ACTOnco®+ Report

REPORT SUMMARY

REPORT DETAILS

APPENDIX

PATIENT AND SAMPLE INFORMATION

PATIENT	SPECIMEN	ORDERING PHYSICIAN
Name: 魏光三	Type: FFPE tissue	Name: 楊慕華醫師
Gender: Male	Date received: Nov 25, 2021	Facility: 臺北榮總
Date of Birth: Mar 07, 1950	Collection site: Neck, soft tissue	Tel: 886-228712121
Patient ID: 46690840	Specimen ID: S11035953A	Address: 臺北市北投區石牌路二段 201 號
Diagnosis: Non small cell lung cancer	Lab ID: AA-21-05764	
	D/ID: NA	

VARIANT(S) WITH CLINICAL RELEVANCE

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

SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
FOXP1	Y470*	138	28.3%	-
KEAP1	E593fs	1162	29.2%	-
KMT2D	G1467fs	934	25.9%	-
NOTCH1	G1320fs	369	32.0%	COSM6935066
SERPINB4	C279*	207	59.9%	-
TP53	R273L	1243	40.5%	COSM10779

COPY NUMBER VARIANTS (CNVS)

Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on **37%** tumor purity.

Amplification (Copy number ≥ 8)

Chr	Gene	Copy Number
chr8	*FGFR1*	6¥
chr19	*AKT2*	7¥
chr17	*CDK12*	10

Homozygous deletion (Copy number=0)

Chr	Gene
ND	ND

Heterozygous deletion (Copy number=1)

Chr	Gene
chr9	*CDKN2A*

¥ Increased gene copy number was observed.

ND, Not Detected

TUMOR MUTATIONAL BURDEN (TMB)

18.2 muts/Mb **(TMB-High)**

Muts/Mb, mutations per megabase

MICROSATELLITE INSTABILITY (MSI)

Microsatellite stable (MSS)

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

Variant Analysis:
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檢字第 015647 號

Yun Yu Chen

Sign Off
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Yun Yu Chen

魏光三
Project ID: C21-M001-01337
Report No.: AA-21-05764_ONC
Date Reported: Dec 08, 2021

THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3B		
CDKN2A Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	**sensitive**

‡ Refer to "ONGOING CLINICAL TRIALS" section for detailed trial information.

Note: Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence.

Level		Description
1		FDA-recognized biomarker predictive of response to an FDA approved drug in this indication
2		Standard care biomarker (recommended as standard care by the NCCN or other expert panels) predictive of response to an FDA approved drug in this indication
3	A	Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor
	B	Biomarkers that serve as inclusion criteria for clinical trials
4		Biomarkers that show plausible therapeutic significance based on small studies, few case reports or preclinical studies

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IMMUNE CHECKPOINT INHIBITORS (ICI) THERAPIES

Approved for PATIENT's Tumor Type

Therapies	Genomic Alterations	Effect	Ongoing Clinical Trials
Durvalumab Nivolumab Pembrolizumab Ipilimumab Atezolizumab Cemiplimab-rwlc Dostarlimab-gxly	**TMB-High** (18.2 muts/Mb)	**Sensitive**	NCT03516981 NCT04589845

Approved for OTHER Tumor Types

Therapies	Genomic Alterations	Effect	Ongoing Clinical Trials
Avelumab	**TMB-High** (18.2 muts/Mb)	**Sensitive**	-

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

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

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

MMR, mismatch repair; ND, not detected

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

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CHEMOTHERAPIES

Therapies	Genomic Alterations	Effect	Gene / Variant Level Evidence	Cancer Type
Platinum- and taxane-based regimens	***TP53*** R273L	**less sensitive**	Clinical	Ovarian cancer

HORMONAL THERAPIES

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

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 (18.2 mutations / Mb)

The patient's tumor harbors 18.2 mutations / Mb and is classified as high tumor mutational burden (TMB). 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].

FOXP1 Y470*

Biological Impact

FOXP1 belongs to forkhead box transcription factor family and regulates a program of gene expression that is essential for the development of lung, thymocyte, esophagus, cortical neuron, hair follicle and jaw tissues[11][12][13][14][15][16][17]. Reduced or loss of FOXP1 expression are frequently observed in endometrial adenocarcinoma and ovarian tumor[18][19].

Y470* mutation results in a premature truncation of the FOXP1 protein at amino acid 470 (UniProtKB). This mutation is predicted to lead to a loss of FOXP1 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

A systematic review and accumulated evidence indicated that decreased FOXP1 expression was correlated with better overall survival in lymphoma patients while in patients with solid tumor, such as ovarian cancer, prostate cancer, colorectal cancer, melanoma, non-small cell lung cancer and breast cancer, decreased expression of FOXP1 was associated with worse prognosis[20][21][19][22][23][24][25][26].

KEAP1 E593fs

Biological Impact

The Kelch-Like ECH-Associated Protein 1 (KEAP1) gene encodes a subunit of an E3 ubiquitin ligase complex that negatively regulates the nuclear factor erythroid 2-related factor 2 (NRF2) protein stability. Under the unstressed condition, low basal levels of NRF2 protein are maintained via proteasomal degradation by binding to KEAP1. Oxidative stress triggers the oxidation of KEAP1 and releases the NRF2 proteins. Then the NRF2 protein translocates and accumulates in the nucleus, and promoting the expression of genes involved in anti-oxidation responses. The loss of KEAP1 has been demonstrated to promote the accumulation of NRF2[27].

KEAP1 mutations have been reported in non-small cell lung cancer (NSCLC)[28][29], biliary cancer[30], and epithelial ovarian cancer (EOC)[31]. In particular, mutations have been detected throughout the whole KEAP1 gene sequence in lung adenocarcinoma patients with strong smoking exposure[32].

E593fs mutation results in a change in the amino acid sequence beginning at 593, likely to cause premature truncation of the functional KEAP1 protein (UniProtKB). This mutation is predicted to lead to a loss of KEAP1 protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

Lung adenocarcinoma (LAC) patients harboring mutations in the KEAP1/NFE2L2 pathway had significantly worse clinical outcomes after chemotherapy, compared to those with wild-type KEAP1/NFE2L2 LAC[33]. Besides, co-occurring mutations of KRAS and KEAP1/ NFE2L2 is an independent prognostic factor associated with shorter duration of response to initial platinum-based chemotherapy and immune checkpoint inhibitors in non-small cell lung cancer[34]. Tumors with KEAP1 mutations are generally considered as cold tumors and can promote immune evasion[35].

Preclinical data indicated that loss of KEAP1 may alter cell metabolism with cell proliferation, and modulate the response to vemurafenib, trametinib, erlotinib and crizotinib in BRAF-, NRAS-, KRAS-, EGFR-, and ALK-mutant lung cancer cell lines[36].

***KMT2D* G1467fs**

Biological Impact

KMT2D (Lysine methyltransferase 2D) gene encodes the histone methyltransferase MLL2, which methylates lysine residue 4 on the tail of histone H3 (H3K4) and regulates gene expression via modulating chromatin structures[37]. KMT2D mutations have been reported in bladder cancer, diffuse large B cell lymphoma (DLBCL), non-Hodgkin lymphoma, and acute myeloid leukemia[38][39][40][41], and deletion of KMT2D has been reported to lead to genomic instability in vitro[42].

G1467fs mutation results in a change in the amino acid sequence beginning at 1467, likely to cause premature truncation of the functional KMT2D protein (UniProtKB). This mutation is predicted to lead to a loss of KMT2D protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

A study of non-small cell lung cancer patients (n=194) indicated that patients harboring mutant KMT2D had shorter overall survival and progression-free survival compared with patients with wild-type KMT2D. However, this correlation had not found in small cell lung cancer patients[43].

Low levels of KMT2D expression was associated with better overall survival in pancreatic ductal adenocarcinoma (PDAC)[44], esophageal squamous cell carcinoma (ESCC)[45], and better disease-free survival in prostate cancer[46]. However, low expression of KMT2D had been reported to correlate with advanced stages and imatinib resistance in chronic myeloid leukemia (CML)[47].

NOTCH1 G1320fs

Biological Impact

The NOTCH1 gene encodes for a transmembrane receptor and transcription factor which exist in a wide range of tissue and organisms[48]. NOTCH1 is proposed to be an oncogene or tumor suppressor in human cancer development[49]. The inactivation of NOTCH1 has been linked to squamous cell differentiation is also suggested by studies using cultured cervical and esophageal keratinocytes[50][51]. Somatic mutations in NOTCH1 have been reported to highly associate betel quid chewing, which are involved in the occurrence and development of head and neck squamous cell carcinoma (HNSCC)[52].

G1320fs mutation results in a change in the amino acid sequence beginning at 1320, likely to cause premature truncation of the functional NOTCH1 protein (UniProtKB). This mutation is predicted to lead to a loss of NOTCH1 protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

Omipalisib and bimiralisib, PI3K/mTOR inhibitors, induced cell apoptosis in head and neck squamous cell carcinoma (HNSCC) cell lines with NOTCH1 loss-of-function mutations and reduced tumor growth in xenograft models[53]. Of note, a clinical trial evaluating bimiralisib in HNSCC patients harboring NOTCH1 loss of function mutations is ongoing (NCT03740100).

Loss of NOTCH1 was found to be associated with poor survival and shorter time to recurrence in patients with early stage hepatocellular carcinoma undergoing hepatectomy[54].

Head and neck squamous cell carcinoma (HNSCC) patients harboring NOTCH1 somatic mutations in EGF-like domain had significantly higher recurrence rate and lower survival rate[52].

SERPINB4 C279*

Biological Impact

SERPINB4 encodes a protein of the serpin family of serine protease inhibitors. SERPINB4 is a close human homolog of SERPINB3 with which shares 92% protein sequence identity. SERPINB3 and SERINB4 proteins have overlapping functions and are involved in both oncogenesis and immunity[55][56].

C279* mutation results in a premature truncation of the SERPINB4 protein at amino acid 279 (UniProtKB). This mutation is predicted to lead to a loss of SERPINB4 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

Results from a clinical study showed that somatic mutations in SERPINB3 and SERPINB4 predicted improved survival from treatment with anti-CTLA4 therapy in two independent cohorts of patients with melanoma (n=174)[57].

TP53 R273L

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[58]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[59].

TP53 R273L is a hotspot mutation located in the DNA-binding domain (DBD) of the p53 protein[60]. This mutation results in decreased p53 transactivation and decreased transcriptional repression of p53 targets in vitro[61][62].

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)[63].

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[64]. 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[65].

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[66][67][68]. 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)[69]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[70][71]. 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[72].

TP53 oncomorphic mutations, including P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L, and R282W have been shown to predict resistance to platinum- and taxane-based chemotherapy in advanced serous ovarian carcinoma patients[73].

AKT2 Amplification

Biological Impact

The v-akt murine thymoma viral oncogene homolog 2 (AKT2 , also known as HIHGHH, PRKBB, PKBBETA, RAC-BETA, PKBB) gene encodes an AKT family of serine/threonine protein kinases, including AKT1 and AKT3 isoforms, that act as a downstream effector of the pro-oncogenic PI3-kinase signaling pathway[74][75][76][77][78]. Whereas somatic AKT2 mutations have been described rarely in cancer, germline autosomal dominant mutations in AKT2 are associated with familial diabetes mellitus in humans[79].

Therapeutic and prognostic relevance

A preclinical study demonstrated that an AKT2-amplified pancreatic cancer cell line exhibited resistance to erlotinib. Besides, amplification of AKT2 was predominantly expressed across pancreatic cancer patients in TCGA datasets and correlated with high mRNA expression. Patients with a high AKT2 expression tended to have poor response to erlotinib plus gemcitabine[80].

CDK12 Amplification

Biological Impact

The cyclin-dependent kinase 12 (CDK12) gene encodes a tumor suppressor involved in the alternative RNA splicing by forming complex with cyclin L1 and L2[81]. CDK12 plays a role in the maintenance of genomic stability via regulation of the transcription of homologous recombination repair (HRR) genes, including BRCA1, ATR, FANCI and FAND2[82].

Concurrent amplification of CDK12 and HER2 genes has been observed frequently in breast cancer patients, which accounts for about 90% of HER2+ breast cancer[83][84][85]. CDK12 amplification was associated with elevated CDK12 expression levels[86], and CDK12 overexpression in HER2+ breast cancers promotes CSC-like properties and enhances tumor formation ability through activating WNT/b-catenin/TCF and IRS1-mediated ErbB-PI3K signaling pathways[86].

Therapeutic and prognostic relevance

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate[87].

In addition, CDK12 alterations have been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in prostate cancer[88], and niraparib efficacy in pancreatic cancer (NCT03553004).

Survival analyses of breast cancer patients showed that CDK12 expression was associated with shorter OS and DFS regardless of the subtype of breast cancer[86]. In addition, CDK12 amplification has been demonstrated to associate

with poor anti-HER2 treatment response in HER2-positive breast cancer patients. The median PFS of patients received anti-HER2 therapy with CDK12 amplification (n=28) and without CDK12 amplification (n=79) were 4.3 and 6.9 months respectively[89]. In vitro and in vivo studies indicated that CDK12 overexpression in HER2+ breast cancers reduces susceptibility to trastuzumab by activating oncogenic signaling pathways like ErbB-PI3K-AKT and WNT cascades[86].

***CDKN2A* Heterozygous deletion**

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein[90][91]whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53[92]. CDKN2A has been reported as a haploinsufficient tumor suppressor with one copy loss that may lead to weak protein expression and is insufficient to execute its original physiological functions[93]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[94][95].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[96][97]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[98][99][100]. However, there are clinical studies that demonstrated CDKN2A nuclear expression, CDKN2A/CDKN2B co-deletion, or CDKN2A inactivating mutation was not associated with clinical benefit from CDK4/6 inhibitors, such as palbociclib and ribociclib, in RB-positive patients[101][102][103]. However, CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for the treatment of ER+ and HER2- breast cancer[97][104][105].

In a Phase I trial, a KRAS wild-type squamous non-small cell lung cancer (NSCLC) patient with CDKN2A loss had a partial response when treated with CDK4/6 inhibitor abemaciclib[99]. Administration of combined palbociclib and MEK inhibitor PD-0325901 yield promising progression-free survival among patients with KRAS mutant non-small cell lung cancer (NSCLC) (AACR 2017, Abstract CT046). Moreover, MEK inhibitor in combination with CDK4/6 inhibitor demonstrates significant anti-KRAS-mutant NSCLC activity and radiosensitizing effect in preclinical models[106].

A retrospective analysis demonstrated that concurrent deletion of CDKN2A with EGFR mutation in patients with non-small cell lung cancer (NSCLC), predicts worse overall survival after EGFR-TKI treatment[107].

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FGFR1 Amplification

Biological Impact

The fibroblast growth factor receptor 1 (FGFR1) gene encodes a receptor tyrosine kinase that plays crucial roles in cellular proliferation, survival, migration and angiogenesis[108][109]. Several studies have demonstrated that FGFR1 amplification correlates with FGFR1 overexpression[110][111][112][113][114][115]. Overexpression of FGFR1 has also been shown to enhance both ligand-dependent, and independent activation of downstream signaling pathways such as the phosphoinositide-3 kinase (PI3K) and the extracellular signal-regulated kinase 1/2 (ERK1/2) cascades[116][117][118]. Amplification of FGFR1 has been associated with early relapse, and poor survival, specifically in ER+ breast cancer[116][119], and may be associated with progression of breast cancer from in situ-to-invasive transition[120].

FGFR1 amplifications have been reported in various types of cancer, including lung cancer[121], breast cancer[116], oral squamous cell carcinoma (OSCC)[122], prostate cancer[123], and esophageal cell carcinoma[124]. Besides, activating mutations (C381R and N330I) have been identified in giant cell lesions of the jaw[125].

Therapeutic and prognostic relevance

Non-selective TKI-targeting inhibitors such as pazopanib, regorafenib, and ponatinib are multi-kinase inhibitors with inhibitory activities towards FGFR1[126][127].

To date, Erdafitinib (BALVERSATM), is the first and only pan-FGFR kinase inhibitor approved by U.S. FDA, for the treatment of patients with locally advanced or metastatic bladder cancer with FGFR3 mutations or FGFR2/FGFR3 fusions. Addition of the erdafitinib to palbociclib/fulvestrant induced complete responses of FGFR1-amplified/ER+ patient-derived-xenografts[128].

A case report of a patient with HR+, HER2- breast cancer harboring FGFR1 amplification responded well to pazopanib[129].

FGFR1 amplification has been selected as an inclusion criteria for the trial examining erdafitinib, ponatinib, regorafenib, sunitinib, and infigratinib efficacies in multiple tumor types (NCT03390504, NCT03473743, NCT03238196, NCT02272998, NCT02795156, NCT02693535, NCT04233567, NCT02150967).

Several small molecule FGFR inhibitors such as AZD-4547 and NVP-BGJ398 (Infigratinib) are under clinical evaluation, although mainly in the early stages of trials[130]. Infigratinib has shown antitumor activity and manageable safety profile in patients with a variety of solid tumors, including FGFR1-amplified squamous cell lung cancer (sqNSCLC) and FGFR3-mutant bladder/urothelial cancers[131]. Meanwhile, Dovitinib, a potent FGFR inhibitor, in combination with fulvestrant showed promising clinical activity in the FGF pathway-amplified postmenopausal patients with HR+, HER2- advanced breast cancer[132].

In ER-positive breast cancer, FGFR1 amplification has been implicated as an acquired mechanism of resistance to

endocrine therapies[133], such as letrozole, 4-hydroxytamoxifen, and anastrozole-containing regimen[134][116][135]. Besides, FGFR1/2 amplification or activating mutations were detected in ctDNA from post-progression ER-positive breast cancer patients after the fulvestrant plus palbociclib treatment. According to the subgroup analysis from MONALEESA-2 clinical trial, ER-positive breast cancer patients with FGFR1 amplification exhibited a shorter progression-free survival when treated with letrozole plus ribociclib[128].

Meanwhile, in non-small cell lung carcinoma (NSCLC), FGFR1 is considered as an alternative acquired mechanism of resistance to EGFR tyrosine kinase inhibitors[136]. For example, upregulated FGFR1-FGF2 autocrine loop was identified in a gefitinib-resistant cell model[137], and focal FGFR1 amplification was observed in an NSCLC patient who developed resistance to osimertinib treatment[138].

The BOLERO-2 clinical trial (everolimus plus exemestane) suggested that FGFR1 amplification and CCND1 amplification may be correlated with lessened progression-free survival (PFS) with the mTOR inhibitor everolimus[139][140].

In preclinical study, thyroid cancer cell with FGFR1 amplification is sensitive to lenvatinib treatment[141][142]. Ponatinib, a multi-targeted tyrosine kinase inhibitor, demonstrated anti-proliferative activity in lung cancer, breast cancer, and Ewing's sarcoma cells overexpressing FGFR1[143][126][144].

US FDA-APPROVED DRUG(S)

Abemaciclib (VERZENIO)

Abemaciclib is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. Abemaciclib is developed and marketed by Eli Lilly under the trade name VERZENIO.

FDA Approval Summary of Abemaciclib (VERZENIO)

monarchE NCT03155997	**Breast cancer** (Approved on 2021/10/12) **HR-positive, HER2-negative** Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3[145] NCT00246621	**Breast cancer** (Approved on 2018/02/26) **HR-positive, HER2-negative** Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 1[146] NCT02102490	**Breast cancer** (Approved on 2017/09/28) **HR-positive, HER2-negative** Abemaciclib [ORR(%): 19.7 vs. 17.4]
MONARCH 2[105] NCT02107703	**Breast cancer** (Approved on 2017/09/28) **HR-positive, HER2-negative** Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]

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 TC ≥1%** 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[147] 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]
IMpassion130[148] NCT02425891	**Breast cancer** (Approved on 2019/03/08) **PD-L1** Atezolizumab plus nab-paclitaxel vs. Nab-paclitaxel [PFS(M): 7.4 vs. 4.8]
OAK[149] NCT02008227	**Non-small cell lung carcinoma** (Approved on 2016/10/18) **PD-L1** Atezolizumab vs. Docetaxel [OS(M): 13.8 vs. 9.6]
POPLAR[150] NCT01903993	**Non-small cell lung carcinoma** (Approved on 2016/10/18) **PD-L1** Atezolizumab vs. Docetaxel [OS(M): 12.6 vs. 9.7]
Imvigor 210[8] NCT02108652	**Urinary bladder urothelial carcinoma** (Approved on 2016/05/18) **PD-L1** Atezolizumab [ORR(%): 14.8]

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[151] 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[152] 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 TPS >= 50%
	Cemiplimab-rwlc vs. Platinum-based chemotherapy [PFS(M): 6.2 vs. 5.6, OS(M): 22.1 vs. 14.3]
Study 1620 NCT03132636	**Metastatic basal cell carcinoma (mbcc)** (Approved on 2021/02/09)
	-
	Cemiplimab-rwlc [ORR(%): 21.0, DOR(M): NR]
Study 1620 NCT03132636	**Locally advanced basal cell carcinoma (labcc)** (Approved on 2021/02/09)
	-
	Cemiplimab-rwlc [ORR(%): 29.0, 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)

CASPIAN[153] 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[154] NCT02125461	**Non-small cell lung carcinoma** (Approved on 2018/02/16)
	-
	Durvalumab vs. Placebo [PFS(M): 16.8 vs. 5.6]
CD-ON-MEDI4736-1108[155] NCT01693562	**Bladder urothelial carcinoma** (Approved on 2017/05/01)
	-
	Durvalumab [ORR(All)(%): 17.0, ORR(PD-L1 high)(%): 26.3, ORR (PD-L1 low/negative)(%): 4.1]

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-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 tumor expression >= 1%
	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[156] 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[157] NCT02231749	**Renal cell carcinoma** (Approved on 2018/04/16)
	-
	Nivolumab plus ipilimumab vs. Sunitinib [OS(M): 67.1 vs. 55.5]
EORTC 18071[158] NCT00636168	**Melanoma** (Approved on 2015/10/28)
	-
	Ipilimumab vs. Placebo [RFS(M): 26 vs. 17]
MDX010-20[159] NCT00094653	**Melanoma** (Approved on 2011/03/25)
	-
	Ipilimumab vs. Peptide vaccine with incomplete freund's adjuvant (gp100) [OS(M): 10 vs. 6]

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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-274 NCT02632409	**Urothelial carcinoma** (Approved on 2021/08/19)
	-
	Nivolumab vs. Placebo [DFS(M): 20.8 vs. 10.8, DFS(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 tumor expression >= 1%
	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 032 NCT01928394	**Lung small cell carcinoma** (Approved on 2018/08/16)
	-
	Nivolumab [ORR(%): 12.0]
CheckMate 040 NCT01658878	**Hepatocellular carcinoma** (Approved on 2017/09/22)
	-
	Nivolumab [ORR(%): 14.3]
CheckMate 142 NCT02060188	**Colorectal cancer** (Approved on 2017/07/31)
	MSI-H or dMMR
	Nivolumab [ORR(%): 32.0]
CheckMate 275[160] NCT02387996	**Urinary bladder urothelial carcinoma** (Approved on 2017/02/02)
	-
	Nivolumab [ORR(%): 19.6]
CheckMate 141[161] 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 039[162] NCT01592370	**Hodgkin's lymphoma** (Approved on 2016/05/17)
	-
	Nivolumab [ORR(%): 66.0]
CheckMate 205[163] NCT02181738	**Hodgkin's lymphoma** (Approved on 2016/05/17)
	-
	Nivolumab [ORR(%): 66.0]
CheckMate 067[164] NCT01844505	**Melanoma** (Approved on 2016/01/23)
	-
	Ipilimumab vs. Placebo [PFS(M): 11.5 vs. 2.9]

CheckMate 066[165] NCT01721772	**Melanoma** (Approved on 2015/11/24) **BRAF V600 wild-type** Nivolumab vs. Dacarbazine [OS(M): Not Reached vs. 10.8]
CheckMate 025[166] NCT01668784	**Renal cell carcinoma** (Approved on 2015/11/23) - Nivolumab vs. Everolimus [OS(M): 25 vs. 19.6]
CheckMate 057[167] NCT01673867	**Non-small cell lung carcinoma** (Approved on 2015/10/09) - Nivolumab vs. Docetaxel [OS(M): 12.2 vs. 9.4]
CheckMate 017[168] NCT01642004	**Non-small cell lung carcinoma** (Approved on 2015/03/04) - Nivolumab vs. Docetaxel [OS(M): 9.2 vs. 6]
CheckMate 037[169] NCT01721746	**Melanoma** (Approved on 2014/12/22) - Nivolumab vs. Dacarbazine or carboplatin + paclitaxel [ORR(%): 32.0]

Palbociclib (IBRANCE)

Palbociclib is an oral, cyclin-dependent kinase (CDK) inhibitor specifically targeting CDK4 and CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Palbociclib is developed and marketed by Pfizer under the trade name IBRANCE.

FDA Approval Summary of Palbociclib (IBRANCE)

PALOMA-2[170] NCT01740427	**Breast cancer** (Approved on 2017/03/31) **ER+, HER2-** Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[171] NCT01942135	**Breast cancer** (Approved on 2016/02/19) **ER+, HER2-** Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

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-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 (CPS ≥1)
	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)
	Not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
	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 (CPS >= 10)
	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; >= 10 mutations/megabase
	Pembrolizumab (tmb-h) vs. Pembrolizumab (non–tmb-h) [ORR(%): 29.0 vs. 6.0]
KEYNOTE-146 NCT02501096	**Endometrial carcinoma** (Approved on 2019/09/17)
	not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR)
	Pembrolizumab + lenvatinib [ORR(%): 38.3, DOR(M): NR]
KEYNOTE-426[172] 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[173] NCT02267603	**Merkel cell carcinoma** (Approved on 2018/12/19)
	-
	Pembrolizumab [ORR(%): 56.0]
KEYNOTE-224[174] NCT02702414	**Hepatocellular carcinoma** (Approved on 2018/11/09)
	-
	Pembrolizumab [ORR(%): 17.0]

KEYNOTE-407[175] 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[175] NCT02578680	**Nonsquamous non-small cell lung carcinoma** (Approved on 2018/08/20)
	-
	Pembrolizumab + pemetrexed + platinum vs. Pemetrexed + platinum [PFS(M): 8.8 vs. 4.9, OS(M): NR vs. 11.3]
KEYNOTE-170 NCT02576990	**Mediastinal large b-cell lymphoma** (Approved on 2018/06/13)
	-
	Pembrolizumab [ORR(%): 45.0]
KEYNOTE-158 NCT02628067	**Cervical cancer** (Approved on 2018/06/13)
	-
	Pembrolizumab [ORR(%): 14.3]
KEYNOTE-059 NCT02335411	**Gastric adenocarcinoma, Gastroesophageal junction adenocarcinoma** (Approved on 2017/09/22)
	-
	Pembrolizumab [ORR(%): 13.3]
KEYNOTE-158 NCT02628067	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-164 NCT02460198	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-028[176][177] NCT02054806	**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-012[178][179][180][181] NCT01848834	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-052 NCT02335424	**Urinary bladder urothelial carcinoma** (Approved on 2017/05/18)
	-
	Pembrolizumab [ORR(%): 29.0]
KEYNOTE-045[182] NCT02256436	**Urinary bladder urothelial carcinoma** (Approved on 2017/05/18)
	-
	Pembrolizumab vs. Chemotherapy [ORR(%): 21.0 vs. 11.0]
KEYNOTE-087[183] NCT02453594	**Hodgkin's lymphoma** (Approved on 2017/03/14)
	-
	Pembrolizumab [ORR(%): 69.0]
KEYNOTE-024[184] NCT02142738	**Non-small cell lung carcinoma** (Approved on 2016/10/24)
	PD-L1 expression (TPS >= 50%)
	Pembrolizumab vs. Chemotherapy [PFS(M): 10.3 vs. 6]
KEYNOTE-012[179] NCT01848834	**Head and neck squamous cell carcinoma** (Approved on 2016/08/05)
	-
	Pembrolizumab [ORR(%): 16.0]
KEYNOTE-006[185] NCT01866319	**Melanoma** (Approved on 2015/12/18)
	-
	Pembrolizumab vs. Ipilimumab (3mg/kg every 3 weeks) [OS(M): NR vs. 16]
KEYNOTE-010[186] NCT01905657	**Non-small cell lung carcinoma** (Approved on 2015/10/02)
	PD-L1 expression (TPS >= 1%)
	Pembrolizumab [OS(M): 10.4 vs. 8.5]

KEYNOTE-002[187] NCT01704287	**Melanoma** (Approved on 2014/09/24)
	-
	Pembrolizumab vs. Chemotherapy [PFS(M): 2.9 vs. 2.7]

Ribociclib (KISQALI)

Ribociclib is a cyclin-dependent kinase (CDK) inhibitor specifically targeting cyclin D1/CDK4 and cyclin D3/CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Ribociclib is developed by Novartis and Astex Pharmaceuticals and marketed by Novartis under the trade name KISQALI.

FDA Approval Summary of Ribociclib (KISQALI)

MONALEESA-2[104] NCT01958021	**Breast cancer** (Approved on 2017/03/13)
	HR+, HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

d=day; w=week; m=month

ONGOING CLINICAL TRIALS

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

IMMUNE CHECKPOINT INHIBITORS

Drugs	Pembrolizumab
NCT ID	NCT03516981
Phase	II
Content	This study will investigate the utility of biomarker-based triage for study participants with advanced non-small cell lung cancer (NSCLC) without prior systemic therapy. Study participants within groups defined by a biomarker-based classifier (gene expression profile [GEP] and tumor mutational burden [TMB]) will be randomized to receive pembrolizumab in combination with quavonlimab (MK-1308), favezelimab (MK-4280), or lenvatinib. The primary hypotheses are as follows: In participants receiving pembrolizumab in combination with either quavonlimab, favezelimab, or lenvatinib, the Objective Response Rate (ORR) will be 1) greater than 5% among participants with low GEP and low TMB, 2) greater than 20% among participants with low GEP and high TMB, 3) greater than 20% among participants with high GEP and low TMB, and 4) greater than 45% among participants with high GEP and high TMB.
Contact	Name: Toll Free Number Phone: 1-888-577-8839 Email: Trialsites@merck.com
Location	Status: Recruiting Country: Taiwan City: Kaohsiung Name: Kaohsiung Chang Gung Memorial Hospital (Site 1203) Status: Recruiting Country: Taiwan City: Tainan Name: National Cheng Kung University Hospital (Site 1202)

	Status: Recruiting Country: Taiwan City: Taipei Name: National Taiwan University Hospital (Site 1200) Status: Recruiting Country: Taiwan City: Taipei Name: Taipei Veterans General Hospital (Site 1204)

Drugs	**Atezolizumab**
NCT ID	NCT04589845
Phase	II
Content	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 www.roche.com/about_roche/roche_worldwide.htm 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: Recruiting Country: Taiwan City: Zhongzheng Dist. Name: National Taiwan University Hospital; Oncology

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Project ID: C21-M001-01337
Report No.: AA-21-05764_ONC
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DETAILED TEST RESULTS

SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Gene	Chr	Exon	Accession Number	cDNA Change	Amino Acid Change	Coverage	Allele Frequency	COSMIC ID
ADAMTS6	5	7	NM_197941	c.976T>C	C326R	519	49.3%	-
ATR	3	38	NM_001184	c.6490A>G	I2164V	159	22.6%	-
BAP1	3	13	NM_004656	c.1445C>T	S482L	946	5.4%	COSM2853466
BMPR1A	10	11	NM_004329	c.1319T>A	M440K	624	20.8%	-
BRAF	7	7	NM_004333	c.958G>T	A320S	1320	36.9%	-
CASP8	2	3	NM_033355	c.126G>C	L42F	1569	10.4%	-
CD19	16	14	NM_001178098	c.1624G>T	D542Y	965	11.5%	-
CREBBP	16	6	NM_004380	c.1369A>G	I457V	1519	41.5%	-
DPYD	1	10	NM_000110	c.1027A>T	T343S	956	19.5%	-
EPHA7	6	5	NM_004440	c.1010A>T	N337I	613	33.8%	-
ETV4	17	13	NM_001079675	c.1298C>T	P433L	754	52.9%	-
FAT1	4	8	NM_005245	c.4475C>G	T1492S	1227	48.2%	-
FOXP1	**3**	**16**	**NM_032682**	**c.1410T>A**	**Y470***	**138**	**28.3%**	**-**
GRIN2A	16	8	NM_000833	c.1529G>T	G510V	670	27.2%	-
HGF	7	-	NM_000601	c.1865-4C>T	Splice region	1498	23.3%	-
IRF4	6	9	NM_002460	c.1264G>A	G422R	785	16.6%	-
KEAP1	**19**	**6**	**NM_203500**	**c.1777_1778insGTCCCAGATA CAGACACCTGGAGCG**	**E593fs**	**1162**	**29.2%**	**-**
KMT2D	**12**	**15**	**NM_003482**	**c.4400del**	**G1467fs**	**934**	**25.9%**	**-**
MED12	X	24	NM_005120	c.3434A>G	D1145G	625	34.6%	-
MUTYH	1	14	NM_001128425	c.1420C>T	R474C	1741	27.6%	COSM162695
NOTCH1	9	23	NM_017617	c.3685G>T	V1229F	443	37.7%	-
NOTCH1	**9**	**24**	**NM_017617**	**c.3959del**	**G1320fs**	**369**	**32.0%**	**COSM6935066**
NOTCH2	1	14	NM_024408	c.2301G>C	Q767H	683	27.8%	-
PARP1	1	20	NM_001618	c.2783A>C	N928T	1136	35.1%	-
PIK3C2G	12	2	NM_004570	c.568G>C	E190Q	679	23.3%	-
PRDM1	6	5	NM_001198	c.1400C>T	P467L	620	39.4%	-
PRKCB	16	9	NM_212535	c.945G>T	K315N	2176	16.8%	COSM8788679
RHOA	3	2	NM_001664	c.118G>A	E40K	1084	16.4%	COSM4118493
ROS1	6	35	NM_002944	c.5743G>A	G1915R	904	67.1%	COSM6768582
ROS1	6	15	NM_002944	c.2173G>A	D725N	2491	33.1%	COSM277104
ROS1	6	22	NM_002944	c.3389C>T	A1130V	761	28.4%	COSM6938923
SDHA	5	3	NM_004168	c.187G>C	D63H	1831	20.0%	-
SDHB	1	7	NM_003000	c.765G>C	K255N	1313	29.7%	-
SERPINB4	**18**	**8**	**NM_002974**	**c.837T>A**	**C279***	**207**	**59.9%**	**-**
SYNE1	6	102	NM_182961	c.18999G>C	L6333F	1082	12.4%	-
TBX3	12	3	NM_016569	c.691C>T	Q231*	1199	25.5%	COSM6908586
TGFBR2	3	4	NM_003242	c.893A>G	N298S	1387	46.5%	COSM6943547
TP53	**17**	**8**	**NM_000546**	**c.818G>T**	**R273L**	**1243**	**40.5%**	**COSM10779**
USH2A	1	13	NM_206933	c.2802T>G	C934W	1173	41.4%	-

Mutations with clinical relevance are highlighted in red.

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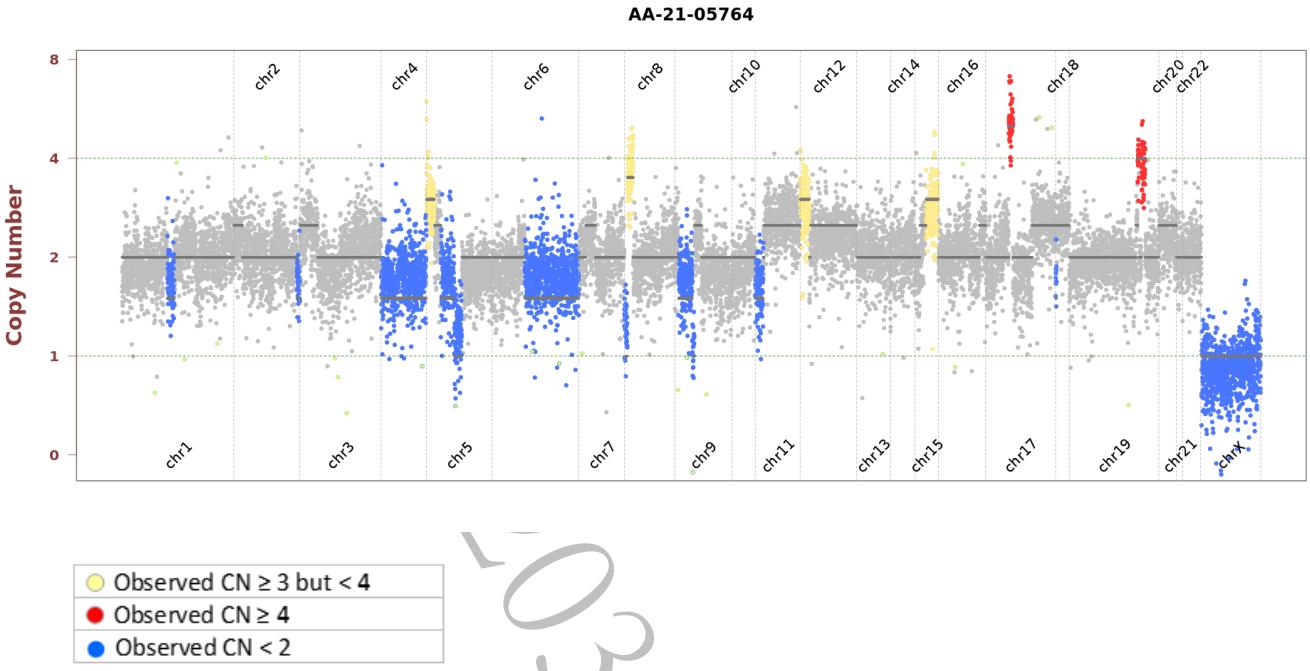
COPY NUMBER VARIANTS (CNVS)

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



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HOTSPOT GENOTYPES

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

Gene	Variant	Genotype Detected
BRAF	V600X	Not detected
EGFR	A763_Y764insFQEA, E709K, E709_T710delinsD, Exon 19 deletion, Exon 19 insertion, Exon 20 insertion, G719A/C/D/S, L747P, L833V, L858R, L861Q/R, S768I, T790M	Not detected
IDH2	R140Q, R172G/K/M/S	Not detected
KIT	A502_Y503dup, D419del, D579del, D816F/V/Y, D820A/E/G/Y, E554_I571del, E554_K558del, E554_V559del, Exon 11 mutation, F522C, H697Y, I563_L576del, I653T, K550_W557del, K558N, K558_E562del, K558_V559del, K558delinsNP, K642E, M552_W557del, N505I, N564_Y578del, N822H/I/K/Y, P551_M552del, P573_D579del, P577_D579del, P577_W582delinsPYD, P838L, Q556_K558del, T417_D419delinsI, T417_D419delinsRG, T574_Q575insTQLPYD, V530I, V555_L576del, V555_V559del, V559A/C/D/G, V559_V560del, V559del, V560D/G, V560del, V569_L576del, V654A, W557G/R, W557_K558del, Y553N, Y553_K558del, Y570H, Y578C	Not detected
KRAS	A146T/V/P, G12X, G13X, Q61X	Not detected
MET	D1028H/N/Y	Not detected
NRAS	G12X, G13X, Q61X	Not detected
PDGFRA	A633T, C450_K451insMIEWMI, C456_N468del, C456_R481del, D568N, D842I/V, D842_H845del, D842_M844del, D846Y, E311_K312del, G853D, H650Q, H845Y, H845_N848delinsP, I843del, N659K/R/S, N848K, P577S, Q579R, R560_V561insER, R748G, R841K, S566_E571delinsR, S584L, V469A, V536E, V544_L545insAVLVLLVIVIISLI, V561A/D, V561_I562insER, V658A, W559_R560del, Y375_K455del, Y555C, Y849C/S	Not detected
PIK3CA	C420R, E542K/V, E545A/D/G/K, H1047X, Q546E/R	Not detected

V600X= any mutation in the valine (V) at amino acid 600 being replaced by a different amino acid.
G12X = any mutation in the glycine (G) at amino acid 12 being replaced by a different amino acid.
G13X= any mutation in the glycine (G) at amino acid 13 being replaced by a different amino acid.
Q61X = any mutation in the glutamine (Q) at amino acid 61 being replaced by a different amino acid.
H1047X = any mutation in the histidine (H) at amino acid 1047 being replaced by a different amino acid.

Gene	Copy Number Detected
CDK4	2
EGFR	2
ERBB2	2
MET	2

Copy number ≥ 8 is considered amplification

Other known alterations that are associated with sensitivity, resistance, and toxicity to therapies.

Gene	Variant	Genotype Detected
AKT1	E17K	Not detected
ALK	C1156Y, D1203N, G1202R, L1152R, S1206Y, T1151_L1152insT	Not detected
BRAF	K601E, L597V/Q/R/S	Not detected
DPYD	D949V, I560S, splice-site mutation	Not detected
EGFR	A750P, C797S/Y, S492R	Not detected
ERBB2	V659E	Not detected
ESR1	D538G, E380Q, L469V, L536H/P/Q/R, S432L, S463P, V422del, V534E, Y537C/N/S	Not detected
FGFR3	G370C, G380R, K650E/N/R/M/T/Q, R248C, S249C, S371C, Y373C	Not detected
IDH1	R132C/G/H/L/Q/S	Not detected
MAP2K1	D67N, E203K, F53L, K57E/N, P124S, Q56P, Q56_V60del, R47Q, R49L, S222D	Not detected
PTEN	R130*/fs/G/L/P/Q	Not detected
TPMT	A154T, Y240C	Not detected

Gene	Copy Number Detected
FGFR1	6
MDM2	2
MDM4	2

Copy number ≥ 8 is considered amplification

TEST DETAILS

ABOUT ACTOnco®+

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

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

DATABASE USED

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

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

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite (version 5.10). Coverage depth was calculated using Torrent Coverage Analysis plug-in. Single nucleotide variants (SNVs) and short insertions/deletions (INDELs) were identified using the Torrent Variant Caller plug-in (version 5.10). The coverage was down-sampled to 4000. VEP (Variant Effect Predictor) (version 100) was used to annotate every variant using databases from Clinvar (version 20210208), COSMIC v.92 and Genome Aggregation database r2.1.1. Variants with coverage ≥ 25, allele frequency ≥ 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 r2.1.1 with > 1% minor allele frequency (MAF) were

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

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

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

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

STANDARD OPERATING PROCEDURES (SOPS)

Standard operating procedures (SOPs) are shown below:

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

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

LIMITATIONS

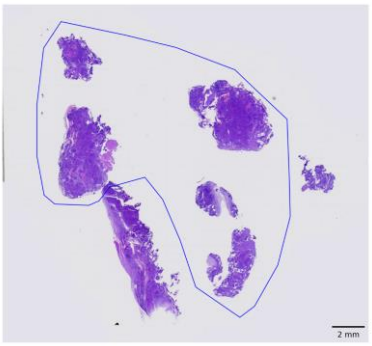
This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject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

NOTES

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

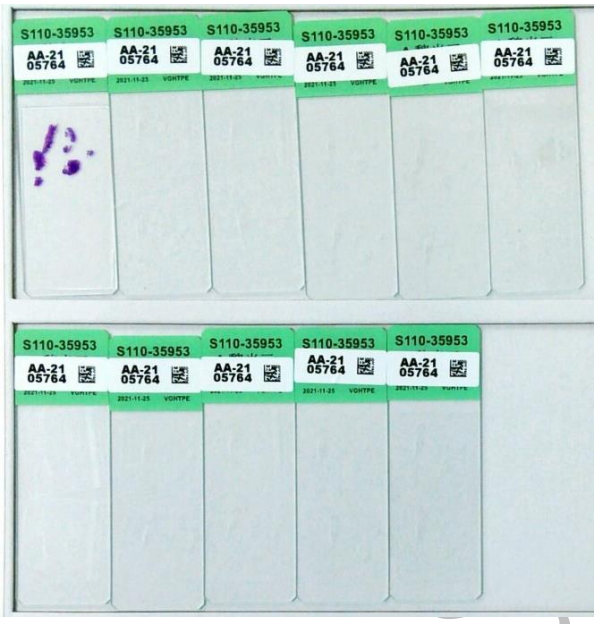
PATHOLOGY EVALUATION

- H&E-stained section No.: S11035953A
- Collection site: Neck, soft tissue
- Examined by: Dr. Yeh-Han Wang
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 40%
  The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 50%
  The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
  The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
  Additional comment: NA
- Manual macrodissection: Performed on the highlighted region



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

SPECIMEN PHOTO(S)



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

RUN QC

- Panel: ACTOnco®+
- Mean Depth: 939x
- Target Base Coverage at 100x: 94%

魏光三
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ACTOnco®+ GENE LIST

ABCB1*	AURKB	CBL	CDKN2B	E2F3	FAT1	GRIN2A	JAK2	MED12	NOTCH4	PMS1	RAD51D	SLCO1B3*	TNFRSF14
ABCC2*	AXIN1	CCNA1	CDKN2C	EGFR	FBXW7	GSK3B	JAK3	MEF2B	NPM1	PMS2	RAD52	SMAD2	TNFSF11
ABCG2*	AXIN2	CCNA2	CEBPA*	EP300	FCGR2B	GSTP1*	JUN*	MEN1	NQO1*	POLB	RAD54L	SMAD3	TOP1
ABL1	AXL	CCNB1	CHEK1	EPCAM	FGF1*	GSTT1*	KAT6A	MET	NRAS	POLD1	RAF1	SMAD4	TP53
ABL2	B2M	CCNB2	CHEK2	EPHA2	FGF10	HGF	KDM5A	MITF	NSD1	POLE	RARA	SMARCA4	TPMT*
ADAMTS1	BAP1	CCNB3	CIC	EPHA3	FGF14	HIF1A	KDM5C	MLH1	NTRK1	PPARG	RB1	SMARCB1	TSC1
ADAMTS13	BARD1	CCND1	CREBBP	EPHA5	FGF19*	HIST1H1C*	KDM6A	MPL	NTRK2	PPP2R1A	RBM10	SMO	TSC2
ADAMTS15	BCL10	CCND2	CRKL	EPHA7	FGF23	HIST1H1E*	KDR	MRE11	NTRK3	PRDM1	RECQL4	SOCS1*	TSHR
ADAMTS16	BCL2*	CCND3	CRLF2	EPHB1	FGF3	HNF1A	KEAP1	MSH2	PAK3	PRKAR1A	REL	SOX2*	TYMS
ADAMTS18	BCL2L1	CCNE1	CSF1R	ERBB2	FGF4*	HR	KIT	MSH6	PALB2	PRKCA	RET	SOX9	U2AF1
ADAMTS6	BCL2L2*	CCNE2	CTCF	ERBB3	FGF6	HRAS*	KMT2A	MTHFR*	PARP1	PRKCB	RHOA	SPEN	UBE2A*
ADAMTS9	BCL6	CCNH	CTLA4	ERBB4	FGFR1	HSP90AA1	KMT2C	MTOR	PAX5	PRKCG	RICTOR	SPOP	UBE2K
ADAMTSL1	BCL9	CD19	CTNNA1	ERCC1	FGFR2	HSP90AB1	KMT2D	MUC16	PAX8	PRKCI	RNF43	SRC	UBR5
ADGRA2	BCOR	CD274	CTNNB1	ERCC2	FGFR3	HSPA4	KRAS	MUC4	PBRM1	PRKCQ	ROS1	STAG2	UGT1A1*
ADH1C*	BIRC2	CD58	CUL3	ERCC3	FGFR4	HSPA5	LCK	MUC6	PDCD1	PRKDC	RPPH1	STAT3	USH2A
AKT1	BIRC3	CD70*	CYLD	ERCC4	FH	IDH1	LIG1	MUTYH	PDCD1LG2	PRKN	RPTOR	STK11	VDR*
AKT2	BLM	CD79A	CYP1A1*	ERCC5	FLCN	IDH2	LIG3	MYC	PDGFRA	PSMB8	RUNX1	SUFU	VEGFA
AKT3	BMPR1A	CD79B	CYP2B6*	ERG	FLT1	IFNL3*	LMO1	MYCL	PDGFRB	PSMB9	RUNX1T1	SYK	VEGFB
ALDH1A1*	BRAF	CDC73	CYP2C19*	ESR1	FLT3	IGF1	LRP1B	MYCN	PDIA3	PSME1	RXRA	SYNE1	VHL
ALK	BRCA1	CDH1	CYP2C8*	ESR2	FLT4	IGF1R	LYN	MYD88	PGF	PSME2	SDHA	TAF1	WT1
AMER1	BRCA2	CDK1	CYP2D6	ETV1	FOXL2*	IGF2	MALT1	NAT2*	PHOX2B*	PSME3	SDHB	TAP1	XIAP
APC	BRD4	CDK12	CYP2E1*	ETV4	FOXP1	IKBKB	MAP2K1	NBN	PIK3C2B	PTCH1	SDHC	TAP2	XPO1
AR	BRIP1	CDK2	CYP3A4*	EZH2	FRG1	IKBKE	MAP2K2	NEFH	PIK3C2G	PTEN	SDHD	TAPBP	XRCC2
ARAF	BTG1*	CDK4	CYP3A5*	FAM46C	FUBP1	IKZF1	MAP2K4	NF1	PIK3C3	PTGS2	SERPINB3	TBX3	ZNF217
ARID1A	BTG2*	CDK5	DAXX	FANCA	GATA1	IL6	MAP3K1	NF2	PIK3CA	PTPN11	SERPINB4	TEK	
ARID1B	BTK	CDK6	DCUN1D1	FANCC	GATA2	IL7R	MAP3K7	NFE2L2	PIK3CB	PTPRD	SETD2	TERT	
ARID2	BUB1B	CDK7	DDR2	FANCD2	GATA3	INPP4B	MAPK1	NFKB1	PIK3CD	PTPRT	SF3B1	TET1	
ASXL1	CALR	CDK8	DICER1	FANCE	GNA11	INSR	MAPK3	NFKBIA	PIK3CG	RAC1	SGK1	TET2	
ATM	CANX	CDK9	DNMT3A	FANCF	GNA13	IRF4	MAX	NKX2-1*	PIK3R1	RAD50	SH2D1A*	TGFBR2	
ATR	CARD11	CDKN1A	DOT1L	FANCG	GNAQ	IRS1	MCL1	NOTCH1	PIK3R2	RAD51	SLC19A1*	TMSB4X*	
ATRX	CASP8	CDKN1B	DPYD	FANCL	GNAS	IRS2*	MDM2	NOTCH2	PIK3R3	RAD51B	SLC22A2*	TNF	
AURKA	CBFB	CDKN2A	DTX1	FAS	GREM1	JAK1	MDM4	NOTCH3	PIM1	RAD51C	SLCO1B1*	TNFAIP3	

*Analysis of copy number alteration not available.

DISCLAIMER

Legal Statement

This test was developed by ACT Genomics and its performing characteristics were determined by ACT Genomics. This test result is to be used for clinical consultative purposes only and is not intended as a substitute for a clinical guidance of your doctor or another qualified medical practitioner. It should not be regarded as investigational or used for research.

The detection of genomic alterations does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; the detection of no genomic alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Treatment Decisions are the Responsibility of the Physician

Decisions on clinical care and treatment should be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, including physical examinations, information from other diagnostics tests and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test, or the information contained in this report.

In terms of consulting a different treating physician, the patient must file an application and fulfill the listed criteria for ACT Genomics to provide the patient's report to the assigned physician. The report may not be copied or reproduced except in its totality.

Genetic Alterations and Drugs Not Presented in Ranked Order

In this report, neither any biomarker alteration nor any drug associated with a potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

Level of Evidence Provided

Drugs with a potential clinical benefit (or potential lack of clinical benefit) are evaluated for level of published evidence with at least one clinical efficacy case report or preclinical study. We endeavor to keep the information in the report up to date. However, customers must be aware that scientific understanding and technologies change over time, and we make no warranty as to the accuracy, suitability or currency of information provided in this report at any time.

No Guarantee of Clinical Benefit

This report makes no promises or guarantees about the effectiveness of a particular drug or any treatment procedure in any disease or in any patient. This report also makes no promises or guarantees that a drug without an association of reportable genomic alteration will, in fact, provide no clinical benefit.

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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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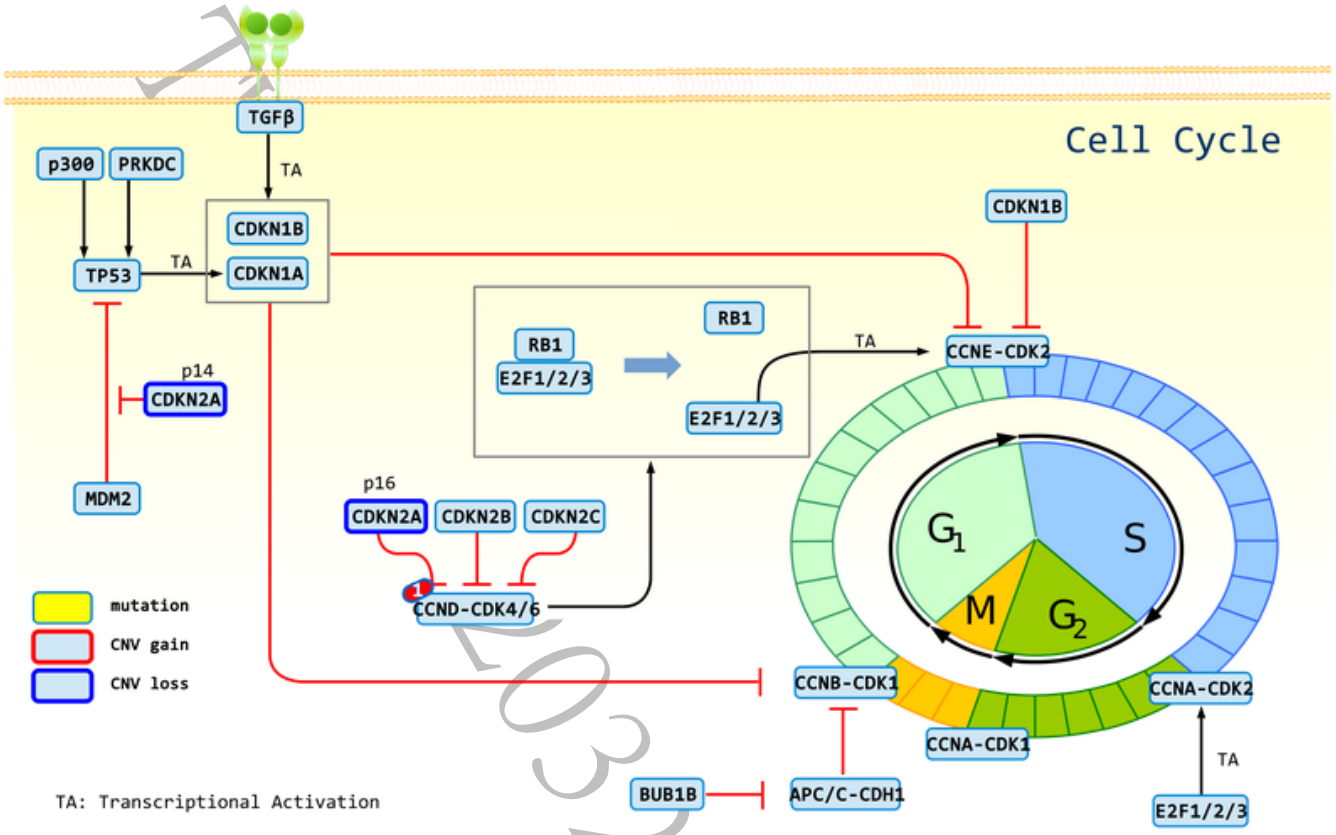
Project ID: C21-M001-01337
Report No.: AA-21-05764_ONC
Date Reported: Dec 08, 2021

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Palbociclib, Ribociclib, Abemaciclib

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