黃奕凱
Project ID: C23-M001-01065
Report No.: AA-23-02015_ONC
Date Reported: Apr 21, 2023

ACT Onco® + Report

PATIENT		
Identifier: 黃奕凱		Patient ID: 48485832
Date of Birth: Sep 09, 1970		Gender: Male
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11214471A	Collection site: Lung	Type: FFPE tissue
Date received: Apr 10, 2023	Lab ID: AA-23-02015	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	
BRCA2 S270*	-	-	Niraparib, Olaparib, Rucaparib, Talazoparib
BRCA2 Heterozygous deletion	-	-	Niraparib, Olaparib, Rucaparib, Talazoparib
EGFR L858R	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-	-
EGFR T790M	Osimertinib	Afatinib, Dacomitinib, Erlotinib, Gefitinib	-

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
PTEN I224fs	Olaparib, Rucaparib	Cetuximab, Panitumumab, Erlotinib, Gefitinib, Trastuzumab
PTEN Heterozygous deletion	Olaparib, Rucaparib	Cetuximab, Panitumumab, Erlotinib, Gefitinib, Trastuzumab
RB1 Q395*	-	Abemaciclib, Palbociclib, Ribociclib
RB1 Heterozygous deletion	-	Abemaciclib, Palbociclib, Ribociclib

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
BRCA2	S270*	27.6%
DPYD	R74*	20.4%
EGFR	L858R	59.0%
EGFR	T790M	3.9%
PTEN	I224fs	54.1%
RB1	Q395*	47.8%
TP53	R213*	54.0%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr10	*PTEN*	Heterozygous deletion	1
Chr13	*BRCA2, RB1*	Heterozygous deletion	1
Chr17	*FLCN, TP53*	Heterozygous deletion	1
Chr19	*STK11*	Heterozygous deletion	1
Chr3	*MLH1*	Heterozygous deletion	1
Chr5	*RICTOR*	Amplification	6
Chr5	*TERT*	Amplification	7

- Fusions

Fusion Gene & Exon	Transcript ID
No fusion gene detected in this sample	

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	3.2 muts/Mb
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 66% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is < 30%.

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 1		
EGFR L858R	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	**sensitive**
EGFR T790M	Osimertinib	**sensitive**
Level 2		
EGFR T790M	Afatinib, Dacomitinib, Erlotinib, Gefitinib	**resistant**
Level 3A		
BRCA2 S270*	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
BRCA2 Heterozygous deletion	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
Level 3B		
PTEN I224fs	Olaparib, Rucaparib	**sensitive**
PTEN Heterozygous deletion	Olaparib, Rucaparib	**sensitive**
Level 4		
PTEN I224fs	Cetuximab, Panitumumab, Erlotinib, Gefitinib, Trastuzumab	**resistant**
PTEN Heterozygous deletion	Cetuximab, Panitumumab, Erlotinib, Gefitinib, Trastuzumab	**resistant**
RB1 Q395*	Abemaciclib, Palbociclib, Ribociclib	**resistant**
RB1 Heterozygous deletion	Abemaciclib, Palbociclib, Ribociclib	**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)

No genomic alterations detected to confer sensitivity or lack of benefit to immune checkpoint therapies.

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
EGFR aberration	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
RB1 Q395* Heterozygous deletion	Cisplatin	**Sensitive**	Clinical	Bladder carcinoma
RB1 Q395* Heterozygous deletion	FAC, T/FAC, taxane/doxorubicin	**Sensitive**	Clinical	Breast cancer

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
RB1 Q395* Heterozygous deletion	Tamoxifen	**Resistant**	Clinical	Breast cancer

OTHERS

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

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

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VARIANT INTERPRETATION

BRCA2 S270*, Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[1]. BRCA2 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[2]. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia[3]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[4].

S270* mutation results in a premature truncation of the BRCA2 protein at amino acid 270 (UniProtKB). This mutation is predicted to lead to a loss of BRCA2 function, despite not having characterized in the literature.

Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

Therapeutic and prognostic relevance

Multiple PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have been approved by the U.S. FDA for the treatment of cancer. Olaparib is approved for multiple settings in advanced ovarian cancer, metastatic breast cancer with BRCA mutations, metastatic pancreatic cancer, and mCRPC with HRR gene mutations, including BRCA mutations. Rucaparib is approved for maintenance treatment of recurrent ovarian cancer with BRCA mutations and mCRPC with BRCA mutations. Niraparib is approved for maintenance treatment of advanced ovarian cancer and recurrent ovarian cancer with BRCA mutations. Talazoparib is approved for locally advanced or metastatic breast cancer with BRCA mutations.

According to the NCCN guidelines, rucaparib is recommended as recurrence therapy for patients with BRCA-mutated ovarian cancer who have been treated with multiple lines of chemotherapy. It is also recommended as maintenance therapy for patients with metastatic pancreatic cancer who have undergone prior platinum-based therapy and harbor germline or somatic BRCA mutations. Additionally, niraparib is recommended as maintenance therapy for ovarian cancer patients with BRCA mutations.

DPYD R74*

Biological Impact

The DPYD gene encodes a pyrimidine catabolic enzyme, dihydropyrimidine dehydrogenase (DPD), which is the initial and rate-limiting factor in the pathway of uracil and thymine catabolism. DPD is responsible for the elimination of over 80% of systemic of 5-Fluorouracil (5-FU) and the oral 5-FU prodrug capecitabine[5][6]. Genetic variants, missense mutations, silent mutations, and nonsense mutations that result in DPD deficiency are significantly associated with thymine-uraciluria and an increased risk of toxicity with fluoropyrimidine chemotherapy treatments, such as fluorouracil[7][8][6].

R74* mutation results in a premature truncation of the DPYD protein at amino acid 74 (UniProtKB). This mutation is predicted to lead to a loss of DPYD function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

Under the fluoropyrimidine treatment, patients with DPD deficiency had an increased risk of developing severe (grade III/IV) adverse effects, including potential fetal neutropenia, mucositis, and diarrhea[9][10][11][12]. Recommendations of fluoropyrimidine dose reductions for cancer patients with variants associated with DPD deficiency were included in some pharmacogenetics guidelines[13][14].

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EGFR L858R, T790M

Biological Impact

The EGFR gene encodes for the Epidermal Growth Factor Receptor, a receptor tyrosine kinase which binds to its ligands, including Epidermal Growth Factor (EGF) and Transforming Growth Factor-alpha (TGF-alpha), activates downstream signaling pathways, including the canonical oncogenic MAPK and PI3K/AKT/mTOR signaling cascades[15]. Increased EGFR activity by mutations and/or amplification of the EGFR gene has been described in a wide range of cancers, such as lung, brain, colorectal and head and neck cancer[16]. Mutations in the kinase domain of EGFR are commonly observed in non-small cell lung cancer (NSCLC), resulting in a constitutively activated form of the receptor[17]. On the other hand, in the brain and colorectal cancers, the most prevalent EGFR alteration is copy number amplification that results in receptor overexpression[18].

EGFR L858R is a missense mutation at position 858, located in exon 21, which encodes part of the kinase domain, from a leucine to an arginine residue[19]. The two most common EGFR alterations, L858R mutation and exon 19 deletions can result in constitutive activation of signal transduction pathways, leading to cell proliferation or anti-apoptosis without ligand binding[20].

EGFR T790M lies within the ATP-binding pocket of EGFR and is a gatekeeper mutation[21]. T790M is a common secondary somatic mutation that results in increased EGFR kinase activity and resistance to reversible tyrosine kinase inhibitors[21][22]. Several studies also reported the T790M mutation of the pretreatment specimens with EGFR mutations using different methods and sample types[23][24][25].

Therapeutic and prognostic relevance

There is accumulated clinical evidence suggested that patients with MDM2/MDM4 amplification 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) inhibitors therapies[26](Annals of Oncology (2017) 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376).

The first- and second-generation EGFR-TKIs, including dacomitinib, erlotinib, gefitinib, and afatinib, have been approved by the U.S. FDA as first-line treatments for non-small cell lung cancer patients with EGFR exon 19 deletion or L858R mutation. Osimertinib, a third-generation EGFR-TKI, has also been approved by the U.S. FDA. It is indicated for adjuvant treatment or first-line treatment of metastatic NSCLC patients with EGFR exon 19 deletion or L858R mutation.

A phase III trial (NCT01774721) show that dacomitinib significantly improved PFS over gefitinib in first-line treatment of patients with EGFR-mutation-positive NSCLC[27]. Another phase III trial (NCT00949650) demonstrated that median PFS among lung cancer patients with exon 19 deletion or L858R EGFR mutation (n=308) was 13.6 months for afatinib and 6.9 months for chemotherapy[28]. Results from a double-blind, phase 3 trial further showed that osimertinib significantly demonstrated longer PFS than standard EGFR-TKIs (18.9 months vs. 10.2 months) in previously untreated EGFR mutation–positive (exon 19 deletion or L858R) advanced NSCLC[29].

Osimertinib has also been approved by the U.S. FDA for Treatment of adult patients with metastatic NSCLC whose tumors have EGFR T790M mutation and have progressed on or after EGFR-TKI therapy.

The EGFR T790M mutation has been demonstrated to confer resistance to TKIs (dacomitinib, gefitinib, erlotinib, and afatinib) in preclinical and clinical studies[30][31][32][33].

PTEN I224fs, Heterozygous deletion

Biological Impact

The phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene encodes a lipid/protein phosphatase that is important for the regulation of cell proliferation, survival, homologous recombination and maintenance of genomic integrity[34][35]. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway[36]. PTEN is a haploinsufficient tumor suppressor gene, in which having only one copy of the wild-type allele does not produce enough protein product to execute wild-type functions[37][38][39]. Germline loss-of-function PTEN mutations are found in approximately 80% of patients with Cowden syndrome, a disorder that is associated with high-penetrance breast and thyroid cancer[40][41][42]. Somatic mutations or monoallelic loss of PTEN is regularly observed in a significant fraction of human cancers, including sporadic breast cancer, colon cancer, endometrial cancer, prostate cancer, and glioblastoma[43][44][45][46][47].

I224fs mutation results in a change in the amino acid sequence beginning at 224, likely to cause premature truncation of the functional PTEN protein (UniProtKB). This mutation is predicted to lead to a loss of PTEN protein function, despite not being characterized in the literature.

Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

Therapeutic and prognostic relevance

Somatic loss of PTEN results in aberrant activation of PI3K/AKT/mTOR signaling pathway and provides a mechanistic rationale for PI3K pathway inhibitors treatment[48][49]. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes[50][51][52][53][54][55]. Although early clinical data indicated that PTEN loss was associated with improved response and survival in solid tumor patients treated with mTORC1 inhibitor, everolimus[56][57][58], several phase II trials showed no clinical benefit of everolimus or temsirolimus treatment in patients with advanced solid tumors harboring PTEN loss[59][60][61].

Several groups found that PTEN loss was generally associated with poor response to trastuzumab therapy, whether this agent was administered in the neoadjuvant, adjuvant, or metastatic settings[62][63][64][65][66]. Also, loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab[67][68][69][70][71][72].Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib[73][74]. Inhibition of the PI3K/AKT/mTOR signal pathway has been shown to be an effective strategy to radiosensitize NSCLC cells harboring the EGFR activating mutation that acquires resistance to both TKIs due to PTEN loss or inactivation mutations[75].Loss or biallelic inactivation of PTEN is associated with resistance to anti-PD-1 checkpoint blockade therapies, including pembrolizumab and nivolumab in melanoma and leiomyosarcoma patients[76][77][78].

PTEN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in metastatic biliary tract cancer (NCT04042831); talazoparib efficacy in HER2-negative solid tumors (NCT02401347); rucaparib efficacy in prostate cancer (NCT02952534, NCT03533946), and niraparib efficacy in breast cancer (NCT04508803) or any malignancy (except prostate) cancer (NCT03207347). Clinical data also suggested that PTEN deficient cancers may be sensitive to olaparib[79]. However, in a phase II trial (NCT02286687), 13 patients with advanced solid tumors harboring PTEN mutation or loss (by IHC) had limited response to talazoparib treatment; only one patient with PTEN mutation had prolonged SD (Mol Cancer Ther 2018;17(1 Suppl):Abstract nr A096; NCT02286687). Besides, in a phase I trial (NCT00749502), no association between loss of PTEN expression and the efficacy of niraparib was identified in patients with castration-resistant prostate cancer[80].

In a preclinical study, PTEN null cancer cells were sensitive to rucaparib treatment in vitro[81].

RB1 Q395*, Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[82]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[83]. RB1 has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[84][85][86]. Deletion or inactivating mutation of RB1 is found in a number of tumors, including lung, prostate, bladder, breast cancers and sarcomas. RB1 mutations are found in approximately half of all retinoblastoma cases[87].

Q395* mutation results in a premature truncation of the RB1 protein at amino acid 395 (UniProtKB). This mutation is predicted to lead to a loss of RB1 function, despite not having characterized in the literature. Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

Therapeutic and prognostic relevance

A deleterious mutation in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response and better overall survival to cisplatin-based chemotherapy for muscle-invasive bladder cancer patients[88]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytoxan (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy[89].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[90][91].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[92]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[93].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[94][95]. Analyses of repeat biopsy samples from patients with EGFR-mutant adenocarcinoma that had transformed to the SCLC subtype have revealed that 100% of these patients have loss of RB1 and may be the alteration that induces this non-small-cell to small-cell transformation[91][96].

TP53 R213*, Heterozygous deletion

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[97]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[37].

R213* mutation results in a premature truncation of the p53 protein at amino acid 213 (UniProtKB). This mutation is predicted to lead to a loss of p53 function, despite not having characterized in the literature.

Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

Therapeutic and prognostic relevance

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)[98].

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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[99]. 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[100].

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[101][102][103]. 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)[104]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[105][106]. 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[107].

FLCN Heterozygous deletion

Biological Impact

The FLCN gene encodes the tumor suppressor, Folliculin, a GTPase activating protein (GAP) for RagC/D GTPase proteins involved in amino acid sensing and signaling to mTORC1[108]. FLCN has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[109][110]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[111][112]. Germline mutation of the FLCN gene causes the Birt-Hogg-Dubé syndrome, a rare disorder that is characterized by benign hamartomatous skin lesions and an increased risk of pneumothorax and renal tumors[113].

Therapeutic and prognostic relevance

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTC) patients who had PI3K/mTOR/AKT alterations, including TSC2, FLCN or NF1, showed impressive progression-free survival (PFS) of 15.2 months after receiving everolimus[114]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[115].

MLH1 Heterozygous deletion

Biological Impact

The MutL protein homolog 1 (MLH1) gene encodes a tumor suppressor that dimerizes with PMS2 protein to form a component of the DNA mismatch repair (MMR) system[116]. Deletion of one copy of the MLH1 gene resulted in haploinsufficiency in the correction of small insertions/deletions (indels), and could be a driving force in pancreatic and renal carcinogenesis[117]. Genetic alterations such as mutation, loss of heterozygosity or epigenetic silencing could lead to inactivation of MLH1 and are associated with a broad spectrum of cancers, including a subset of sporadic colon, gastric and endometrial cancers, as well as the hereditary non-polyposis colon cancer (HNPCC, also known as Lynch syndrome)[118][119][120].

Therapeutic and prognostic relevance

Currently, there are no FDA-approved medications specifically targeting MLH1. A screening test for microsatellite instability (MSI) is commonly used to identify an MMR-deficient tumor in the clinic[121][122]. Pembrolizumab (KEYTRUDA), an inhibitor targeting programmed cell death 1 (PD-1), has been approved by the U.S. FDA for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient cancer. Down-regulation of genes involved in the MMR pathway such as MLH1, MSH2 and, MSH6 in high-grade serous epithelial ovarian cancer cell lines rendered cells sensitive to PARP inhibitors[123].

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RICTOR Amplification

Biological Impact

The RICTOR (rapamycin-insensitive companion of mTOR) gene encodes a core component of the mTOR complex-2 (mTOR2) which phosphorylated downstream kinases such as AKT and regulated cell proliferation and survival[124][125][126]. Amplification of the RICTOR locus is observed in melanoma[127] and lung cancer[128].

Therapeutic and prognostic relevance

A non-small cell lung cancer (NSCLC) patient harboring RICTOR-amplified tumor achieved stable disease for more than 18 months from the treatment with dual mTOR1/2 inhibitors CC-223 and MLN0128[128]. Preclinical data showed that a RICTOR-amplified patient-derived cancer cell line is sensitive to mTORC1/2 inhibitor (AZD2014)[129]. RICTOR amplification and mutation have been determined as an inclusion criterion for the trial examining everolimus efficacy in patients with prostate cancer (NCT03580239).

Several studies have demonstrated that patients with a RICTOR-amplified tumor have lower overall survival in small cell lung cancer, colorectal cancer, and esophageal squamous cell carcinoma[130][131][132][133]. Overexpression of RICTOR is positively associated with tumor progression and poor survival in hepatocellular carcinoma, gastric cancer, pituitary adenoma, and endometrial carcinoma[134][135][136][137].

STK11 Heterozygous deletion

Biological Impact

The serine/threonine kinase 11 (STK11, also known as LKB1) gene encodes the multifunctional serine/threonine kinase, a tumor suppressor that functions as an inhibitor for the mTOR signaling pathway[138][139]. STK11 is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[140][141]. In the mouse model, loss of STK11 promotes aggressive endometrial and squamous cell carcinomas[142][143]. Mutations in STK11 have been found in lung, breast, cervical, testicular, and liver cancers, as well as malignant melanoma, pancreatic and biliary carcinoma[144]. Germline mutations in STK11 are found in 30-70% of Peutz-Jeghers syndrome[145].

Therapeutic and prognostic relevance

A clinical study in a pancreatic cancer patient with Peutz-Jeghers syndrome whose tumor harboring an STK11 D194E mutation coupled with the loss of heterozygosity of the other STK11 allele displayed partial response to the everolimus treatment[146]. In another clinical case study, an adrenocorticotropic pituitary carcinoma patient whose tumor bearing an STK11 inactivating mutation responded to a combination of everolimus and radiotherapy[147].

Preclinical data suggested that lung cancer cell lines with STK11 inactivating mutations may confer increased sensitivity to the MEK-1 and MEK-2 inhibitor, trametinib[148].

Inactivating mutations of STK11 was shown to be associated with resistance to immune checkpoint blockade in KRAS-mutant lung adenocarcinoma (LUAC) and NSCLC (DOI: 10.1200/JCO.2017.35.15_suppl.9016)[149][150][151]. It was proposed that loss of STK11 negatively impacts the number and function of tumor-infiltrating T cells (TILs) and PD-L1 expression on tumor cells and therefore results in an ineffective response to PD-1-targeting antibodies[152].

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TERT Amplification

Biological Impact

The TERT gene encodes the catalytic subunit of telomerase, an enzyme that maintains telomere length and genomic integrity[153]. Upregulation of TERT promotes cancer development and progression via modulation of Wnt-catenin and nuclear factor kappa B signaling[154][155], and mitochondrial RNA processing[156]. Activating mutations in the TERT promoter have been identified in a number of cancer types including melanoma, hepatocellular carcinoma, urothelial carcinoma, medulloblastoma, and glioma whereas TERT gene amplification is implicated in lung cancer, cervical cancer, breast cancer, Merkel cell carcinoma, neuroblastoma and adrenocortical carcinoma[157][158][159][160][161].

Therapeutic and prognostic relevance

Imetelstat (GRN163L), a telomere inhibitor which has been shown to inhibit cell proliferation in various cancer cell lines and tumor xenografts is currently in clinical trials[153].

TERT gene amplification is an independent poor prognostic marker for disease-free survival in non-small cell lung cancer (NSCLC) and breast cancer[162][163][164].

US FDA-APPROVED DRUG(S)

Afatinib (GILOTRIF)

Afatinib acts as an irreversible covalent inhibitor of the ErbB family of receptor tyrosine kinases, including epidermal growth factor receptor (EGFR) and erbB-2 (HER2). Afatinib is developed and marketed by Boehringer Ingelheim under the trade name GILOTRIF (United States) and GIOTRIF (Europe).

- FDA Approval Summary of Afatinib (GILOTRIF)

LUX-Lung 8[165] NCT01523587	**Non-small cell lung carcinoma** (Approved on 2016/04/15)
	EGFR ex19del or L858R
	Afatinib vs. Erlotinib [PFS(M): 2.4 vs. 1.9]
LUX-Lung 3[166] NCT00949650	**Non-small cell lung carcinoma** (Approved on 2013/07/13)
	EGFR ex19del or L858R
	Afatinib vs. Pemetrexed + cisplatin [PFS(M): 11.1 vs. 6.9]

Binimetinib (MEKTOVI)

Binimetinib is an oral kinase inhibitor that targets MEK. Binimetinib is developed and marketed by Array BioPharma under the trade name MEKTOVI.

- FDA Approval Summary of Binimetinib (MEKTOVI)

MEKTOVI[167] NCT01909453	**Melanoma** (Approved on 2018/06/27)
	BRAF V600E/K
	Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3]

Cobimetinib (COTELLIC)

Cobimetinib is a reversible inhibitor which targets MEK1 and MEK2. Cobimetinib is developed by Exelixis and Genentech, and marketed by Genentech under the trade name COTELLIC.

- FDA Approval Summary of Cobimetinib (COTELLIC)

coBRIM[168] NCT01689519	**Melanoma** (Approved on 2015/11/10)
	BRAF V600E/K
	Cobimetinib + vemurafenib vs. Placebo + vemurafenib [PFS(M): 12.3 vs. 7.2]

Dacomitinib (VIZIMPRO)

Dacomitinib is an oral kinase inhibitor that targets EGFR. Dacomitinib is developed and marketed by Pfizer under the trade name VIZIMPRO.

- FDA Approval Summary of Dacomitinib (VIZIMPRO)

ARCHER 1050[27] NCT01774721	**Non-small cell lung carcinoma** (Approved on 2018/09/27)
	EGFR ex19del or L858R
	Dacomitinib vs. Gefitinib [PFS(M): 14.7 vs. 9.2]

Erlotinib (TARCEVA)

Erlotinib is a small molecule, reversible inhibitor of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase. Erlotinib is developed by OSI Pharmaceuticals, Genentech and Roche, and marketed by Astellas Pharm Global Development under the trade name TARCEVA.

- FDA Approval Summary of Erlotinib (TARCEVA)

RELAY NCT02411448	**Non-small cell lung carcinoma** (Approved on 2020/05/29)
	EGFR ex19del or L858R
	Erlotinib + ramucirumab vs. Erlotinib + placebo [PFS(M): 19.4 vs. 12.4]
EURTAC[169] NCT00446225	**Non-small cell lung carcinoma** (Approved on 2013/05/14)
	EGFR ex19del or L858R
	Erlotinib vs. Cisplatin + gemcitabine or cisplatin + docetaxel or carboplatin + gemcitabine or carboplatin + docetaxel [PFS(M): 10.4 vs. 5.2]
PA.3[170] NCT00026338	**Pancreatic cancer** (Approved on 2005/11/02)
	-
	Gemcitabine vs. Placebo [OS(M): 6.4 vs. 6]

Everolimus (AFINITOR)

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

- FDA Approval Summary of Everolimus (AFINITOR)

RADIANT-4[171] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[172] NCT00863655	**Breast cancer** (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
EXIST-2 NCT00790400	**Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma** (Approved on 2012/04/26)
	-
	Everolimus vs. Placebo [ORR(%): 41.8 vs. 0]
RADIANT-3[57] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[173] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[174] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

Gefitinib (IRESSA)

Gefitinib is a small molecule inhibitor of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase. Gefitinib is developed and marketed by AstraZeneca under the trade name IRESSA.

- FDA Approval Summary of Gefitinib (IRESSA)

IFUM[175] NCT01203917	**Non-small cell lung carcinoma** (Approved on 2015/07/13)
	EGFR ex19del or L858R
	Gefitinib [ORR(%): 50.0]

Niraparib (ZEJULA)

Niraparib is an oral, small molecule inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1 and -2 (PARP-1, -2). Niraparib is developed and marketed by Tesaro under the trade name ZEJULA.

- FDA Approval Summary of Niraparib (ZEJULA)

PRIMA NCT02655016	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2020/04/29)
	-
	Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
NOVA[176] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27)
	-
	Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

Olaparib (LYNPARZA)

Olaparib is an oral, small molecule inhibitor of poly (ADP-ribose) polymerase-1, -2, and -3 (PARP-1, -2, -3). Olaparib is developed by KuDOS Pharmaceuticals and marketed by AstraZeneca under the trade name LYNPARZA.

- FDA Approval Summary of Olaparib (LYNPARZA)

OlympiA NCT02032823	**Her2-negative high-risk early breast cancer** (Approved on 2022/03/11)
	HER2-/gBRCA mutation
	Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound[177] NCT02987543	**Prostate cancer** (Approved on 2020/05/19)
	HRR genes mutation
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1[178] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[179] NCT02184195	**Pancreatic adenocarcinoma** (Approved on 2019/12/27)
	gBRCA mutation
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1[180] NCT01844986	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19)
	gBRCA mutation or sBRCA mutation
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]

OlympiAD[181] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[182] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA mutation
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19[183] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

Osimertinib (TAGRISSO)

Osimertinib is a third-generation tyrosine kinase inhibitor (TKI) for patients with tumors harboring EGFR T790M mutation. Osimertinib is developed and marketed by AstraZeneca under the trade name TAGRISSO.

- FDA Approval Summary of Osimertinib (TAGRISSO)

ADAURA NCT02511106	**Non-small cell lung carcinoma** (Approved on 2020/12/18)
	EGFR ex19del or L858R
	Osimertinib vs. Placebo + adjuvant chemotherapy [DFS(M): NR vs. 19.6]
FLAURA[29] NCT02296125	**Non-small cell lung carcinoma** (Approved on 2018/04/18)
	EGFR ex19del or L858R
	Osimertinib vs. Gefitinib or erlotinib [PFS(M): 18.9 vs. 10.2]
AURA3[184] NCT02151981	**Non-small cell lung carcinoma** (Approved on 2017/03/30)
	EGFR T790M
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA[185] NCT01802632	**Non-small cell lung carcinoma** (Approved on 2015/11/13)
	EGFR T790M
	Osimertinib [ORR(%): 59.0]

Rucaparib (RUBRACA)

Rucaparib is an inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1, -2 and -3 (PARP-1, -2, -3). Rucaparib is developed and marketed by Clovis Oncology under the trade name RUBRACA.

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[186] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	-
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]

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Talazoparib (TALZENNA)

Talazoparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2. Talazoparib is developed and marketed by Pfizer under the trade name TALZENNA.

- FDA Approval Summary of Talazoparib (TALZENNA)

EMBRACA[187] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

Temsirolimus (TORISEL)

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

- FDA Approval Summary of Temsirolimus (TORISEL)

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

Trametinib (MEKINIST)

Trametinib is an anti-cancer inhibitor which targets MEK1 and MEK2. Trametinib is developed and marketed by GlaxoSmithKline (GSK) under the trade name MEKINIST.

- FDA Approval Summary of Trametinib (MEKINIST)

CDRB436G2201 NCT02684058	**Low-grade glioma** (Approved on 2023/03/09)
	BRAF V600E
	Dabrafenib + trametinib vs. Carboplatin + vincristine [ORR(%): 46.6 vs. 10.8]
BRF117019, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060,NCT02124772	**Cancer** (Approved on 2022/06/22)
	BRAF V600E
	Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0]
BRF117019[189] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[190] NCT01336634	**Non-small cell lung cancer** (Approved on 2017/06/22)
	BRAF V600E
	Trametinib + dabrafenib vs. Dabrafenib [ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9]
COMBI-d[191] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[192] NCT01245062	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

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

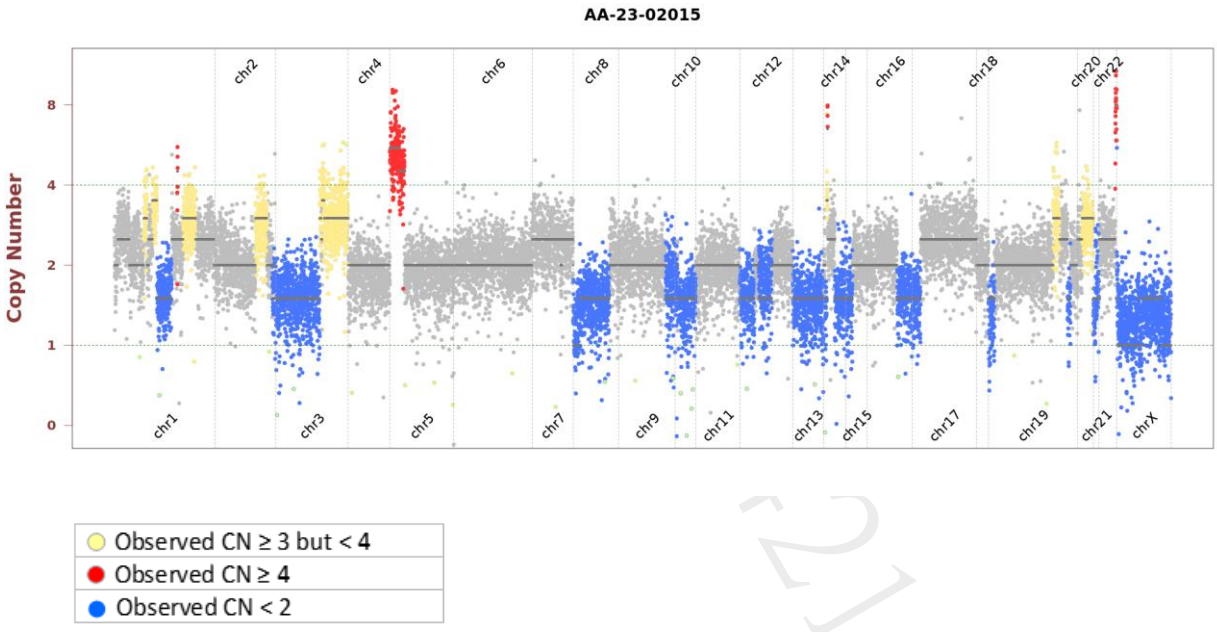
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
BRCA2	S270*	10	c.809C>G	NM_000059	-	27.6%	181
DPYD	R74*	3	c.220C>T	NM_000110	-	20.4%	412
EGFR	L858R	21	c.2573T>G	NM_005228	COSM6224	59.0%	1383
EGFR	T790M	20	c.2369C>T	NM_005228	COSM6240	3.9%	636
PTEN	I224fs	7	c.670_688del	NM_000314	-	54.1%	438
RB1	Q395*	12	c.1183C>T	NM_000321	COSM936	47.8%	207
TP53	R213*	6	c.637C>T	NM_000546	COSM10654	54.0%	611

- Copy Number Alterations

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



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OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ADGRA2	V431M	9	c.1291G>A	NM_032777	-	73.6%	269
AXL	T443A	11	c.1327A>G	NM_021913	-	67.5%	926
ETV4	P463R	13	c.1388C>G	NM_001079675	-	50.8%	388
HIST1H1C	I80M	1	c.240C>G	NM_005319	COSM1672274	34.2%	994
MUC16	T13351M	49	c.40052C>T	NM_024690	COSM1397845	46.6%	451
POLD1	Splice region	-	c.1893-7A>G	NM_001256849	-	49.4%	314
PRKDC	S1408P	34	c.4222T>C	NM_006904	-	73.8%	781
RUNX1	Q370R	6	c.1109A>G	NM_001001890	COSM26028	27.0%	337

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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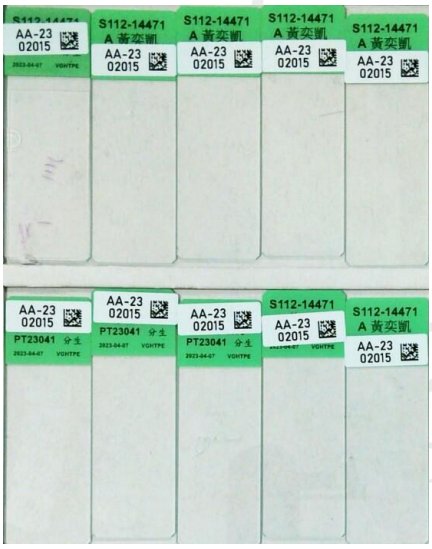
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Mar 31, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11214471A
- Collection site: Lung
- Examined by: Dr. Yeh-Han Wang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 30%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 30%
    3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
    4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
    5. Additional comment: NA
- Manual macrodissection: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 766x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 103

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LIMITATIONS

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

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RNA test

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

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

DATABASE USED

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

Variant Analysis:
醫檢師張筑芃 博士
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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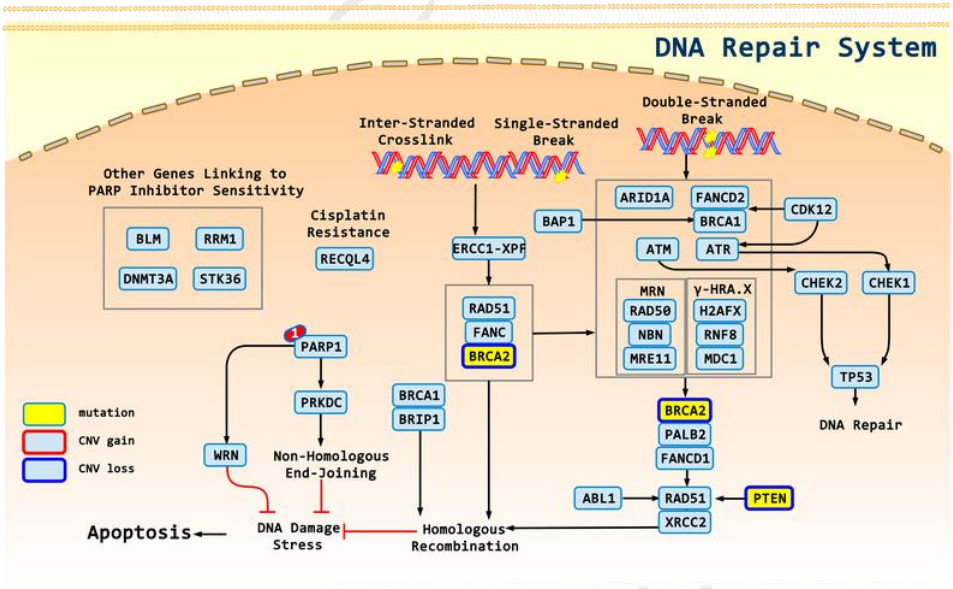
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
STK11	Binimetinib, Cobimetinib, Trametinib, Everolimus, Temsirolimus,	**sensitive**
FLCN	Everolimus, Temsirolimus	**sensitive**
MLH1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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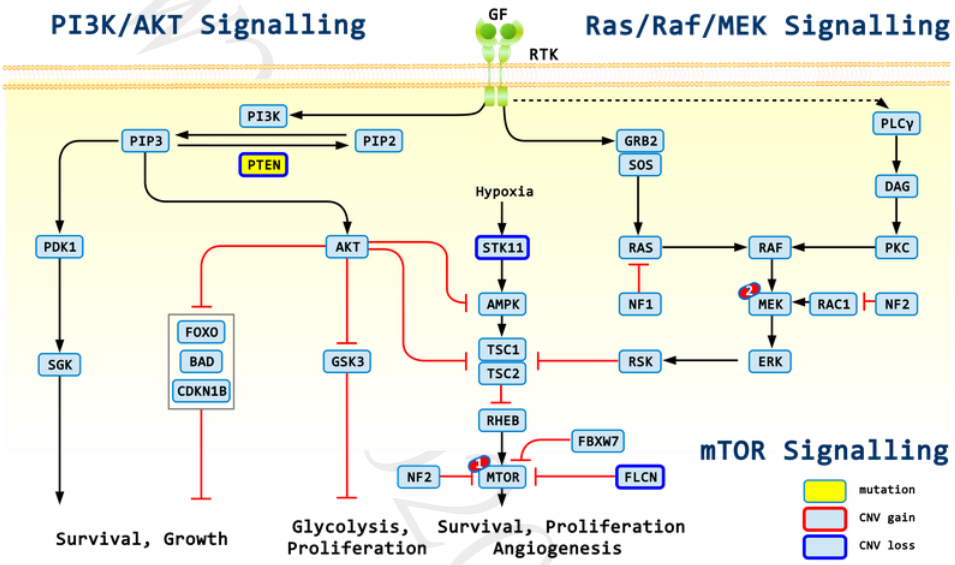
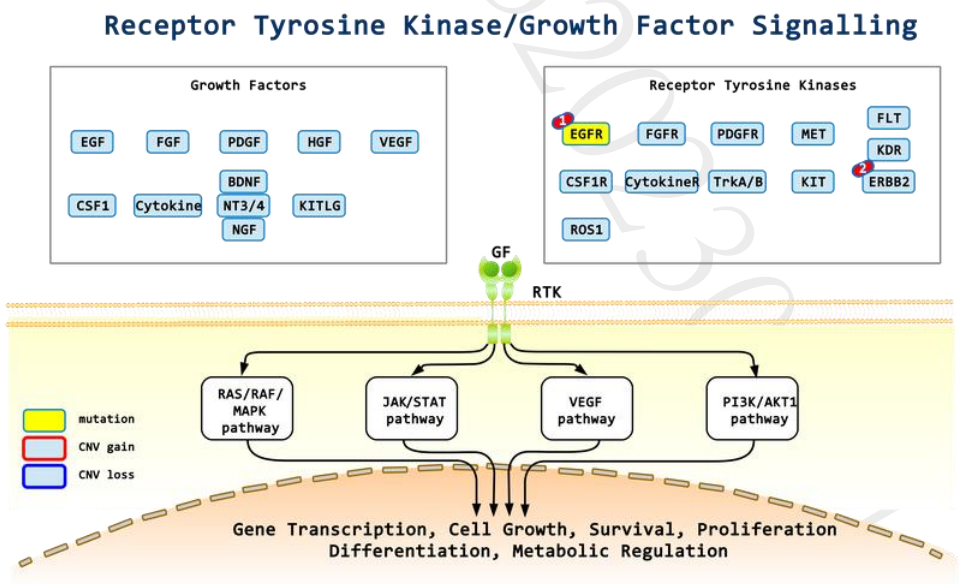


1: Everolimus, Temsirolimus; 2: Trametinib, Cobimetinib, Binimetinib



1: Erlotinib, Afatinib, Gefitinib, Osimertinib, Dacomitinib; 2: Afatinib

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DISCLAIMER

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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。
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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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PATIENT		
Identifier: 黃奕凱		Patient ID: 48485832
Date of Birth: Sep 09, 1970		Gender: Male
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
Name: 陳育民醫師		Tel: 886-228712121
Facility: 臺北榮總		
Address: 臺北市北投區石牌路二段 201 號		
SPECIMEN		
Specimen ID: S11214471A	Collection site: Lung	Type: FFPE tissue
Date received: Apr 10, 2023	Lab ID: AA-23-02015	D/ID: NA
Date reported: Apr 21, 2023	Project ID: C23-M001-01065	Testing panel: ACTOnco+

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene Alterations	Allele Frequency	Classification
BRCA2 c.809C>G (S270*)	27.6%	Deleterious

Notes:

The addendum report further provides the AMP/ACMG classification of deleterious and suspected deleterious BRCA1/2 mutations if detected by ACTOnco assay based on the reimbursement requirement of Taiwan National Health Insurance.

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Yeh-Han Wang M.D.

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