2032
RBM10	Splice donor	-	c.502+1G>T	NM_005676	-	21.1%	810

- 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
ABL1	R589C	11	c.1765C>T	NM_005157	COSM1106019	45.8%	754
ADAMTSL1	T1305I	21	c.3914C>T	NM_001040272	-	53.4%	1018
ADGRA2	R357H	8	c.1070G>A	NM_032777	-	48.9%	333
ALK	A704S	12	c.2110G>T	NM_004304	-	18.3%	633
ALK	W1366R	28	c.4096T>C	NM_004304	-	5.1%	453
ARID1A	P109S	1	c.325C>T	NM_006015	-	51.4%	257
AURKA	Splice region	-	c.1029+7C>T	NM_198436	-	50.0%	1045
BCOR	N1459S	10	c.4376A>G	NM_001123385	COSM403987	21.5%	1022
BRCA2	N108S	4	c.323A>G	NM_000059	-	49.9%	1063
CARD11	A581T	13	c.1741G>A	NM_032415	COSM3663142	58.1%	668
CHEK1	R160H	6	c.479G>A	NM_001114121	COSM35410	48.1%	320
EPHA5	Splice region	-	c.1403-4G>T	NM_001281765	-	17.7%	843
ERBB2	R143Q	3	c.428G>A	NM_004448	COSM1382867	59.6%	1397
FANCD2	Splice region	-	c.696-4A>T	NM_001018115	-	22.5%	1136
FGF10	R194K	3	c.581G>A	NM_004465	-	12.9%	495
FLCN	P28R	4	c.83C>G	NM_144997	-	29.5%	444
GRIN2A	E266*	4	c.795_796delinsTT	NM_000833	-	27.0%	664
KDM6A	R165L	6	c.494G>T	NM_021140	-	15.4%	947
MUC16	D6322F	3	c.18964_18965delinsTT	NM_024690	-	49.6%	908
MUC16	G14120F	74	c.42358_42359delinsTT	NM_024690	-	19.4%	1076
MUC16	P7856T	3	c.23566C>A	NM_024690	-	19.5%	922
NOTCH1	G2051V	33	c.6152G>T	NM_017617	-	14.9%	375
PIK3C2G	V336L	5	c.1006G>T	NM_004570	-	20.3%	231
PTCH1	T416S	9	c.1247C>G	NM_000264	COSM27114	46.8%	568
RAD50	R1017H	22	c.3050G>A	NM_005732	-	65.3%	617
RAD51C	R368Q	9	c.1103G>A	NM_058216	COSM981989	37.7%	1216
RPTOR	T548M	15	c.1643C>T	NM_020761	-	62.7%	585
SMO	T179M	2	c.536C>T	NM_005631	COSM6927006	52.6%	840
SPEN	R2796G	11	c.8386C>G	NM_015001	COSM2088048	48.4%	599
STAG2	E194K	8	c.580G>A	NM_001042751	COSM6917310	15.8%	885
TET2	Q341K	3	c.1021C>A	NM_001127208	-	18.6%	1360
TSHR	H32Y	1	c.94C>T	NM_000369	-	55.7%	1886
USH2A	C3223S	49	c.9667T>A	NM_206933	-	17.0%	1118
USH2A	V2228E	35	c.6683T>A	NM_206933	-	43.2%	1385

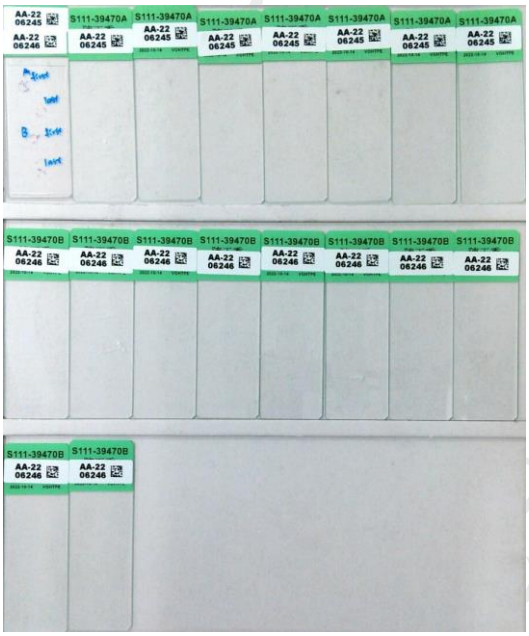
Note:

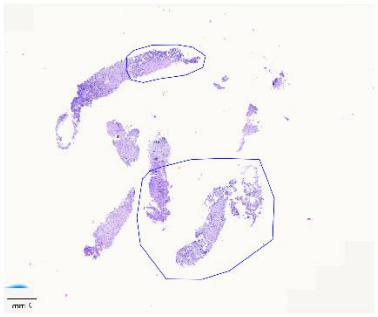
- This table enlists variants detected by the panel other than those with clinical relevance (reported in Testing Result section). The clinical impact of a genetic variant is determined according to ACT Genomics in-house clinical knowledge database. A negative result does not necessarily indicate absence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

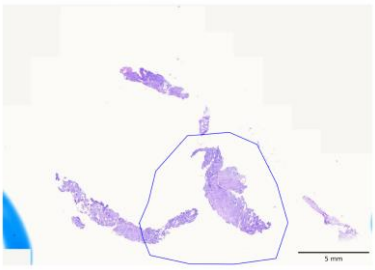
ACTOnco®+ Report

TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW







- Collection date: Sep 30, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11139470A/B
- Collection site: Lung
- Examined by: Dr. Yun-An Chen
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 60%/50%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 75%/70%
    3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 2%/0%
    4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%/0%
    5. Additional comment: N/A/N/A
- Manual macrodissection: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 828x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 19

ACT Onco® + Report

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).

ACT Onco® + Report

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
Chu-Yuan Chang Ph.D.
檢字第 020115 號

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

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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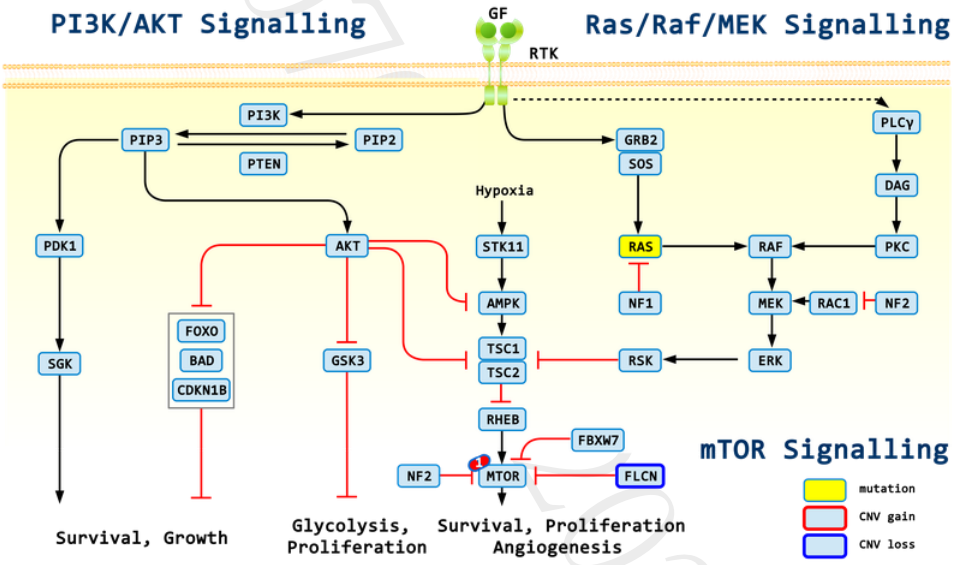
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
FLCN	Everolimus, Temsirolimus	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Everolimus, Temsirolimus

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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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REFERENCE

1. PMID: 26559592; 2015, N Engl J Med;373(20):1984
Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma.

2. PMID: 26359337; 2015, Science;350(6257):207-211
Genomic correlates of response to CTLA-4 blockade in metastatic melanoma.

3. PMID: 28251903; 2017, Sci Transl Med;9(379):
Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance.

4. PMID: 26997480; 2016, Cell;165(1):35-44
Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma.

5. PMID: 25765070; 2015, Science;348(6230):124-8
Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.

6. PMID: 26028255; 2015, N Engl J Med;372(26):2509-20
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency.

7. PMID: 29863979; 2018, N Engl J Med;379(4):341-351
PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma.

8. PMID: 26952546; 2016, Lancet;387(10031):1909-20
Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial.

9. PMID: 27009843; 2016, Oncotarget;7(16):22857-64
Analysis of ultra-deep targeted sequencing reveals mutation burden is associated with gender and clinical outcome in lung adenocarcinoma.

10. PMID: 24839032; 2014, Breast Cancer Res Treat;146(1):211-20
Somatic mutation load of estrogen receptor-positive breast tumors predicts overall survival: an analysis of genome sequence data.

11. PMID: 2453289; 1988, Cell;53(4):549-54
Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes.

12. PMID: 2114981; 1990, Eur J Clin Invest;20(3):225-35
ras oncogenes: their role in neoplasia.

13. PMID: 20617134; 2010, J Biomed Biotechnol;2010():150960
Clinical relevance of KRAS in human cancers.

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

15. PMID: 3047672; 1988, Nucleic Acids Res;16(16):7773-82
KRAS codon 12 mutations occur very frequently in pancreatic adenocarcinomas.

16. PMID: 3587348; 1987, Nature;327(6120):293-7
Prevalence of ras gene mutations in human colorectal cancers.

17. PMID: 1942608; 1991, Nihon Shokakibyo Gakkai Zasshi;88(8):1539-44
[Prevalence of K-ras gene mutations in human colorectal cancers].

18. PMID: 2252272; 1990, Am Rev Respir Dis;142(6 Pt 2):S27-30
The ras oncogenes in human lung cancer.

19. PMID: 1486840; 1992, Environ Health Perspect;98():13-24
Role of proto-oncogene activation in carcinogenesis.

20. PMID: 23455880; 2013, J Cancer Res Clin Oncol;139(6):953-61
KRAS allel-specific activity of sunitinib in an isogenic disease model of colorectal cancer.

21. PMID: 25414119; 2014, Drugs;74(18):2111-28
The biology and clinical development of MEK inhibitors for cancer.

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

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

24. PMID: 25265494; 2014, N Engl J Med;371(20):1867-76
Combined vemurafenib and cobimetinib in BRAF-mutated melanoma.

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

26. PMID: 26075998; 2014, Gynecol Oncol Rep;10():28-9
Response to MEK inhibitor in small cell neuroendocrine carcinoma of the cervix with a KRAS mutation.

27. PMID: 29946554; 2018, Gynecol Oncol Rep;25():41-44
Binimetinib (MEK162) in recurrent low-grade serous ovarian cancer resistant to chemotherapy and hormonal treatment.

28. PMID: 25722381; 2015, Ann Oncol;26(5):894-901
A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC)†.

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

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

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

32. PMID: 26369631; 2016, Clin Cancer Res;22(2):405-14
Sensitivity of KRAS-Mutant Colorectal Cancers to Combination Therapy That Cotargets MEK and CDK4/6.

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

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

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

36. PMID: 25605843; 2015, J Clin Oncol;33(7):692-700
Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer.

37. PMID: 27422777; 2016, Tumour Biol;37(9):11645-11655
Potential biomarkers for anti-EGFR therapy in metastatic colorectal cancer.

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

39. PMID: 24666267; 2014, Acta Oncol;53(7):852-64
The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis.

40. PMID: 27722750; 2017, JAMA Oncol;3(2):194-201
Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL and FIRE-3 Trials.

41. PMID: 27736842; 2016, Br J Cancer;115(10):1206-1214
A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer.

42. PMID: 20921465; 2010, J Clin Oncol;28(31):4697-705
Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study.

43. PMID: 24407191; 2014, Br J Cancer;110(5):1148-54
Sorafenib and irinotecan (NEXIRI) as second- or later-line treatment for patients with metastatic colorectal cancer and KRAS-mutated tumours: a multicentre Phase I/II trial.

44. PMID: 23224737; 2013, Clin Cancer Res;19(3):743-51
A phase II study of sorafenib in patients with platinum-pretreated, advanced (Stage IIIb or IV) non-small cell lung cancer with a KRAS mutation.

45. PMID: 26307133; 2016, Clin Cancer Res;22(2):374-82
Copy Number Changes Are Associated with Response to Treatment with Carboplatin, Paclitaxel, and Sorafenib in Melanoma.

46. PMID: 23828442; 2013, Med Oncol;30(3):650
KRAS as prognostic biomarker in metastatic colorectal cancer patients treated with bevacizumab: a pooled analysis of 12 published trials.

47. PMID: 28632865; 2017, JAMA;317(23):2392-2401
Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial.

48. PMID: 18349398; 2008, J Clin Oncol;26(9):1472-8
Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib.

49. PMID: 23401440; 2013, J Clin Oncol;31(8):1112-21
KRAS mutation: should we test for it, and does it matter?

50. PMID: 18024870; 2007, J Clin Oncol;25(33):5240-7
Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer.

51. PMID: 15923428; 2005, Ann Oncol;16 Suppl 4():iv44-49
Prognostic and predictive factors in colorectal cancer: Kirsten Ras in CRC (RASCAL) and TP53CRC collaborative studies.

52. PMID: 26484411; 2015, Br J Cancer;113(9):1254-8
Impact of mutational status on survival in low-grade serous carcinoma of the ovary or peritoneum.

53. PMID: 24549645; 2013, J Pathol;231(4):449-56
KRAS (but not BRAF) mutations in ovarian serous borderline tumour are associated with recurrent low-grade serous carcinoma.

54. PMID: 26662311; 2016, Tumour Biol;37(5):6823-30
G12V and G12A KRAS mutations are associated with poor outcome in patients with metastatic colorectal cancer treated with bevacizumab.

55. PMID: 26372703; 2015, Br J Cancer;113(8):1206-15

Prognostic value of the KRAS G12V mutation in 841 surgically resected Caucasian lung adenocarcinoma cases.

56. PMID: 24530524; 2014, FEBS Lett;588(6):942-7
RBM10 regulates alternative splicing.

57. PMID: 24332178; 2013, Mol Cell;52(5):720-33
RBM5, 6, and 10 differentially regulate NUMB alternative splicing to control cancer cell proliferation.

58. PMID: 20451169; 2010, Am J Hum Genet;86(5):743-8
Massively parallel sequencing of exons on the X chromosome identifies RBM10 as the gene that causes a syndromic form of cleft palate.

59. PMID: 21910224; 2011, Am J Med Genet A;155A(10):2516-20
Long-term survival in TARP syndrome and confirmation of RBM10 as the disease-causing gene.

60. PMID: 24000153; 2013, EMBO Mol Med;5(9):1431-42
Integrative analysis revealed the molecular mechanism underlying RBM10-mediated splicing regulation.

61. PMID: 26853560; 2016, RNA Biol;13(4):466-72
Tumor suppressor properties of the splicing regulatory factor RBM10.

62. PMID: 22980975; 2012, Cell;150(6):1107-20
Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing.

63. PMID: 25079552; 2014, Nature;511(7511):543-50
Comprehensive molecular profiling of lung adenocarcinoma.

64. PMID: 28481359; 2017, Nat Med;23(6):703-713
Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients.

65. PMID: 28091594; 2017, Sci Rep;7():40488
Functional analysis reveals that RBM10 mutations contribute to lung adenocarcinoma pathogenesis by deregulating splicing.

66. PMID: 24095279; 2013, Mol Cell;52(4):495-505
The folliculin tumor suppressor is a GAP for the RagC/D GTPases that signal amino acid levels to mTORC1.

67. PMID: 26342594; 2016, Fam Cancer;15(1):127-32
Birt-Hogg-Dubé syndrome: novel FLCN frameshift deletion in daughter and father with renal cell carcinomas.

68. PMID: 23223565; 2013, J Clin Pathol;66(3):178-86
Birt-Hogg-Dube syndrome: clinicopathological features of the lung.

69. PMID: 19850877; 2009, Proc Natl Acad Sci U S A;106(44):18722-7
Homozygous loss of BHD causes early embryonic lethality and kidney tumor development with activation of mTORC1 and mTORC2.

70. PMID: 24908670; 2014, Hum Mol Genet;23(21):5706-19
Folliculin (Flcn) inactivation leads to murine cardiac hypertrophy through mTORC1 deregulation.

71. PMID: 15956655; 2005, J Natl Cancer Inst;97(12):931-5
High frequency of somatic frameshift BHD gene mutations in Birt-Hogg-Dubé-associated renal tumors.

72. PMID: 29301825; 2018, Clin Cancer Res;24(7):1546-1553
Genomic Correlates of Response to Everolimus in Aggressive Radioiodine-refractory Thyroid Cancer: A Phase II Study.

73. PMID: 26418749; 2015, Oncotarget;6(32):32761-73
Flcn-deficient renal cells are tumorigenic and sensitive to mTOR suppression.

74. PMID: 30280641; 2018, N Engl J Med;379(23):2220-2229
First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer.

75. PMID: 27979383; 2017, Lancet;389(10066):255-265

Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial.

76. PMID: 26970723; 2016, Lancet;387(10030):1837-46
Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial.

77. PMID: 27939400; 2017, Lancet;389(10064):67-76
Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial.

78. PMID: 30779531; 2019, N Engl J Med;380(12):1103-1115
Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.

79. PMID: 27592805; 2016, Lancet Oncol;17(10):1374-1385
Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial.

80. PMID: 31590988; 2019, Lancet;394(10212):1929-1939
Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial.

81. PMID: 28885881; 2017, N Engl J Med;377(20):1919-1929
Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer.

82. PMID: 26703889; 2016, Lancet;387(10022):968-977
Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study.

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

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

85. PMID: 23158522; 2013, Lancet;381(9861):125-32
Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial.

86. PMID: 18653228; 2008, Lancet;372(9637):449-56
Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial.

87. PMID: 28734759; 2017, Lancet Oncol;18(9):1182-1191
Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study.

88. PMID: 29562145; 2018, N Engl J Med;378(14):1277-1290
Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.

89. PMID: 25840693; 2015, Lancet Oncol;16(5):522-30
Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial.

90. PMID: 20525992; 2010, N Engl J Med;363(8):711-23
Improved survival with ipilimumab in patients with metastatic melanoma.

91. PMID: 27718784; 2016, N Engl J Med;375(19):1856-1867
Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck.

92. PMID: 27451390; 2016, Lancet Oncol;17(9):1283-94
Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre,

multicohort, single-arm phase 2 trial.

93. PMID: 25482239; 2015, N Engl J Med;372(4):311-9
PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma.

94. PMID: 26027431; 2015, N Engl J Med;373(1):23-34
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.

95. PMID: 25399552; 2015, N Engl J Med;372(4):320-30
Nivolumab in previously untreated melanoma without BRAF mutation.

96. PMID: 26406148; 2015, N Engl J Med;373(19):1803-13
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma.

97. PMID: 26412456; 2015, N Engl J Med;373(17):1627-39
Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer.

98. PMID: 26028407; 2015, N Engl J Med;373(2):123-35
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer.

99. PMID: 25795410; 2015, Lancet Oncol;16(4):375-84
Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial.

100. PMID: 30779529; 2019, N Engl J Med;380(12):1116-1127
Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.

101. PMID: 27093365; 2016, N Engl J Med;374(26):2542-52
PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma.

102. PMID: 29875066; 2018, Lancet Oncol;19(7):940-952
Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial.

103. PMID: 29658856; 2018, N Engl J Med;378(22):2078-2092
Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer.

104. PMID: 28291584; 2017, Lancet Oncol;18(5):623-630
Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial.

105. PMID: 28489510; 2017, J Clin Oncol;35(22):2535-2541
Safety and Antitumor Activity of Pembrolizumab in Advanced Programmed Death Ligand 1-Positive Endometrial Cancer: Results From the KEYNOTE-028 Study.

106. PMID: 27138582; 2016, J Clin Oncol;34(21):2460-7
Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study.

107. PMID: 28081914; 2017, Lancet Oncol;18(2):212-220
Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study.

108. PMID: 27247226; 2016, Lancet Oncol;17(7):956-965
Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial.

109. PMID: 27157491; 2016, Lancet Oncol;17(6):717-726
Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial.

110. PMID: 28212060; 2017, N Engl J Med;376(11):1015-1026

ACT Onco® + Report

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma.

111. PMID: 28441111; 2017, J Clin Oncol;35(19):2125-2132
Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma.

112. PMID: 27718847; 2016, N Engl J Med;375(19):1823-1833
Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer.

113. PMID: 25891173; 2015, N Engl J Med;372(26):2521-32
Pembrolizumab versus Ipilimumab in Advanced Melanoma.

114. PMID: 26712084; 2016, Lancet;387(10027):1540-50
Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial.

115. PMID: 26115796; 2015, Lancet Oncol;16(8):908-18
Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial.

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