ACT Onco® + Report

PATIENT		
Identifier: 李厚		Patient ID: 719459
Date of Birth: Aug 28, 1963		Gender: Male
Diagnosis: Lung squamous cell carcinoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11201181D	Collection site: Lung	Type: FFPE tissue
Date received: Jan 19, 2023	Lab ID: AA-23-00432	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	
TMB-High	Atezolizumab, Cemiplimab-rwlc, Dostarlimab-gxly, Durvalumab, Ipilimumab, Nivolumab, Pembrolizumab, Tremelimumab	-	Avelumab

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
CCND1 Amplification	Abemaciclib, Palbociclib, Ribociclib	-
CDKN2A Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	-
KRAS Amplification	Sorafenib	Crizotinib, Cetuximab, Panitumumab
MDM2 Amplification	-	Cabozantinib

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
ERCC2	S44L	26.2%
KMT2D	V3089fs	83.7%
LRP1B	Splice donor	22.7%
TP53	G154V	55.6%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr9	*CDKN2A*	Homozygous deletion	0
Chr3	*BCL6, PIK3CA, PRKCI*	Amplification	8
Chr15	*NTRK3*	Amplification	9
Chr7	*CDK6*	Amplification	9
Chr12	*CDKN1B, KDM5A, KRAS*	Amplification	10
Chr12	*MDM2*	Amplification	16
Chr11	*CCND1*	Amplification	63

- 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 63% tumor purity.
- TMB was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is < 30%.

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3B		
CCND1 Amplification	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
CDKN2A Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
Level 4		
KRAS Amplification	Sorafenib	**sensitive**
KRAS Amplification	Crizotinib, Cetuximab, Panitumumab	**resistant**
MDM2 Amplification	Cabozantinib	**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, Tremelimumab	Avelumab

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

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
LRP1B loss-of-function	Likely associated with BETTER response to ICIs
MDM2/MDM4 amplification	Likely associated with WORSE response to ICIs

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

CHEMOTHERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
ERCC2 S44L	Cisplatin	**Sensitive**	Clinical	Transitional cell carcinoma
MDM2 Amplification	Cisplatin	**Less sensitive**	Clinical	Germ cell cancer
PIK3CA Amplification	Platinum- and taxane-based regimens	**Less sensitive**	Clinical	Ovarian cancer

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
CCND1 Amplification	Anastrozole	**Less sensitive**	Clinical	Breast cancer
	Tamoxifen	**Less sensitive**	Clinical	Breast cancer

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OTHERS

Pharmacogenomic implication

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

Clinical Interpretation:
Patients with the AG genotype and cancer who are treated with irinotecan-based regimens may have an increased risk of diarrhea and neutropenia as compared to patients with the GG genotype, or a decreased risk of diarrhea and neutropenia compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk of diarrhea and neutropenia.

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

Level 1A: Clinical annotations describe variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation.
Level 1B: Clinical annotations describe variant-drug combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label.
Level 2A: Variants in Level 2A clinical annotations are found in PharmGKB's Tier 1 Very Important Pharmacogenes (VIPs). These variants are in known pharmacogenes, implying causation of drug phenotype is more likely.

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

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VARIANT INTERPRETATION

Tumor mutational burden (TMB): High (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].

ERCC2 S44L

Biological Impact

The ERCC2 gene encodes a DNA helicase involved in DNA nucleotide excision repair[11]. Germline mutations of ERCC2 lead to trichothiodystrophy, xeroderma pigmentosum and combined xeroderma pigmentosum and Cockayne syndrome[12].

ERCC2 S44L lies within the helicase ATP-binding domain of the ERCC2 protein (UniProtKB). S44L confers a loss of function to the ERCC2 protein as demonstrated by impaired nucleotide excision repair (NER) activity that fails to rescue cells from cisplatin and ultraviolet sensitivity in vitro[13].

Therapeutic and prognostic relevance

Somatic mutations happened in the ERCC2 helicase domain that leads to loss of cellular nucleotide excision repair (NER) function have been reported to confer cisplatin sensitivity in muscle invasive bladder cancer[14][13]

KMT2D V3089fs

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[15]. KMT2D mutations have been reported in bladder cancer, diffuse large B cell lymphoma (DLBCL), non-Hodgkin lymphoma, and acute myeloid leukemia[16][17][18][19], and deletion of KMT2D has been reported to lead to genomic instability in vitro[20].

V3089fs mutation results in a change in the amino acid sequence beginning at 3089, 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[21].

Low levels of KMT2D expression was associated with better overall survival in pancreatic ductal adenocarcinoma (PDAC)[22], esophageal squamous cell carcinoma (ESCC)[23], and better disease-free survival in prostate cancer[24]. However, low expression of KMT2D had been reported to correlate with advanced stages and imatinib resistance in chronic myeloid leukemia (CML)[25].

LRP1B Splice donor

Biological Impact

Low-density lipoprotein receptor protein 1B (LRP1B) is a surface protein involved in the receptor-mediated endocytosis and signal transduction (UniProtKB). LRP1B is known as a tumor suppressor and was reported among the top 10 most significantly deleted genes across 3312 human cancer specimens[26]. Besides deletions, mutations and epigenetic silencing of LRP1B have been previously reported in lung adenocarcinoma[27], hepatocellular carcinoma[28], renal cell carcinoma[29], thyroid cancer[30], gastric cancer[31], esophageal squamous cell carcinoma[32], and colon cancer[33].

LRP1B c.2887+1G>T is a variant located at the splice donor region, which may result in the exon skipping.

Therapeutic and prognostic relevance

The prevalence of genetic alterations (mostly loss-of-function mutations) in the LRP1B gene was significantly higher in patients who responded to PD-1 blockade than that of the non-responders (11 vs. 1 mutations, 34% vs. 3%, respectively, P = 0.008). Moreover, an analysis of TCGA dataset showed that melanomas patients with LRP1B mutations had significantly higher tumor mutational load when compared with those without LRP1B mutations[34][35], as well as prolonged survival in response to immunotherapy. In addition, a retrospective study has shown that pathogenic and likely pathogenic alternations of LRP1B gene are associated with higher ORR, improved PFS and OS in ICI treated advanced or metastatic malignancies (DOI: 10.1200/JCO.2020.38.15_suppl.3007)[36]. However, there were several limitations in this study, including limited sample size and unmeasured confounders. Therefore, further clinical validations are still needed.

A retrospective study has demonstrated that deletion or downregulation of LRP1B showed significant correlation with acquired chemotherapy resistance in patients with high-grade serous ovarian cancer (HGSC). Functional studies also showed that reducing LRP1B expression was sufficient to reduce the sensitivity of HGSC cell lines to liposomal doxorubicin but not to doxorubicin[37]. Furthermore, deletion of LRP1B has been reported to be significantly associated with poor progression-free survival (6.4 m vs. 10.1 m) and overall survival (13.4 m vs. 17.8 m) in patients with glioblastoma[38].

TP53 G154V

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[39]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[40].

TP53 G154V lies within the DNA-binding domain of the p53 protein (UniProtKB). G154V confers a loss of function to the p53 protein as demonstrated by decreased p53 transactivation activity in vitro[41].

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)[42].

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[43]. 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[44].

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[45][46][47]. 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)[48]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[49][50]. 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[51].

BCL6 Amplification

Biological Impact

BCL6 (B-cell CLL/lymphoma 6) gene encodes a zinc-finger transcriptional repressor which plays essential roles in lymphocyte differentiation, cell cycle progression and apoptosis[52][53][54][55]. BCL6 amplification and/or rearrangement were frequently observed in diffuse large B-cell Lymphoma (DLBCL)[56][55], non-Hodgkin's lymphoma[57], and nodular lymphocyte-predominant Hodgkin Lymphoma[58]. Besides, overexpression of BCL6 has been identified in gallbladder carcinoma[59], and ovarian cancer[60][61].

Therapeutic and prognostic relevance

In a retrospective study, BCL6 gene amplification could cause BCL6 mRNA upregulation and overexpression of BCL6 protein in muscle-invasive urinary bladder urothelial carcinoma (UBUC) patients. BCL6 gene amplification and overexpression of BCL6 protein were associated with poor prognosis in UBUC. The UBUC patients with high BCL6 expression level had poor disease-specific and metastasis-free survivals[62].

CCND1 Amplification

Biological Impact

The cyclin D1 (CCND1) gene encodes a protein involved in the control of cell growth, proliferation, transcription, and DNA repair[63]. CCND1 forms a complex with CDK4 and CDK6, leading to G1-S cell-cycle transition by inhibiting the retinoblastoma (RB) protein[63]. Amplification or overexpression of CCND1 could be oncogenic and is associated with carcinogenesis of various cancer types[64].

Therapeutic and prognostic relevance

Several CDK4 inhibitors, including palbociclib (PD0332991), LEE011, and LY2835219 have entered clinical trials for tumors with CCND1 amplification[65][66]. In the Phase II study of palbociclib and letrozole in patients with ER-positive HER2-negative metastatic breast cancer, patient selection based on CCND1 amplification or p16 loss did not further improve patient outcome[67]. Preclinical studies also demonstrated conflicting results regarding the correlation between high-level CCND1 and palbociclib sensitivity[68][69][70].

CCND1 amplification has been implicated in predicting poor clinical outcomes in postmenopausal breast cancer patients treated with either anastrozole or tamoxifen[71]. In lung cancer patients, the increased CCND1 copy number is associated with poorer overall survival[72]. A retrospective study showed that melanoma patients whose tumor harboring CCND1, cRAF or KRAS gene copy number gain had better treatment response with CPS (carboplatin, paclitaxel, and sorafenib)[73]. Of note, 3 of 4 patients treated with ribociclib for the longest duration had CCND1 amplification in a phase I trial[74].

Amplification of CCND1 are frequent and contributes to dedifferentiation and cellular proliferative activity of intrahepatic cholangiocarcinoma (ICC), and also indicates a poor prognosis for ICC patients[75]. Of note, CCND1 amplification has been selected as an inclusion criterion for the trial examining CDK4/6 inhibitors in different types of malignant solid tumors (NCT02187783, NCT02896335, NCT03526250, NCT02693535, NCT01037790, NCT03454919,

NCT03310879, and NCT03356223).

CDK6 Amplification

Biological Impact

CDK6 encodes the cyclin-dependent kinase 6, a serine/threonine kinase that controls the checkpoint at G1-S phase. Binding of CDK4/6 to cyclin D is negatively regulated by p16INK4a, a cyclin-dependent kinase inhibitor encoded by CDKN2A[76][77]. As CDK4 and CDK6 play overlapping and redundant physiological roles in the regulation of cell cycle, increased CDK6 activity could also promote tumorigenesis in a way similar to CDK4[78]. Amplification of CDK6 has been observed in esophageal carcinoma[79][80][81], leukemia and lymphoma[82][83][84].

Therapeutic and prognostic relevance

CDK6 amplification has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in several types of solid tumors (NCT02693535).

Results from two cohort studies (n=45 and n=46) showed that CDK6 overexpression was correlated with shorter median time to progression in ER+ breast cancer patients who had received fulvestrant (2.5 vs. 8.2 months and 3.4 vs. 8.9 months for CDK6 overexpression vs. normal expression) but was not correlated with other lines of treatment (N=68, tamoxifen or endocrine therapy). In vitro study further confirmed that cells exhibiting upregulation of CDK6 were resistant to fulvestrant[85].

In a case report, a patient with CDK6-amplified osteosarcoma was treated with ribociclib in combination with gemcitabine and resulted in stable disease for 10 cycles of the treatment[86]. However, a preclinical study showed that transformed cells harboring acquired CDK6 amplification were resistant to abemaciclib, as demonstrated by reduced response of the CDK4/6 target, phospho-Rb (pRb)[87].

CDKN1B Amplification

Biological Impact

The CDKN1B gene encodes cyclin-dependent kinase (CDK) inhibitor 1B, also called p27, which is a member of the Cip/Kip protein family. The p27 protein is ubiquitously expressed and located both in the nucleus and in the cytoplasm. Nuclear p27 functions as a tumor suppressor by controlling cell cycle progression from G1 to S phase, specifically by inhibiting the binding of cyclin A and E to CDK2[88]. It has been demonstrated that haploinsufficiency of CDKN1B contributed to leukemogenesis in T-cell prolymphocytic leukemia[89].

Therapeutic and prognostic relevance

Low CDKN1B levels due to increased protein degradation are prevalent in several different types of epithelial tumors and are commonly correlated with aggressive tumor growth and poor clinical outcome[90][91][92]. Loss of p27 expression is associated with poor prognosis in a variety of tumors, including pancreatic cancer[93], colorectal cancer[94], gastroenteropancreatic neuroendocrine tumors[95], and breast cancer[96].

In vitro data demonstrated that Src inhibitors could increase p27 stability and restore tamoxifen sensitivity in tamoxifen-resistant breast cancer cells[97].

CDKN1B amplification has been found to correlate with poor prognosis in gastric cancer[98].

CDKN2A Homozygous 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 whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53[99][100][101]. 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[102]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[103][104].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[105][67]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[106][107][108]. 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[109][74][110]. 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).

The phase II TAPUR trial demonstrated clinical benefits to palbociclib monotherapy in advanced NSCLC or head and neck cancer harboring a CDKN2A mutation or copy number loss. However, pancreatic and biliary cancer patients harboring a CDKN2A mutation or copy number loss did not demonstrate an objective response or stable disease when treated with palbociclib monotherapy for 16 weeks (DOI: 10.1200/JCO.2021.39.15_suppl.6043)[111][112].

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[67][113][114].

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[107]. 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[115].

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[116].

KDM5A Amplification

Biological Impact

KDM5A (lysine demethylase 5A) gene encodes a histone demethylase for histone 3 lysine 4 (H3K4)[117]which regulates cell cycle progression and cellular differentiation by chromatin remodeling and transcriptional silencing[118][119][120][121]. KDM5A gene amplification has been reported in breast cancer, glioblastoma, and head and neck cancer[122][123][124]which is associated with angiogenesis, tumor progression, and treatment resistance[125][126][127]. Rearrangements of KDM5A with NUP98 has been reported in acute leukemia patients[128].

Therapeutic and prognostic relevance

Several in vitro studies have reported that amplification of KDM5A was correlated with drug resistance such as temozolomide in glioblastoma[123], gefitinib in NSCLC[127], and erlotinib in breast cancer[122].

KRAS Amplification

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[129]. KRAS mutations occur primarily in three hotspots G12, G13 and Q61, and less frequently in codon A146[129][130]. These are activating mutations that lead to constitutive activation and persistent stimulation of the downstream signaling pathways[131][132]. Mutations in KRAS have been reported in a diverse spectrum of human malignancies, including pancreatic carcinomas (>80%)[129][133], colon carcinomas (40-50%)[134][135], and lung carcinomas (30-50%)[136][137], but are also present in biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer, liver cancer, myeloid leukemia and breast cancer[130].

Therapeutic and prognostic relevance

Except for KRAS G12C, other KRAS mutants are not currently targetable, but the downstream MEK serves as a potential target[138]. 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[139][140][141][142].

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[143]. 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[144]. 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[145].

Both clinical and preclinical studies demonstrated a limited response to monotherapy using MEK inhibitors[146]. Moreover, several clinical trials are in progress to evaluate the combination of MEK and mTOR inhibition as a new potential therapeutic strategy in CRC[147], and in patient-derived xenografts of RAS-mutant CRC, inhibition of MEK and mTOR suppressed tumor growth, but not tumor regression[148]. 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[149].

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[150]. 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)[151][152]. 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[153][154][155][156][157][158][159].

Sorafenib, a multi-kinase inhibitor, has been shown to be beneficial in KRAS-mutant CRC[160], KRAS-mutant NSCLC[161], and KRAS-amplified melanoma[73].

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))[162][163].

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[164][165][166].

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[167].

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[168]. In ovarian serous borderline tumor with recurrent low-grade serous carcinoma, patient harboring KRAS G12V mutation appeared to have shorter survival time[169].

Metastatic colorectal cancer patients harboring KRAS amplification were resistant to anti-EGFR therapy such as cetuximab and panitumumab[170][171].

Some in vitro studies showed that activation of the RAS, due to either KRAS/NRAS mutations or to KRAS amplification, rendered lung cancer cells resistant to ROS1 inhibition by crizotinib[172][173][174].

MDM2 Amplification

Biological Impact

The Mouse double minute 2 proto-oncogene (MDM2) gene encodes a E3-ubiquitin ligase that negatively regulates the protein level of p53[175][176][177]. Overexpression or amplification of MDM2 has been shown to disrupt the MDM2/p53 balance, leading to the malignant transformation in a wide range of cancers[178].

Therapeutic and prognostic relevance

Small molecules inhibiting the MDM2-p53 protein-protein interaction to reactivate p53 function are currently under preclinical studies and in early clinical trials[179]. Nutlin-3, a MDM2 inhibitor, when synergized with cisplatin, has been shown to disrupt the interaction between MDM2 and TP53, and induce apoptosis in TP53 wild-type ovarian cancer cells[180], non-small cell lung cancer (NSCLC) cells[181], and nasopharyngeal carcinoma cells[182]. Clinical and preclinical studies showed that overexpression of MDM2 can confer resistance to cisplatin[183][184].

The retrospective studies demonstrated that EGFR-mutated NSCLC patients harboring MDM2 amplification were associated with resistance to EGFR-TKIs and showed poor prognosis after treatment[185][186][187][188].

MDM2 amplification was shown to be a potential mechanism of primary or acquired resistance to cabozantinib and MDM2 inhibitors in clinical development can be targeted therapeutics (Journal of Clinical Oncology, 34, 9068-9068).

Importantly, results from a study suggested that patients with amplification of the MDM2 family members, including MDM2 and MDM4, or EGFR aberrations exhibited poor clinical outcome and demonstrated a significantly increased rate of tumor growth (hyper-progression) after receiving immune checkpoint (PD-1/PD-L1) therapy[189].

NTRK3 Amplification

Biological Impact

The Neurotrophic Receptor Tyrosine Kinase Genes NTRK1, NTRK2, and NTRK3 encode tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC, respectively. NTRK3 can function as both oncogene and tumor-suppressor gene. Upon neurotrophin binding, NTRK3 initiates signaling cascades and leads to cell growth and differentiation. In the unbound state, NTRK3 induces apoptosis[190].

Increased expression of NTRK3 has been identified in neuroblastomas, medulloblastomas and desmoplastic small round cell tumors[191][192][193].

Therapeutic and prognostic relevance

In a retrospective study, NTRK3 gene amplification has been demonstrated to associate with better prognosis in ovarian cancer patients treated with platinum-based chemotherapy. The median time to recurrence of patients with non-amplified NTRK3 (n=23) and amplified (n=18) were 5 and 18 months respectively. 12 cases without NTRK3 amplification were platinum-resistant recurrences (recurrence within 6 months) and 15 cases with NTRK3 amplification were platinum-sensitive (recurrence more than 6 months)[194].

PIK3CA Amplification

Biological Impact

The PIK3CA gene encodes the catalytic subunit (p110α) of phosphatidylinositol 3-kinase (PI3K) that plays a key role in the PI3K/AKT signaling pathway and is involved in the regulation of cellular functions such as proliferation, metabolism and protein synthesis, angiogenesis and apoptosis. PIK3CA has long been described as an oncogene and the PIK3CA gene amplification, deletion, and mutations have been reported in a wide range of cancers, including colorectal, breast, brain, liver, ovarian, stomach and lung cancers[195][196][197][198]. Mutations located in the exon 9 that encodes the PI3K helical (like E542K, E545K) and the exon 20 that encodes the catalytic/kinase domain (like H1047R, H1047L, H1047Y) have been shown to result in the constitutively activated mutant, which could enhance downstream signaling and oncogenic transformation in vitro and in vivo[196][199][200][201].

Therapeutic and prognostic relevance

Results of a phase I study (n=60) showed that one platinum-refractory epithelial ovarian cancer patient with PTEN loss and PIK3CA amplification had a partial response to PI3K inhibitor pictilisib (GDC-0941)[202].

In a preclinical study, buparlisib (BKM120) exerted antitumor activity in lung squamous cell carcinoma cells overexpressing wild-type PIK3CA in culture[203]. Other preclinical studies of triple-negative breast cancer (TNBC), head and neck squamous cell carcinoma, ovarian cancer, lung small cell carcinoma, and PIK3CA-amplified cell lines were sensitive to PIK3 inhibitors pictilisib[204], BEZ235[205], pilaralisib[206], and PIK3CA/PIK3CD inhibitor PF-4989216[207], respectively.

PIK3CA amplification is a biomarker predicting ovarian cancer lack of response to taxane- and platinum-based chemotherapy in ovarian cancer patients[208].

PIK3CA amplification is associated with poor prognosis among patients with gastric cancer[209], esophageal squamous cell carcinoma[210], and non-lymph node metastatic head and neck squamous cell carcinoma[211].

PRKCI Amplification

Biological Impact

The PRKCI gene encodes a member of the atypical protein kinase C (PKC). PKCs are a family of lipid-dependent serine/threonine kinases that represent a branch of the AGC kinase group which are central components of many signaling pathways that regulate diverse cellular functions including proliferation, cell cycle, differentiation, survival, cell migration, and polarity[212][213][214]. PRKCI resides on chromosome 3q26, one of the most frequently amplified genomic regions in human cancers, including cervical, head and neck, lung squamous and serous ovarian cancers[215][216][217][218]. PKCi is frequently overexpressed in the majority of tumor types[219]. As reviewed in[220][219][221], PKCi is required for multiple aspects of the transformed phenotype and appears to participate in the initiation, progression and metastatic stages of cancer.

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Therapeutic and prognostic relevance

In NSCLC, the PB1-PB1 interaction between PKCi and Par6 is required for the transformed phenotype and Rac1 activation[222]. A high throughput screen for small molecular weight compounds identified gold-containing compounds such as aurothioglucose (ATG), aurothiomalate (ATM) (FDA-approved for treatment of rheumatoid arthritis patients), and auranofin (ANF) as selective and potent inhibitors of PKCi and Par6 binding[223]. Phase I studies suggested that ATM is well tolerated in patients with NSCLC and ovarian cancer (NCT00575393). However, currently, there is no FDA-approved PKCi inhibitor for patients with cancer.

Increased PRKCI gene copy number and/or increased PKCi protein expression level are associated with decreased progression-free survival and overall survival in various cancer types, including lung[216], pancreatic cancer[224], cholangiocarcinoma[225], ovarian cancer[217][226]. Moreover, a correlation between PKCi expression and prostate cancer recurrence was reported[227].

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)

MONARCH E NCT03155997	**Breast cancer** (Approved on 2021/10/12)
	HR+/HER2-
	Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3[228] NCT02246621	**Breast cancer** (Approved on 2018/02/26)
	HR+/HER2-
	Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 2[114] NCT02107703	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1[229] NCT02102490	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib [ORR(%): 19.7 vs. 17.4]

Atezolizumab (TECENTRIQ)

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

- FDA Approval Summary of Atezolizumab (TECENTRIQ)

ML39345 NCT03141684	**Alveolar soft part sarcoma** (Approved on 2022/12/09)
	-
	Atezolizumab [ORR(%): 24.0]
IMpower010 NCT02486718	**Non-small cell lung carcinoma** (Approved on 2021/10/15)
	PD-L1
	Atezolizumab vs. Best supportive care (bsc) [DFS (PD-L1 TC≥1%)(M): not reached vs. 35.3]
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[230] 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[231] NCT02008227	**Non-small cell lung carcinoma** (Approved on 2016/10/18)
	PD-L1
	Atezolizumab vs. Docetaxel [OS(M): 13.8 vs. 9.6]
POPLAR[232] NCT01903993	**Non-small cell lung carcinoma** (Approved on 2016/10/18)
	PD-L1
	Atezolizumab vs. Docetaxel [OS(M): 12.6 vs. 9.7]

IMvigor210[233] 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[234] 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[235] NCT02155647	**Merkel cell carcinoma** (Approved on 2017/03/23)
	-
	Avelumab [ORR(%): 33.0, DOR(M): 2.8 to 23.3+]

Cemiplimab-rwlc (LIBTAYO)

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

- FDA Approval Summary of Cemiplimab-rwlc (LIBTAYO)

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

Dostarlimab-gxly (JEMPERLI)

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

- FDA Approval Summary of Dostarlimab-gxly (JEMPERLI)

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

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[236] 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[237] NCT02125461	**Non-small cell lung carcinoma** (Approved on 2018/02/16)
	-
	Durvalumab vs. Placebo [PFS(M): 16.8 vs. 5.6]

Ipilimumab (YERVOY)

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

- FDA Approval Summary of Ipilimumab (YERVOY)

CHECKMATE-648 NCT03143153	**Esophagus squamous cell carcinoma** (Approved on 2022/05/27)
	-
	Nivolumab and ipilimumab vs. Chemotherapy [OS(M): 12.8 vs. 10.7]
CHECKMATE-743 NCT02899299	**Pleural mesothelioma** (Approved on 2020/10/02)
	-
	Nivolumab + ipilimumab vs. Pemetrexed + cisplatin [OS(M): 18.1 vs. 14.1]

CHECKMATE-9LA NCT03215706	**Non-small cell lung carcinoma** (Approved on 2020/05/26)
	-
	Nivolumab + ipilimumab + platinum-doublet chemotherapy vs. Platinum-doublet chemotherapy [OS(M): 14.1 vs. 10.7]
CHECKMATE-227 NCT02477826	**Non-small cell lung carcinoma** (Approved on 2020/05/15)
	PD-L1
	Nivolumab + ipilimumab vs. Platinum-doublet chemotherapy [OS(M): 17.1 vs. 14.9]
CHECKMATE-040 NCT01658878	**Hepatocellular carcinoma** (Approved on 2020/03/10)
	-
	Nivolumab + ipilimumab [ORR(%): 33.0]
CHECKMATE-142[238] 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[239] NCT02231749	**Renal cell carcinoma** (Approved on 2018/04/16)
	-
	Nivolumab plus ipilimumab vs. Sunitinib [OS(M): 67.1 vs. 55.5]
EORTC 18071[240] NCT00636168	**Melanoma** (Approved on 2015/10/28)
	-
	Ipilimumab vs. Placebo [RFS(M): 26 vs. 17]
MDX010-20[241] NCT00094653	**Melanoma** (Approved on 2011/03/25)
	-
	Ipilimumab vs. Peptide vaccine with incomplete freund's adjuvant (gp100) [OS(M): 10 vs. 6]

Nivolumab (OPDIVO)

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

- FDA Approval Summary of Nivolumab (OPDIVO)

CHECKMATE-648 NCT03143153	**Esophagus squamous cell carcinoma** (Approved on 2022/05/27)
	-
	Nivolumab and ipilimumab vs. Chemotherapy [OS(M): 12.8 vs. 10.7]
CHECKMATE-648 NCT03143153	**Esophagus squamous cell carcinoma** (Approved on 2022/05/27)
	-
	Nivolumab, fluorouracil, and cisplatin vs. Chemotherapy [OS(M): 13.2 vs. 10.7]
CHECKMATE-816 NCT02998528	**Non-small cell lung cancer (nsclc)** (Approved on 2022/03/04)
	-
	Nivolumab plus platinum-doublet chemotherapy vs. Platinum-chemotherapy [EFS(M): 31.6 vs. 20.8]
CHECKMATE-274 NCT02632409	**Bladder urothelial carcinoma** (Approved on 2021/08/19)
	-
	Nivolumab [DFS (all randomized)(M): 20.8 vs. 10.8, DFS (PD-L1 ≥ 1%)(M): NR vs. 8.4]
CHECKMATE-577 NCT02743494	**Gastroesophageal junction adenocarcinoma** (Approved on 2021/05/20)
	-
	Nivolumab vs. Placebo every 4 weeks beginning at week 17 for up to one year of treatment [DFS(M): 22.4 vs. 11]

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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[242] 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[243] NCT02181738	**Hodgkin's lymphoma** (Approved on 2016/05/17)
	-
	Nivolumab [ORR(%): 66.0]
CheckMate 039[244] NCT01592370	**Hodgkin's lymphoma** (Approved on 2016/05/17)
	-
	Nivolumab [ORR(%): 66.0]
CheckMate 067[245] NCT01844505	**Melanoma** (Approved on 2016/01/23)
	-
	Ipilimumab vs. Placebo [PFS(M): 11.5 vs. 2.9]
CheckMate 066[246] NCT01721772	**Melanoma** (Approved on 2015/11/24)
	BRAF V600 wild-type
	Nivolumab vs. Dacarbazine [OS(M): Not Reached vs. 10.8]
CheckMate 025[247] NCT01668784	**Renal cell carcinoma** (Approved on 2015/11/23)
	-
	Nivolumab vs. Everolimus [OS(M): 25 vs. 19.6]
CheckMate 057[248] NCT01673867	**Non-small cell lung carcinoma** (Approved on 2015/10/09)
	-
	Nivolumab vs. Docetaxel [OS(M): 12.2 vs. 9.4]

CheckMate 017[249] NCT01642004	**Non-small cell lung carcinoma** (Approved on 2015/03/04)
	-
	Nivolumab vs. Docetaxel [OS(M): 9.2 vs. 6]
CheckMate 037[250] 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[251] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+/HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[252] 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-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]

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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[253] 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[254] NCT02267603	**Merkel cell carcinoma** (Approved on 2018/12/19)
	-
	Pembrolizumab [ORR(%): 56.0]
KEYNOTE-224[255] NCT02702414	**Hepatocellular carcinoma** (Approved on 2018/11/09)
	-
	Pembrolizumab [ORR(%): 17.0]
KEYNOTE-407[256] 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]

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KEYNOTE-189[256] 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[257][258] NCT02054806	**Cancer** (Approved on 2017/05/23) **MSI-H or dMMR** Pembrolizumab [ORR(%): 39.6]
KEYNOTE-012[259][260][261][262] NCT01848834	**Cancer** (Approved on 2017/05/23) **MSI-H or dMMR** Pembrolizumab [ORR(%): 39.6]
KEYNOTE-045[263] 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[264] NCT02453594	**Hodgkin's lymphoma** (Approved on 2017/03/14) - Pembrolizumab [ORR(%): 69.0]
KEYNOTE-024[265] NCT02142738	**Non-small cell lung carcinoma** (Approved on 2016/10/24) **PD-L1** Pembrolizumab vs. Chemotherapy [PFS(M): 10.3 vs. 6]
KEYNOTE-012[260] NCT01848834	**Head and neck squamous cell carcinoma** (Approved on 2016/08/05) - Pembrolizumab [ORR(%): 16.0]
KEYNOTE-006[266] NCT01866319	**Melanoma** (Approved on 2015/12/18) - Pembrolizumab vs. Ipilimumab (3mg/kg every 3 weeks) [OS(M): NR vs. 16]

KEYNOTE-010[267] NCT01905657	**Non-small cell lung carcinoma** (Approved on 2015/10/02)
	PD-L1
	Pembrolizumab [OS(M): 10.4 vs. 8.5]
KEYNOTE-002[268] 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[113] NCT01958021	**Breast cancer** (Approved on 2017/03/13)
	HR+/HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

Sorafenib (NEXAVAR)

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

- FDA Approval Summary of Sorafenib (NEXAVAR)

DECISION[269] NCT00984282	**Differentiated thyroid carcinoma** (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
SHARP[270] NCT00105443	**Hepatocellular carcinoma** (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]
TARGET[271] NCT00073307	**Renal cell carcinoma** (Approved on 2005/12/20)
	-
	Sorafenib vs. Placebo [PFS(D): 167 vs. 84]

Tremelimumab (IMJUDO)

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

- FDA Approval Summary of Tremelimumab (IMJUDO)

POSEIDON NCT03164616	**Lung non-small cell carcinoma** (Approved on 2022/11/10)
	-
	Durvalumab and platinum-based chemotherapy [PFS(M): 6.2 vs. 4.8, OS(M): 14 vs. 11.7]

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HIMALAYA NCT03298451	**Hepatocellular carcinoma** (Approved on 2022/10/21)
	-
	Tremelimumab + durvalumab vs. Tremelimumab + sorafenib [OS(M): 16.4 vs. 13.9]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

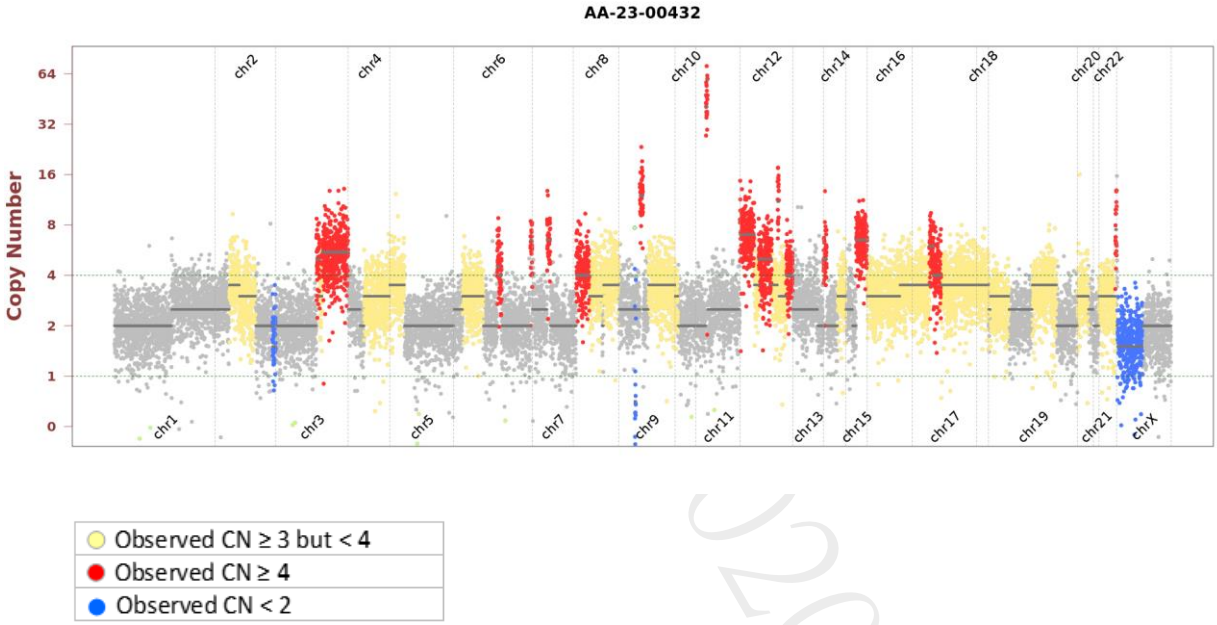
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ERCC2	S44L	3	c.131C>T	NM_000400	COSM1750979	26.2%	355
KMT2D	V3089fs	34	c.9265del	NM_003482	COSM2006975	83.7%	227
LRP1B	Splice donor	-	c.2887+1G>T	NM_018557	-	22.7%	1847
TP53	G154V	5	c.461G>T	NM_000546	COSM6815	55.6%	901

- 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.



OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ADAMTSL1	V461L	12	c.1381G>C	NM_001040272	-	74.6%	1566
ALK	T1012M	18	c.3035C>T	NM_004304	-	59.2%	1523
AMER1	G168S	2	c.502G>A	NM_152424	COSM6854300	75.2%	206
ARID1A	P1575Q	18	c.4724C>A	NM_006015	COSM4995438	84.8%	507
CD19	D238A	4	c.713A>C	NM_001178098	-	38.0%	295
EP300	T1973I	31	c.5918C>T	NM_001429	-	38.6%	417
FANCC	T469M	14	c.1406C>T	NM_000136	-	15.0%	1576
FLT1	A1319G	30	c.3956C>G	NM_002019	-	52.3%	880
HGF	Splice donor	-	c.1864+2T>G	NM_000601	-	26.8%	611
LRP1B	Splice region	-	c.11395+5G>A	NM_018557	-	63.2%	864
MED12	H1823Y	38	c.5467C>T	NM_005120	-	78.6%	448
MSH2	P5Q	1	c.14C>A	NM_000251	-	41.5%	441
MTOR	I1216T	24	c.3647T>C	NM_004958	-	16.7%	1428
MUC16	P11932R	5	c.35795C>G	NM_024690	-	48.4%	878
MYC	N19S	2	c.56A>G	NM_002467	-	42.0%	1178
NSD1	Splice region	-	c.4642-7T>C	NM_022455	-	18.2%	549
PDGFRB	A1045V	22	c.3134C>T	NM_002609	-	84.8%	474
PDGFRB	V823I	18	c.2467G>A	NM_002609	-	17.4%	1001
RAD51C	H95R	2	c.284A>G	NM_058216	-	43.5%	771
SMARCA4	R1157L	26	c.3470G>T	NM_001128844	-	8.6%	370
SOX9	E255V	3	c.764A>T	NM_000346	-	24.5%	388
USH2A	G1723W	25	c.5167G>T	NM_206933	-	6.6%	776
USH2A	T955K	14	c.2864C>A	NM_206933	-	30.2%	739

Note:

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

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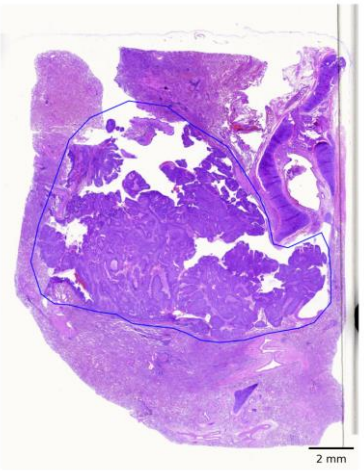
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Jan 09, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11201181D
- Collection site: Lung
- Examined by: Dr. Chien-Ta Chiang
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 20%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 70%
  3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
  4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
  5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 887x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 189

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LIMITATIONS

1. This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject to validation by Sanger or other technologies.
2. The possibility cannot be excluded that certain pathogenic variants detected by other sequencing tools may not be reported in the test because of technical limitation of bioinformatics algorithm or the NGS sequencing platform, e.g. low coverage.
3. This test has been designed to detect fusions in 13 genes sequenced. Therefore, fusion in genes not covered by this test would not be reported. For novel fusions detected in this test, Sanger sequencing confirmation is recommended if residue specimen is available.

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

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RNA test

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

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

DATABASE USED

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

Variant Analysis:
醫檢師張筑芠 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

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GENE LIST

SNV & CNV

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

*Analysis of copy number alterations NOT available.

FUSION

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

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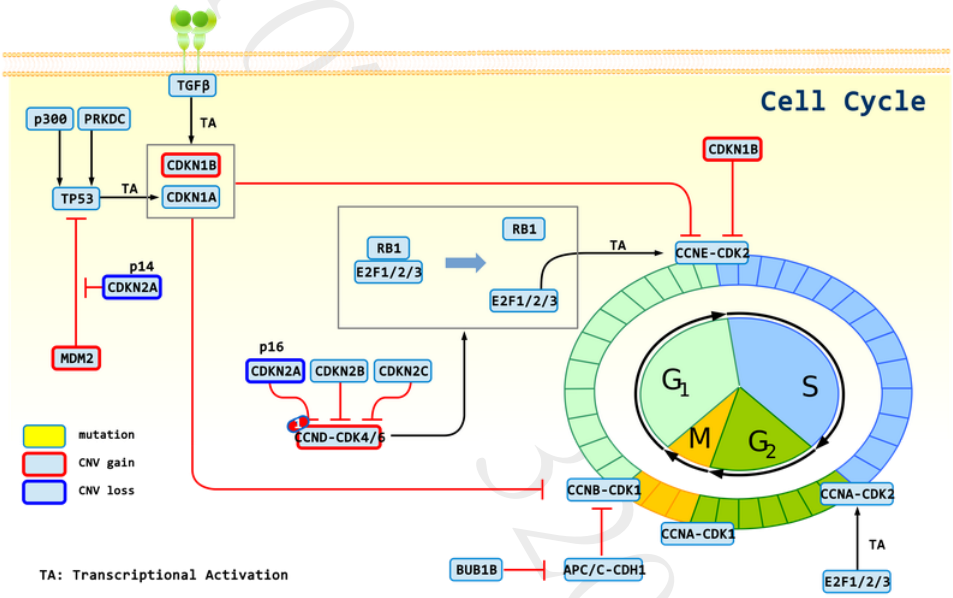
APPENDIX

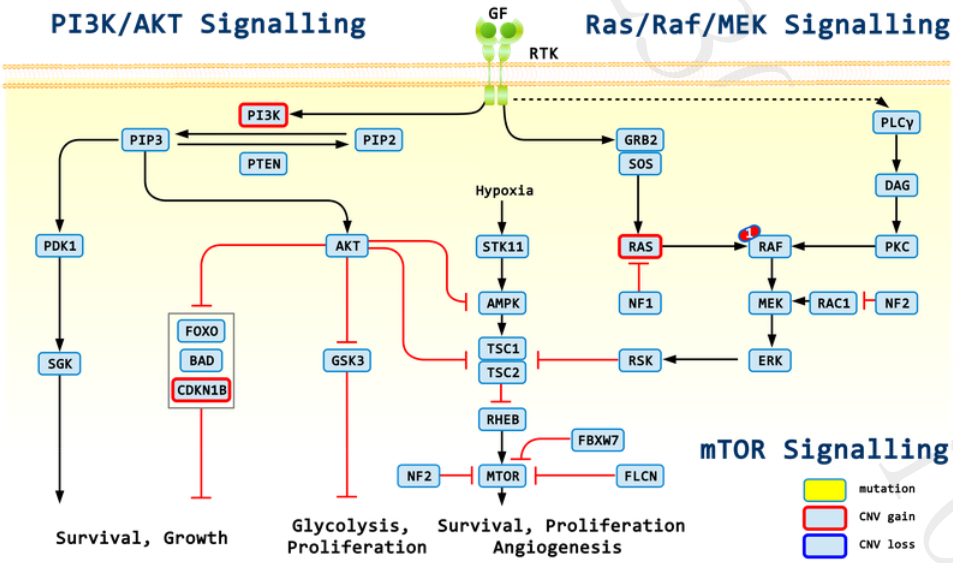
POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Not Applicable.

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Palbociclib, Ribociclib, Abemaciclib



1: Sorafenib

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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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