黃錦美
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ACT Onco® + Report

PATIENT		
Identifier: 黃錦美		Patient ID: 7847849
Date of Birth: Mar 20, 1949		Gender: Female
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: C11139712A	Collection site: Pleural effusion	Type: FFPE tissue
Date received: Nov 22, 2022	Lab ID: AA-22-07081	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 SIsignificance

Genomic Alterations/Biomarkers	Probable Effects in Patient's Cancer Type		Probable Sensitive in Other Cancer Types
	Sensitive	Resistant	
EGFR L747_P753delinsS (Exon 19 deletion)	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-	-
MET Amplification	Capmatinib, Crizotinib, Tepotinib	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-
NRF1(5)-BRAF(9) fusion	-	-	Selumetinib

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
EGFR L747_P753delinsS (Exon 19 deletion)	Mobocertinib	Cetuximab
CDKN2A Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	-
MET Amplification	Cabozantinib	Cetuximab, Panitumumab
NRF1(5)-BRAF(9) fusion	Trametinib	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib, Vemurafenib

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
EGFR	L747_P753delinsS (Exon 19 deletion)	34.7%
TP53	I195fs	24.3%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr9	*CDKN2A*	Homozygous deletion	0
Chr11	*CHEK1*	Heterozygous deletion	1
Chr17	*FLCN*	Heterozygous deletion	1
Chr19	*STK11*	Heterozygous deletion	1
Chr22	*CHEK2, NF2*	Heterozygous deletion	1
Chr7	*KMT2C*	Heterozygous deletion	1
Chr7	*CARD11*	Amplification	6
Chr18	*TYMS*	Amplification	8
Chr7	*MET*	Amplification	14

- Fusions

Fusion Gene & Exon	Transcript ID
NRF1(5)-BRAF(9) fusion	NRF1(NM_005011.4), BRAF(NM_004333.4)

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	5.7 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 34% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- The fusion gene reported above is confirmed to be in-frame and includes the kinase/functional domain. Such alteration may indicate potential benefits from kinase inhibitors. However, for a novel fusion, its functional significance and response to kinase inhibitors are undetermined.
- 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 L747_P753delinsS (Exon 19 deletion)	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	**sensitive**
Level 2		
MET Amplification	Capmatinib, Crizotinib, Tepotinib	**sensitive**
MET Amplification	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	**resistant**
Level 3A		
NRF1(5)-BRAF(9) fusion	Selumetinib	**sensitive**
Level 3B		
CDKN2A Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
MET Amplification	Cabozantinib	**sensitive**
NRF1(5)-BRAF(9) fusion	Trametinib	**sensitive**
Level 4		
EGFR L747_P753delinsS (Exon 19 deletion)	Mobocertinib	**sensitive**
EGFR L747_P753delinsS (Exon 19 deletion)	Cetuximab	**resistant**
MET Amplification	Cetuximab, Panitumumab	**resistant**
NRF1(5)-BRAF(9) fusion	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib, Vemurafenib	**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
TYMS Amplification	Fluorouracil	**Less sensitive**	Clinical	Colorectal cancer
	Pemetrexed	**Less sensitive**	Clinical	Lung cancer

HORMONAL THERAPIES

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

OTHERS

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

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

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VARIANT INTERPRETATION

NRF1(5)-BRAF(9) fusion

Biological Impact

BRAF is a serine/threonine kinase that belongs to the RAF family. The protein plays an essential role in the regulation of mitogen-activated protein kinase (MAPK) cascade, which affects a range of cellular response including cell division, differentiation, and secretion[1][2]. Mutations in the BRAF gene, most commonly the V600 residue, are the most frequently identified oncogenic mutations in melanomas, and have been identified in several types of cancers including non-Hodgkin lymphoma, thyroid cancers, non-small cell lung carcinoma, hairy cell leukemia, glioma, gastrointestinal stromal tumor, and colorectal cancers (CRCs)[3][4]. Of note, in the vast majority of cases, BRAF mutations are non-overlapping with other oncogenic mutations (e.g., NRAS mutations, KIT mutations, etc.) found in melanoma. V600E has been determined to be an activating mutation, which results in enhanced BRAF kinase activity and constitutive activation of downstream MEK/ERK signaling cascade[5][6].

Gene fusions involving the 3' kinase domain of BRAF and various 5' upstream gene partners lead to constitutively activated due to loss of the auto-inhibitory domain of BRAF[7]. BRAF fusions have been identified in pilocytic astrocytoma, melanoma, thyroid cancer, and pancreatic acinar cell carcinoma[8][9][10][11][12][13].

The NRF1-BRAF fusion gene forms by the N-terminus of the NRF1 gene to the BRAF kinase domain in C-terminus. NRF1-BRAF fusion has been identified in urothelial carcinoma and pleomorphic xanthoastrocytoma[14][15]. The NRF1-BRAF fusion demonstrating MAPK pathway activation in patient tumor cells[15].

Therapeutic and prognostic relevance

In the NCCN guidelines for CNS cancers, selumetinib was suggested to treat patients with recurrent or progressive pilocytic astrocytoma harboring BRAF fusion or BRAF V600E mutation[16].

Several clinical studies suggested that BRAF fusion gene is a resistance mechanism for EGFR TKIs and BRAF inhibitor vemurafenib (DOI: 10.1200/JCO.2020.38.15_suppl.e21598)[17][18][19][20][21].

Of note, BRAF fusions have been determined as an inclusion criterion for the trials evaluating trametinib efficacies in cancers (NCT04439279).

In a case report, a urothelial carcinoma patient harboring NRF1-BRAF fusion had a clinical response by trametinib treatment[14].

EGFR L747_P753delinsS (Exon 19 deletion)

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[22]. 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[23]. 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[24]. On the other hand, in the brain and colorectal cancers, the most prevalent EGFR alteration is copy number amplification that results in receptor overexpression[25].

EGFR L747_P753delinsS (exon 19 deletion) lies within the tyrosine kinase domain of EGFR, resulting in a deletion of 7 amino acids from residues 747 to 753 and insertion of a serine residue (UniProtKB). L747_P753delinsS confers a gain-of-function mutation as demonstrated by increased autophosphorylation of the EGFR protein and cell

transformation in vitro[26][27][28].

EGFR exon 19 deletions are in-frame deletions of 9–24 nucleotides in exon 19 centred around codons 746–750 of the kinase domain of EGFR. 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[29].

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[30](Annals of Oncology (2017) 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376).

There is accumulated clinical evidence reported that patients with lung adenocarcinoma or NSCLC harboring EGFR L747_P753delinsS responded to EGFR TKIs[31][32][33]. In preclinical studies, cells expression EGFR L747_P753delinsS were sensitive to mobocertinib, but resistant to cetuximab[34][35].

The first- and second-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs), dacomitinib, erlotinib, gefitinib and afatinib have been approved by the U.S. Food and Drug Administration (FDA) as the first-line treatment in non-small cell lung cancer (NSCLC) patients whose tumor carries EGFR exon 19 deletion or L858R mutation[36][37][38], as detected by a U.S. FDA-approved test. A Phase III clinical trial (NCT01774721) show that dacomitinib significantly improved progression-free survival over gefitinib in first-line treatment of patients with EGFR-mutation-positive NSCLC[36]. Another Phase III clinical trial (NCT00949650) demonstrated that median progression-free survival (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. The EGFR T790M mutation has been demonstrated to confer resistance to TKIs (dacomitinib, gefitinib, erlotinib, and afatinib) in preclinical and clinical studies[39][40][41][42].

Osimertinib, a third-generation irreversible EGFR-TKI that selectively inhibits both EGFR-TKI–sensitizing and EGFR T790M resistance mutations, has been approved by the U.S. FDA for NSCLC patient harboring T790M mutation-positive tumor[43][44][45]. 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[46].

TP53 I195fs

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[47]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[48].

I195fs mutation results in a change in the amino acid sequence beginning at 195, likely to cause premature truncation of the functional p53 protein (UniProtKB). This mutation is predicted to lead to a loss of p53 protein function, despite not being characterized in the literature.

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)[49].

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[50]. 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[51].

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[52][53][54]. 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)[55]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[56][57]. 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[58].

CARD11 Amplification

Biological Impact

CARD11 (caspase recruitment domain 11) gene encodes a cytoplasmic scaffold protein of the CARD11/BCL10/MALT1 (CBM) complex which plays essential roles in regulating apoptosis and NF-κB activation in response to upstream stimuli[59][60]. CARD11 gain-of-function mutations are frequently detected in human diffuse large B-cell lymphoma (DLBCL)[61]and cutaneous squamous cell carcinoma[62]. Moreover, CARD11 gene amplification has been observed in a significant proportion of DLBCL[63]. Biochemical assays revealed that enforced expression of CARD11/BCL10/MALT1 is essential for transformation of B-cell and survival of DLBCL cell[64].

Therapeutic and prognostic relevance

Retrospective studies have shown that high CARD11 expression or CARD11 gene amplification was associated with poor survival in diffuse large B cell lymphoma (DLBCL)[65][63].

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[66][67][68]. 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[69]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[70][71].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[72][73]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[74][75][76]. 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[77][78][79]. 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

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treated with palbociclib monotherapy for 16 weeks (DOI: 10.1200/JCO.2021.39.15_suppl.6043)[80][81].

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[73][82][83].

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[75]. 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[84].

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[85].

CHEK1 Heterozygous deletion

Biological Impact

The checkpoint kinase 1 (CHEK1 or CHK1) gene encodes a protein kinase involved in transducing DNA damage signals and is required for both the intra-S phase and G2/M checkpoints[86]. CHEK1 heterozygosity has been shown to cause haploinsufficient phenotypes that can contribute to tumorigenesis through inappropriate S phase entry, accumulation of DNA damage during replication, and failure to restrain mitotic entry[87][88]. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors[89], and CHEK1 mutations are extremely rare[86]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer[90], breast cancer[91], colorectal cancer[92], non-small cell lung (NSCLC) cancer[93], and nasopharyngeal cancer[94].

Therapeutic and prognostic relevance

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate (NCT02987543)[95].

In addition, CHEK1 has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in advanced solid tumors (NCT03297606; CAPTUR trial), rucaparib efficacy in ovarian cancer (NCT01968213)[96], prostate cancer (NCT03533946), niraparib efficacy in pancreatic cancer (NCT03553004), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in lung cancer (NCT03377556), respectively.

Selective inhibitors for CHEK1 and CHEK2 alone or in combination with other agents are currently being investigated in clinical trials[97].

CHEK2 Heterozygous deletion

Biological Impact

The checkpoint kinase 2 (CHEK2 or CHK2) gene encodes a serine/threonine protein kinase involved in transducing DNA damage signals that are required for both the intra-S phase and G2/M checkpoints[98]. CHEK2 heterozygosity has been shown to cause haploinsufficient phenotypes that can contribute to tumorigenesis through inappropriate S phase entry, accumulation of DNA damage during replication, and failure to restrain mitotic entry[87][88]. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers[99][100][101][102][103].

Therapeutic and prognostic relevance

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate (NCT02987543)[95].

In a phase II trial (TBCRC 048; NCT03344965), 7 metastatic breast cancer patients harboring only germline mutations in CHEK2 were not responded to olaparib treatment (SD: n=3, PD: n=4)[104]. Furthermore, in another phase II trial (TRITON2; NCT02952534), 12 mCRPC patients harboring CHEK2 alteration had limited response to rucaparib treatment. One patient with co-occurring ATM alteration had a radiographic partial response (n=1/9 evaluable patients). The prostate-specific antigen response rate was 16.7% (n=2/12), and the 6-month clinical benefit rate was 37.5% (n=3/8)[105].

In addition, CHEK2 has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in advanced solid tumors (NCT03297606; CAPTUR trial), rucaparib efficacy in ovarian cancer (NCT01968213)[96], and prostate cancer (NCT02952534, NCT03533946)[105], niraparib efficacy in metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma (NCT03840967), melanoma (NCT03925350), pancreatic cancer (NCT03553004, NCT03601923), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative solid tumors (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

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[106]. 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[107][108]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[109][110]. 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[111].

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[112]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[113].

KMT2C Heterozygous deletion

Biological Impact

Lysine methyltransferase 2C (KMT2C) gene encodes the histone methyltransferase MLL3, which methylates lysine residue four on the tail of histone H3 (H3K4)[114]and regulates the gene expression during development and hematopoiesis[115][116][117]. KMT2C is ubiquitously expressed, and its function is essential for normal embryonal development and cell proliferation[118]. Genetic deletion of the region containing KMT2C is the most common chromosomal abnormality in acute myeloid leukemia[119][120], and KMT2C mutation has been reported in breast cancer, cutaneous squamous cell carcinoma, and leukemia[121][122][123][124][125]. KMT2C was implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[126]. Animal studies revealed that MLL3 haploinsufficiency enhances hematopoietic stem cells (HSCs) self-renewal capacity and induces extensive division of HSCs (AACR; Cancer Res 2018;78(13 Suppl): Abstract nr 4996).

Therapeutic and prognostic relevance

Preclinical studies of cell lines and xenograft models demonstrated that cells with reduced KMT2C expression and activity are deficient in homologous recombination-mediated double-strand break DNA repair and therefore, are more sensitive to olaparib, a PARP1/2 inhibitor[127].

A meta-analysis indicated that low levels of KMT2C expression was associated with better overall survival in pancreatic ductal adenocarcinoma (PDAC) patients[128]. However, another study of ER-positive breast cancer patients (n = 401) demonstrated that low KMT2C expression was associated with worse overall survival[129].

MET Amplification

Biological Impact

The Mesenchymal-Epithelial Transition (MET) is an oncogene that encodes the MET receptor tyrosine kinase (c-MET, also called HGFR, hepatocyte growth factor receptor). Binding of HGF leads to autophosphorylation and activation of MET and downstream effectors through the PI3K/AKT and RAS/RAF/MEK pathways, which regulates cell growth, proliferation, migration, and angiogenesis[130][131]. Gene amplification or overexpression of the MET occur in a wide range of cancers, including breast cancer[132], non-small cell lung cancer (NSCLC)[133], prostate cancer[134], renal papillary carcinoma[135][136], glioblastoma[137], hepatocellular carcinoma[138], and gastric cancer[139].

Therapeutic and prognostic relevance

MET amplification is known as an acquired mechanism conferring resistance to 1) EGFR-directed tyrosine kinase inhibitors including gefitinib, afatinib, erlotinib, and osimertinib, in patients with NSCLC[140][141][142][143]; 2) anti-EGFR mAb therapies in colorectal cancer (CRC) and head and neck cancer[144][145][146][147][148]; and 3) sunitinib, a multi-targeted tyrosine kinase inhibitor in renal cell carcinoma cells[149][150]. Furthermore, MET amplification and overexpression has been implicated as a causative factor in acquired cetuximab resistance in head and neck squamous cell carcinoma.

In NCCN guidelines for NSCLC, high-level MET amplification has been suggested as an emerging biomarker for crizotinib, capmatinib and tepotinib in patients with metastatic NSCLC[151](DOI: 10.1200/jco.2014.32.15_suppl.8001). In the phase 2 GEOMETRY mono-1 study (NCT02414139), patients with high-level MET-amplified advanced NSCLC showed responses to capmatinib in both treated and treatment naïve cohorts. The DOR, PFS, and OS were similar in both treated and treatment naïve patients (DOR: ~8 months; PFS: ~4 months. OS: ~10 months)[152]. The results of the phase II VISION trial (NCT02864992) indicated that tepotinib showed meaningful efficacy in advanced NSCLC patients with MET amplification. The overall response rate is 41.7% and the mPFS is 4.2 months (Journal of Clinical Oncology 39, no. 15_suppl 9021-9021). In addition, results from clinical studies of squamous cell carcinoma of lung (SCC), and esophagogastric adenocarcinoma also showed that patients with MET-amplified tumors responded to crizotinib[153][154].

Combinations of EGFR TKIs like gefitinib, erlotinib, osimertinib, and icotinib with c-MET inhibitor crizotinib were proposed to overcome the acquired resistance induced by EGFR-directed TKIs mediated MET amplification and were successfully evaluated in clinical settings[155][156][157][158][159][160]. Besides, there is a case report showed that EGFR-mutated NSCLC patients with acquired MET amplification responded to combination therapy with bevacizumab and erlotinib[161]. A phase Ib/II trial in NSCLC patients who failed EGFR inhibitor therapy showed that patients with mutated EGFR and MET amplification (copy number >6) responded to the combination treatment with capmatinib and gefitinib (Overall response rate: 47%, disease control rate: 75%)[162].

Cabozantinib is a small molecule inhibitor of MET, VEGFR2, KIT and RET and was approved by the U.S. FDA for the treatment of progressive, metastatic medullary thyroid cancer[163][164]. MET amplification has been selected as an inclusion criteria for the trial examining cabozantinib in NSCLC (NCT01639508) (NCT03911193).

MET amplification and exon 14 splice site mutations are associated with higher c-Met protein expression and poor prognosis in patients with NSCLC and esophageal squamous cell carcinoma[165][166]. Besides, the plasma level of c-

MET was associated with poor outcome in patients with hepatocellular carcinoma[167].

NF2 Heterozygous deletion

Biological Impact

The neurofibromin (NF2) gene encodes the protein Merlin, a tumor suppressor that functions as a negative regulator of the PI3K/AKT/mTOR pathway[168][169][170]. NF2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[171]. Inactivation germline mutations in the NF2 are associated with the hereditary neurofibromatosis type 2, a disorder characterized by the growth of noncancerous tumors in the nervous system[168][172]. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas[173], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers[174].

Therapeutic and prognostic relevance

Genomic alterations with activating effects on the mTOR signaling pathway have been identified to confer sensitivity to everolimus across multiple cancer types[175][176][177][178]. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer and urothelial carcinoma[179][180], both harboring NF2 truncating mutations. Preclinical evidence has shown the efficacy of MEK1/2 inhibitor selumetinib in KRAS-mutant thyroid cancer model with NF2 loss[181].

Analysis of afatinib-plus-cetuximab-resistant biopsy specimens revealed a loss-of-function alteration in genes that modulate mTOR signaling pathway, including NF2 and TSC1[182].

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[183][184]. STK11 is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[185][186]. In the mouse model, loss of STK11 promotes aggressive endometrial and squamous cell carcinomas[187][188]. Mutations in STK11 have been found in lung, breast, cervical, testicular, and liver cancers, as well as malignant melanoma, pancreatic and biliary carcinoma[189]. Germline mutations in STK11 are found in 30-70% of Peutz-Jeghers syndrome[190].

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[191]. 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[192].

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[193].

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)[194][195][196]. 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[197].

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TYMS Amplification

Biological Impact

TYMS (Thymidylate Synthetase) gene encodes the thymidylate synthase that catalyzes the methylation of deoxyuridylate to deoxythymidylate. The enzyme is critical for DNA replication and repair[198][199][200]. TYMS polymorphisms may be associated with etiology of neoplasia, including acute lymphoblastic leukemia[201], breast cancer, and response to chemotherapy[202].

Therapeutic and prognostic relevance

Thymidylate synthase gene amplification was associated with pemetrexed resistance in patients with advanced non-small cell lung cancer[203][204][205][206], and 5-FU resistance in CRC patients[207]

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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[208] 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[83] NCT02107703	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1[209] NCT02102490	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib [ORR(%): 19.7 vs. 17.4]

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[210] 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[211] 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[212] NCT01909453	**Melanoma** (Approved on 2018/06/27)
	BRAF V600E/K
	Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3]

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Cabozantinib (COMETRIQ)

Cabozantinib is a small molecule inhibitors of multiple tyrosine kinases, including RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, and TIE-2. Cabozantinib is developed and marketed by Exelixis under the trade names COMETRIQ (capsule) and CABOMETYX (tablet).

- FDA Approval Summary of Cabozantinib (COMETRIQ)

EXAM[213] NCT00704730	**Thyroid cancer** (Approved on 2012/11/29)
	-
	Cabozantinib vs. Placebo [PFS(M): 11.2 vs. 4]

Cabozantinib (CABOMETYX)

Cabozantinib is a small molecule inhibitors of multiple tyrosine kinases, including RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, and TIE-2. Cabozantinib is developed and marketed by Exelixis under the trade names COMETRIQ (capsule) and CABOMETYX (tablet).

- FDA Approval Summary of Cabozantinib (CABOMETYX)

COSMIC-311 NCT03690388	**Differentiated thyroid cancer (dtc)** (Approved on 2021/09/17)
	-
	Cabozantinib vs. Placebo [PFS(M): 11 vs. 1.9, ORR(%): 18.0 vs. 0]
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]
CELESTIAL [214] NCT01908426	**Hepatocellular carcinoma** (Approved on 2019/01/14)
	-
	Cabozantinib vs. Placebo [OS(M): 10.2 vs. 8]
CABOSUN[215] NCT01835157	**Renal cell carcinoma** (Approved on 2017/12/09)
	-
	Cabozantinib vs. Sunitinib [PFS(M): 8.6 vs. 5.3]
METEOR[216] NCT01865747	**Renal cell carcinoma** (Approved on 2016/04/25)
	-
	Cabozantinib vs. Everolimus [PFS(M): 7.4 vs. 3.8]

Capmatinib (TABRECTA)

Capmatinib is an orally bioavailable inhibitor of the proto-oncogene c-Met (also known as hepatocyte growth factor receptor (HGFR)) with potential antineoplastic activity. Capmatinib is developed and marketed by Novartis under the trade name TABRECTA.

- FDA Approval Summary of Capmatinib (TABRECTA)

GEOMETRY mono-1[152] NCT02414139	**Non-small cell lung carcinoma** (Approved on 2020/05/06)
	MET exon 14 skipping
	Capmatinib [ORR (Treatment naive) (%): 68, ORR (Previously treated)(%): 41]

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

Crizotinib (XALKORI)

Crizotinib is an inhibitor of the tyrosine kinases anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1), by competitively binding with the ATP-binding pocket. Crizotinib is developed and marketed by Pfizer under the trade name XALKORI.

- FDA Approval Summary of Crizotinib (XALKORI)

ADVL0912, A8081013 NCT00939770, NCT01121588	**Inflammatory myofibroblastic tumor** (Approved on 2022/08/05)
	ALK+
	Crizotinib [ORR(pediatric patients)(%): 86.0, ORR(adult patients)(%): 71.0]
ADVL0912 NCT00939770	**Alk fusion-positive anaplastic large cell lymphoma (alcl)** (Approved on 2021/01/14)
	ALK fusion
	Crizotinib [ORR(%): 88.0, DOR(M): 39 (maintained response for at least 6 months) vs. 22 (maintained response for at least 12 months)]
PROFILE 1001[218] NCT00585195	**Non-small cell lung carcinoma** (Approved on 2016/03/11)
	ROS1+
	Crizotinib [ORR(%): 66.0]
PROFILE 1014[219] NCT01154140	**Non-small cell lung carcinoma** (Approved on 2015/03/20)
	ALK+
	Crizotinib vs. Pemetrexed + cisplatin or pemetrexed + carboplatin [PFS(M): 10.9 vs. 7]
PROFILE 1007[220] NCT00932893	**Non-small cell lung carcinoma** (Approved on 2013/11/20)
	ALK+
	Crizotinib vs. Pemetrexed or docetaxel [PFS(M): 7.7 vs. 3]

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[36] 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[221] 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[222] 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[223] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[224] 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[225] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[226] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[227] 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[228] NCT01203917	**Non-small cell lung carcinoma** (Approved on 2015/07/13)
	EGFR ex19del or L858R
	Gefitinib [ORR(%): 50.0]

Mobocertinib (EXKIVITY)

Mobocertinib is a first-in-class, oral tyrosine kinase inhibitor (TKI) specifically designed to selectively target epidermal growth factor receptor (EGFR) Exon 20 insertion mutations. Mobocertinib is developed and marketed by Takeda under the trade name EXKIVITY.

- FDA Approval Summary of Mobocertinib (EXKIVITY)

Study 101[229] NCT02716116	**Non-small cell lung carcinoma** (Approved on 2021/09/15)
	EGFR ex20ins
	Mobocertinib [ORR(%): 28.0, DOR(M): 17.5]

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[230] 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[95] 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[231] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[232] 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[233] 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[234] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[235] 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[236] 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[46] 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[237] NCT02151981	**Non-small cell lung carcinoma** (Approved on 2017/03/30)
	EGFR T790M
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA[45] NCT01802632	**Non-small cell lung carcinoma** (Approved on 2015/11/13)
	EGFR T790M
	Osimertinib [ORR(%): 59.0]

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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[238] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+/HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[239] NCT01942135	**Breast cancer** (Approved on 2016/02/19)
	ER+/HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

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

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[96] 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]

Selumetinib (KOSELUGO)

Selumetinib is a kinase inhibitor. Selumetinib is developed and marketed by AstraZeneca under the trade name KOSELUGO.

- FDA Approval Summary of Selumetinib (KOSELUGO)

SPRINT NCT01362803	**Plexiform neurofibromas** (Approved on 2020/04/10)
	-
	Selumetinib [ORR(%): 66.0]

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[240] 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)

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

Tepotinib (TEPMETKO)

Tepotinib is a potent and selective c-Met inhibitor. Tepotinib is developed and marketed by EMD Serono, Inc. under the trade name TEPMETKO.

- FDA Approval Summary of Tepotinib (TEPMETKO)

VISION NCT02864992	**Non-small cell lung carcinoma** (Approved on 2021/02/03)
	MET exon 14 skipping
	Tepotinib [ORR (Treatment naive)(%): 43, ORR (Previously treated)(%): 43]

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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)

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[242] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[243] 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[244] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[245] 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

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

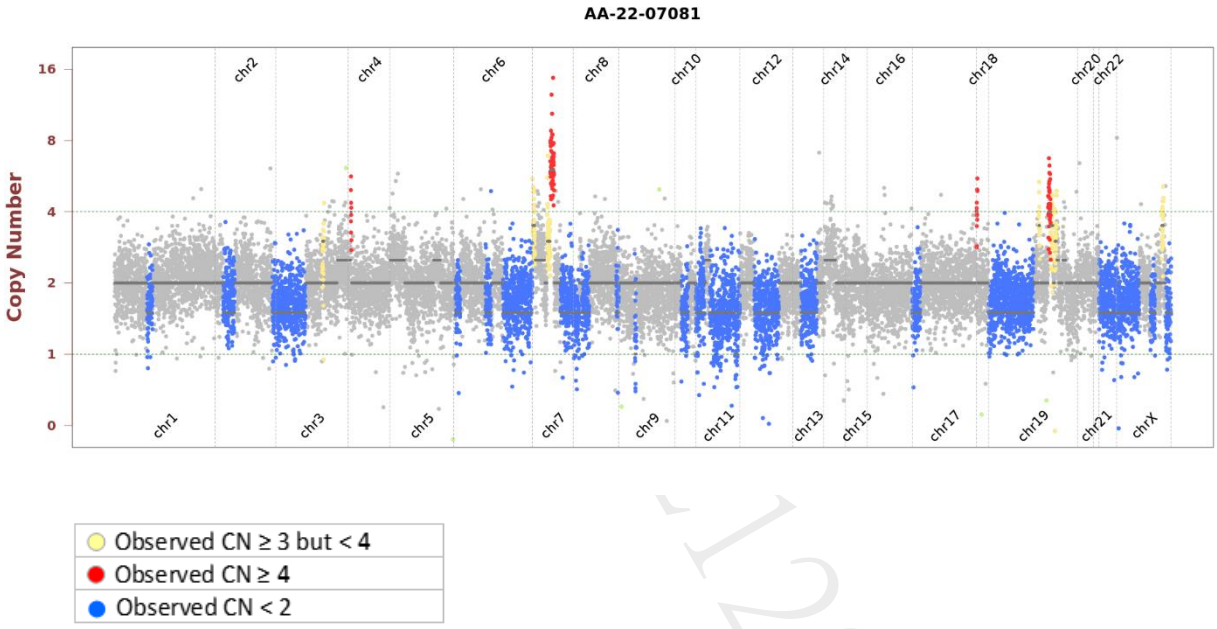
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
EGFR	L747_P753delinsS (Exon 19 deletion)	19	c.2240_2257del	NM_005228	COSM12370	34.7%	3592
TP53	I195fs	6	c.584del	NM_000546	COSM6201897	24.3%	1067

- 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
ABL2	S71fs	2	c.209_210dup	NM_007314	-	9.8%	1373
AKT2	Q353E	11	c.1057C>G	NM_001626	-	59.0%	818
ATR	D2318G	41	c.6953A>G	NM_001184	-	9.1%	809
AXL	D760H	19	c.2278G>C	NM_021913	-	23.4%	1048
CIC	M156I	4	c.468G>A	NM_015125	-	53.9%	3687
CREBBP	T576I	8	c.1727C>T	NM_004380	COSM9180167	32.7%	1997
ERCC4	V81F	2	c.241G>T	NM_005236	-	63.2%	1051
GNAQ	D130N	3	c.388G>A	NM_002072	-	61.9%	1595
MUC16	Q11913P	5	c.35738A>C	NM_024690	-	62.1%	1592
MUC16	I5861V	3	c.17581A>G	NM_024690	-	57.4%	1386
MUC16	T13461N	53	c.40382C>A	NM_024690	-	9.0%	877
MUC6	D440del	11	c.1318_1320del	NM_005961	-	46.9%	207
POLE	R1471C	34	c.4411C>T	NM_006231	COSM6955167	43.2%	528
PTPRT	R1327L	28	c.3980G>T	NM_007050	COSM3291818	7.3%	1766
RECQL4	R372T	5	c.1115G>C	NM_004260	-	57.0%	830
RXRA	Splice region	-	c.431-5C>T	NM_002957	-	34.3%	297
SYNE1	V6898I	112	c.20692G>A	NM_182961	COSM3941562	38.1%	3476
TET2	Y1245N	6	c.3733T>A	NM_001127208	-	29.7%	3031

Note:

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

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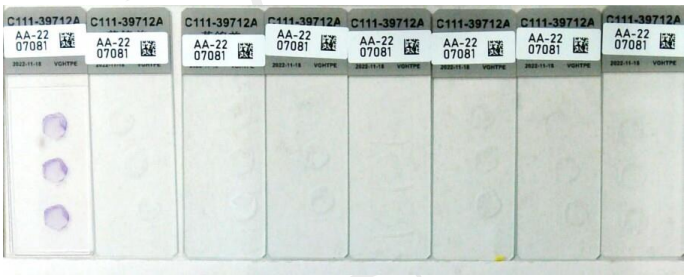
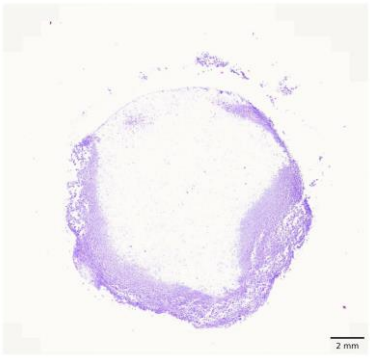
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: Nov 03, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: C11139712A
- Collection site: Pleural effusion
- Examined by: N/A
- Manual macrodissection: N/A

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 1601x
- Target Base Coverage at 100x: 96%

RNA test

- Average unique RNA Start Sites per control GSP2: 120

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.

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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).

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.

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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:
醫藥資訊研究員
楊杭哲 博士
Hang-Che Yang Ph.D.

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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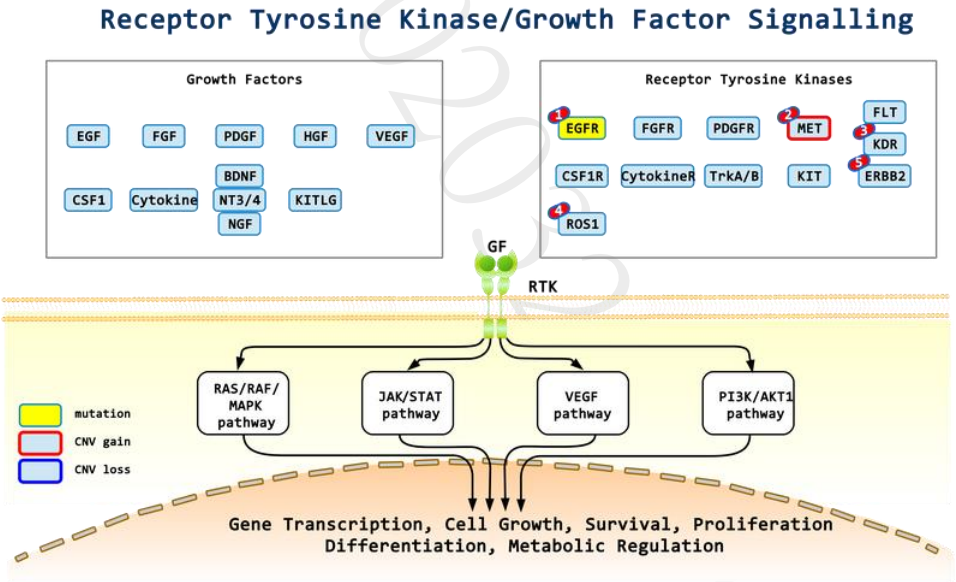
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
STK11	Binimetinib, Cobimetinib, Trametinib, Everolimus, Temsirolimus	**sensitive**
FLCN	Everolimus, Temsirolimus	**sensitive**
NF2	Everolimus, Temsirolimus	**sensitive**
CHEK1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
KMT2C	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Gefitinib, Afatinib, Erlotinib, Osimertinib, Dacomitinib, Mobocertinib; 2: Crizotinib, Cabozantinib, Capmatinib, Tepotinib;

3: Cabozantinib; 4: Crizotinib; 5: Afatinib

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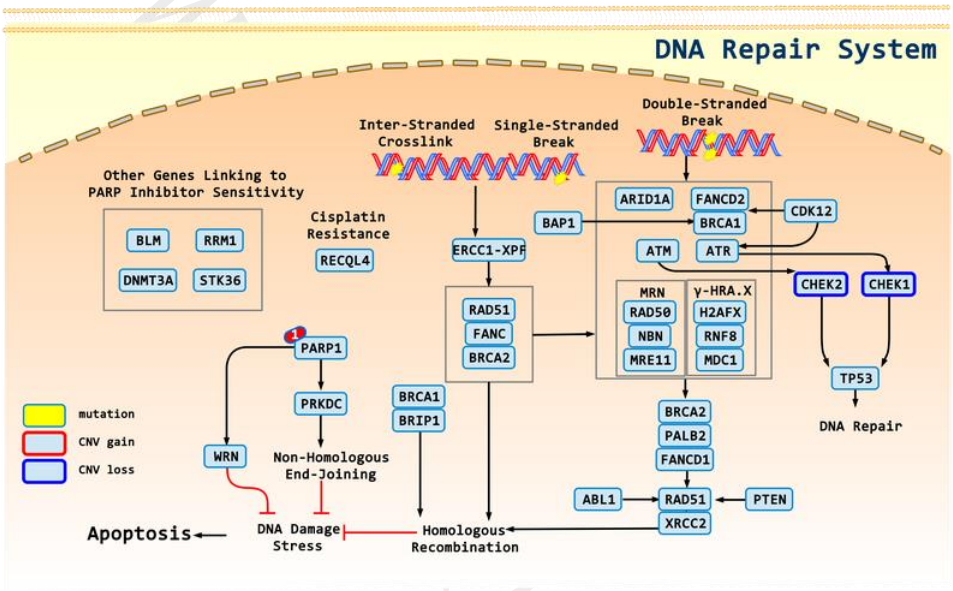
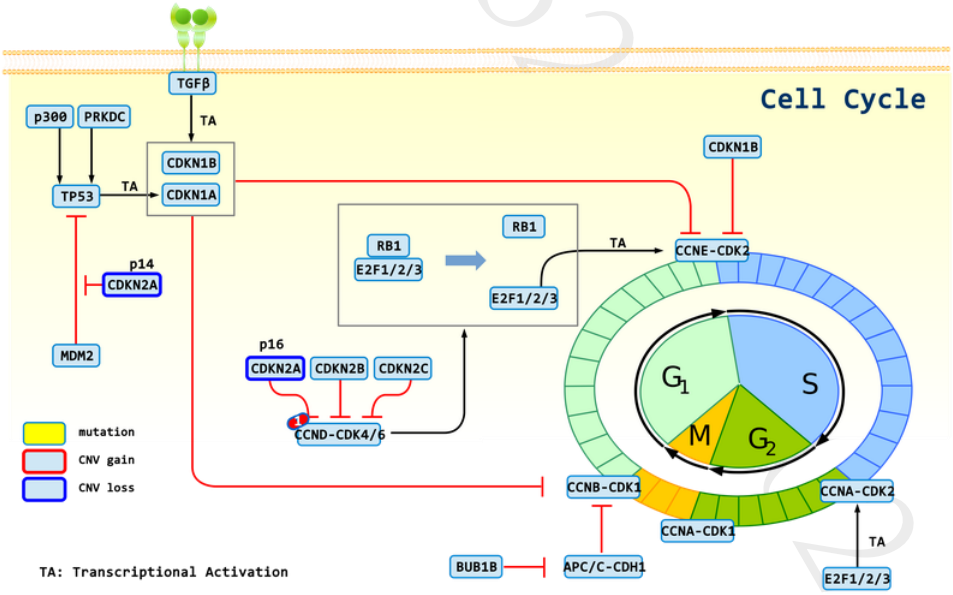


1: Olaparib, Niraparib, Rucaparib, Talazoparib



1: Abemaciclib, Palbociclib, Ribociclib

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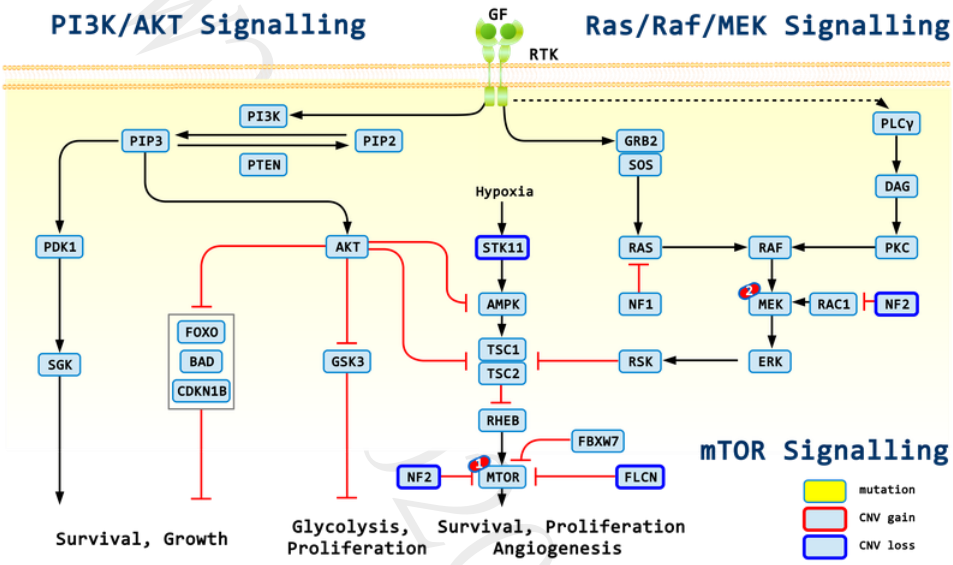

1: Everolimus, Temsirolimus; 2: Trametinib, Cobimetinib, Binimetinib, Selumetinib

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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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