

ACT Onco[®] + Report

PATIENT		
Name: 陳牡丹		Patient ID: 47594796
Date of Birth: Feb 08, 1948		Gender: Female
Diagnosis: Lung small cell carcinoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11125773		Type: FFPE tissue
Collection site: Lung		
Date received: Jul 12, 2022	Lab ID: AA-22-04029	D/ID: NA

ABOUT ACT Onco[®]+

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	
EGFR L858R	-	-	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
EGFR R776H	Afatinib, Erlotinib, Gefitinib, Osimertinib, Cetuximab	-
PTEN Q110*	Everolimus, Temsirolimus, Niraparib, Olaparib, Talazoparib	Erlotinib, Gefitinib, Panitumumab, Cetuximab, Trastuzumab
PTEN Heterozygous deletion	Everolimus, Temsirolimus, Niraparib, Olaparib, Talazoparib	Erlotinib, Gefitinib, Panitumumab, Cetuximab, Trastuzumab

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 criteria 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	L858R	72.7%
EGFR	R776H	70.0%
PTEN	Q110*	93.1%
TP53	R110L	93.3%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr10	PTEN	Heterozygous deletion	1
Chr11	CHEK1, MRE11	Heterozygous deletion	1
Chr13	BRCA2, RB1	Heterozygous deletion	1
Chr16	PALB2	Heterozygous deletion	1
Chr17	FLCN, TP53	Heterozygous deletion	1
Chr19	ERCC1	Heterozygous deletion	1
Chr4	FBXW7	Heterozygous deletion	1
Chr7	KMT2C	Heterozygous deletion	1
Chr9	TSC1	Heterozygous deletion	1
Chr5	RICTOR, TERT	Amplification	6*

* Increased gene copy number was observed.

- 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)	1.9 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 40% 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 3A		
EGFR L858R	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	sensitive
Level 3B		
PTEN Q110*	Everolimus, Temsirolimus, Niraparib, Olaparib, Talazoparib	sensitive
PTEN Heterozygous deletion	Everolimus, Temsirolimus, Niraparib, Olaparib, Talazoparib	sensitive
Level 4		
EGFR R776H	Afatinib, Erlotinib, Gefitinib, Osimertinib, Cetuximab	sensitive
PTEN Q110*	Erlotinib, Gefitinib, Panitumumab, Cetuximab, Trastuzumab	resistant
PTEN Heterozygous deletion	Erlotinib, Gefitinib, Panitumumab, Cetuximab, Trastuzumab	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

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

HORMONAL THERAPIES

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

OTHERS

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

Note:

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

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VARIANT INTERPRETATION

EGFR L858R, R776H

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^[1]. 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^[2]. 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^[3]. On the other hand, in the brain and colorectal cancers, the most prevalent EGFR alteration is copy number amplification that results in receptor overexpression^[4].

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^[5]. 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^[6].

EGFR R776H mutation is located at the kinase domain of the EGFR protein (UniProtKB0). R776H mutation could result in the ligand-independent activation of EGFR, and increase the cell proliferation and cell viability in vitro^{[7][8]}.

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^[9] (Annals of Oncology (2017) 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376).

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^{[10][11][12]}, 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^[10]. 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^{[13][14][15][16]}.

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^{[17][18][19]}. 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^[20].

Several clinical studies showed that NSCLC patients harboring R776H plus another EGFR activating mutation were sensitive to afatinib treatment. NSCLC patients harboring L858R and R776H had a partial response to erlotinib and gefitinib^{[21][22]}. Another NSCLC patient harboring EGFR G724S and R776H with EGFR amplification kept a stable disease (PFS: 17 months) after afatinib treatment^[23]. A case report also showed that a NSCLC patient with EGFR L861Q and R776H achieved a durable response to afatinib (DOI 10.1016/j.lungcan.2021.05.036). However, a NSCLC patient carrying an EGFR R776H did not response to afatinib treatment^[24]. In a retrospective study, two NSCLC patients harboring EGFR R776H achieved partial responses and progression-free survival of 11 and 10 months respectively (J

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Clin Oncol 39, no. 15_suppl (May 20, 2021) abstr e21001).

A preclinical study demonstrated that cells expressing EGFR R776H were sensitivity to gefitinib, erlotinib, afatinib, osimertinib and cetuximab treatment^[25].

PTEN Q110*, 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^{[26][27]}. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway^[28]. 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^{[29][30][31]}. 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^{[32][33][34]}. 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^{[35][36][37][38][39]}.

Q110* mutation results in a premature truncation of the PTEN protein at amino acid 110 (UniProtKB). This mutation is predicted to lead to a loss of PTEN 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

Somatic loss of PTEN results in aberrant activation of PI3K/AKT/mTOR signaling pathway and provides a mechanistic rationale for PI3K pathway inhibitors treatment^{[40][41]}. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes^{[42][43][44][45][46][47]}. Moreover, early clinical data also indicated that PTEN loss was associated with improved response and longer PFS in patients with advanced breast cancer^[48], advanced pancreatic neuroendocrine tumors^[49], and metastatic castration-resistant prostate cancer treated with mTORC1 inhibitor, everolimus^[50].

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^{[51][52][53][54][55]}.

Loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab^{[56][57][58][59][60][61]}. However, encouraging anti-tumor activity of the combination of an EGFR antibody and a mTORC1 inhibitor (everolimus or temsirolimus) have been reported in early-phase clinical studies (J Clin Oncol. 2011;29 (suppl): abstr 3587; J Clin Oncol. 2013;31 (suppl): abstr 608). Ongoing phase I/II studies testing combinations of EGFR antibodies and PI3K/AKT/mTOR pathway inhibitors (e.g., NCT01816984, NCT01252628, NCT01719380) will provide larger numbers of patients to assess the role of PTEN status in therapeutic response.

Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib^{[62][63]}. 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^[64].

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^{[65][66][67]}.

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 breast cancer (NCT02401347),

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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^[68].

TP53 R110L, 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^[69]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[29].

R110L is a missense mutation located in the DNA binding domain of the p53 protein (UniProtKB). This mutation confers a loss-of-function to the p53 protein as demonstrated by coaggregation of the wild-type p53, loss of p53 transcription activity and failure to induce apoptosis in vitro^{[70][71]}. 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)^[72].

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^[73]. 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^[74].

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^{[75][76][77]}. 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)^[78]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[79][80]}. 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^[81].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair^[82]. 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^[83]. 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^[84]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers^[85].

Therapeutic and prognostic relevance

The U.S. FDA has approved olaparib in advanced ovarian cancer under several settings including (1) first-line maintenance treatment for patients with deleterious or suspected deleterious germline or somatic BRCA mutation who are in complete or partial response to first-line platinum-based chemotherapy^[86]; (2) in combination with bevacizumab

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as first-line maintenance treatment for patients with homologous recombination deficiency (HRD)-positive status^[87]; (3) maintenance treatment for patients with germline BRCA-mutated recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy^{[88][89]}; (4) treatment for patients with germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy^[90]. In addition, olaparib has also been approved in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in either neoadjuvant, adjuvant, or metastatic setting^[91] and germline BRCA-mutated metastatic pancreatic cancer^[92]. Of note, 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^[93].

Rucaparib has been approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and patients with BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more chemotherapies^{[94][95]}. In May 2020, the U.S. FDA also approved rucaparib to treat adult patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy (TRITON2, NCT02952534).

The U.S. FDA also approved niraparib for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy and patients who have been treated with three or more prior lines of chemotherapy and associated with HRD positive status^{[96][97][98]}. In addition, talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer^[99].

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^[100]. 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^{[101][102]}. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors^[103], and CHEK1 mutations are extremely rare^[100]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer^[104], breast cancer^[105], colorectal cancer^[106], non-small cell lung (NSCLC) cancer^[107], and nasopharyngeal cancer^[108].

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^[93].

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^[94], 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^[109].

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ERCC1 Heterozygous deletion

Biological Impact

The Excision Repair Cross-Complementation Group 1 (ERCC1) gene encodes a non-catalytic component of a structure-specific DNA repair endonuclease that is responsible for 5' incision. This endonuclease is a heterodimer containing ERCC1 and ERCC4 and is involved in recombinational DNA repair and in the repair of inter-strand crosslinks (ICL). In addition, ERCC1 participates in the processing of anaphase bridge-generating DNA structures. Other genes associated with the nucleotide excision repair pathway includes ERCC1-5, CDK7, DDB1-2, XPA, and XPC^[110]. ERCC1 haploinsufficiency is associated with tumorigenesis in the mouse model^[111].

Therapeutic and prognostic relevance

Loss of expression of ERCC1 has long been implicated in increased sensitivity towards cisplatin in non-small cell lung cancer (NSCLC)^[112] and ovarian carcinoma^{[113][114][115]}. PARP inhibitors demonstrated anti-tumor activity against ERCC1-deficient non-small cell lung cancer (NSCLC) cell line^{[116][117][118]}. Preclinical studies also showed that inhibiting topoisomerase I and PARP1 in combination, as was demonstrated with the combination of ABT-888 and CPT-11, may result in the synergistic decrease in tumor regression for women with triple-negative breast cancer (TNBC)^[119].

FBXW7 Heterozygous deletion

Biological Impact

The F-box/WD repeat-containing protein 7 (FBXW7) gene encodes a protein that belongs to the SCF (SKP1-CUL1-F-box protein) E3 ligase complex. FBXW7 is recognized as a tumor suppressor which is involved in the negative regulation of oncogenes such as c-Myc^{[120][121]}, c-Jun^[122], cyclin E^[123], Notch family members^{[124][125]}, Aurora-A^[126], mTOR^[127], KLF5^[128], and MCL-1^[129]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation^[130]. FBXW7 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^{[128][129][131]}.

Therapeutic and prognostic relevance

Clinical efficacy of mTOR inhibitors was seen in patients harboring aberrations in the FBXW7 gene (one patient with refractory fibrolamellar hepatocellular carcinoma, and one patient with lung adenocarcinoma)^{[132][133]}. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor^[127].

Preclinical studies suggested that mutations or loss of FBXW7 were associated with regorafenib and oxaliplatin resistance in CRC cell lines and gefitinib resistance in lung cancer cells^{[134][135][136][137]}.

Retrospective studies have indicated that a relatively low expression level of FBXW7 is an independent prognostic marker of poor survival for patients with hepatocellular carcinoma, lung adenocarcinoma and squamous cell carcinoma^{[138][136]}.

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^[139]. 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^{[140][141]}. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling^{[142][143]}. 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^[144].

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Therapeutic and prognostic relevance

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTTC) 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^[145]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting^[146].

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)^[147] and regulates the gene expression during development and hematopoiesis^{[148][149][150]}. KMT2C is ubiquitously expressed, and its function is essential for normal embryonal development and cell proliferation^[151]. Genetic deletion of the region containing KMT2C is the most common chromosomal abnormality in acute myeloid leukemia^{[152][153]}, and KMT2C mutation has been reported in breast cancer, cutaneous squamous cell carcinoma, and leukemia^{[154][155][156][157][158]}. 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^[159]. 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^[160].

A meta-analysis indicated that low levels of KMT2C expression was associated with better overall survival in pancreatic ductal adenocarcinoma (PDAC) patients^[161]. However, another study of ER-positive breast cancer patients (n = 401) demonstrated that low KMT2C expression was associated with worse overall survival^[162].

MRE11 Heterozygous deletion

Biological Impact

The MRE11 gene encodes a protein that forms the MRE11-RAD50-NBS (MRN) complex involved in sensing and repairing DNA double-strand breaks via homologous recombination and non-homologous end joining^{[163][164]}. MRE11 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 function^[163]. The carrier of MRE11 mutation may confer elevated risks for numerous types of cancers including breast cancer, ovarian cancer, endometrial cancer, colorectal cancer, and lymphoid cancer^{[163][164][165][166][167][168][169]}.

Therapeutic and prognostic relevance

In a Phase II clinical trial (n=50), one castration-resistant prostate cancer patient harboring an MRE11 inactivating mutation responded to olaparib^[170]. Preclinically, loss of MRE11 also predicted sensitivity to PARP inhibitor talazoparib and ABT-888 in endometrial cancer^[171] and microsatellite unstable colorectal cancer (CRC) cell lines^[172].

CRC patients with tumor deficient of MRE11 showed initially reduced disease-free survival (DFS) and overall survival (OS) but improved long-term DFS and OS compared with patients with an intact MRE11^[173].

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PALB2 Heterozygous deletion

Biological Impact

The partner and localizer of BRCA2 (PALB2) gene encodes a protein that plays a critical role in homologous recombination repair (HRR) through its ability to interact with BRCA2 in nuclear foci, promoting its localization and stability in key nuclear structures^[174]. The Fanconi anemia complementation group (FANC) which includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM and FANCN (also called PALB2) are involved in the repair of DNA double-strand breaks (DSBs) by homologous recombination (HR)^{[175][176][177]}. PALB2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function^[178]. Biallelic germline loss-of-function mutations in PALB2 cause Fanconi anemia, whereas monoallelic loss-of-function mutations are associated with an increased risk of breast cancer and pancreatic cancer^[179]. Fanconi Anemia is an autosomal recessive disease characterized by hematological abnormalities, bone marrow failure, limb deformities, skin hyperpigmentation, and susceptibility to hematologic and solid malignancies, such as acute myeloid leukemia and head and neck carcinoma^{[180][181]}.

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^[93].

PALB2 loss of function mutation has been determined as an inclusion criterion for the trial evaluating rucaparib efficacy in ovarian cancer^[94] or prostate cancer^[182]; talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556); niraparib efficacy in pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), or any malignancy (except prostate) cancer (NCT03207347).

A case report demonstrated an exceptional response to mitomycin C and cisplatin treatment in a gemcitabine-resistant pancreatic cancer patient with biallelic inactivation of PALB2^[183].

RB1 Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication^[184]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis^[185]. 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^{[186][187][188]}. 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^[189].

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^[190]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytosine (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy^[191].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer^{[192][193]}.

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Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment^[194]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib^[195].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)^{[196][197]}. 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^{[193][198]}.

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^{[199][200][201]}. Amplification of the RICTOR locus is observed in melanoma^[202] and lung cancer^[203].

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^[203]. Preclinical data showed that a RICTOR-amplified patient-derived cancer cell line is sensitive to mTORC1/2 inhibitor (AZD2014)^[204]. 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^{[205][206][207][208]}. Overexpression of RICTOR is positively associated with tumor progression and poor survival in hepatocellular carcinoma, gastric cancer, pituitary adenoma, and endometrial carcinoma^{[209][210][211][212]}.

TERT Amplification

Biological Impact

The TERT gene encodes the catalytic subunit of telomerase, an enzyme that maintains telomere length and genomic integrity^[213]. Upregulation of TERT promotes cancer development and progression via modulation of Wnt-catenin and nuclear factor kappa B signaling^{[214][215]}, and mitochondrial RNA processing^[216]. 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^{[217][218][219][220][221]}.

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^[213].

TERT gene amplification is an independent poor prognostic marker for disease-free survival in non-small cell lung cancer (NSCLC) and breast cancer^{[222][223][224]}.

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TSC1 Heterozygous deletion

Biological Impact

The tuberous sclerosis complex 1 (TSC1) gene encodes a tumor suppressor, hamartin, a key negative regulator of the mammalian target of rapamycin (mTOR) pathway^{[225][226]}. Mutations in TSC1/TSC2 tumor suppressor genes that result in inactivation of the complex are commonly found in patients with tuberous sclerosis^{[227][228][229]}, while LOH in TSC1/TSC2 has been identified in head and neck squamous cell carcinoma (HNSCC)^[230] and endometrial cancer^[231]. Loss of single TSC1 allele (haploinsufficiency) may provide a growth advantage to bladder epithelial cells, contributing to bladder cancer development^[232]. Both TSC1 and TSC2 mutations cause the autosomal dominant genetic disorder tuberous sclerosis complex (TSC), in which individuals develop a variety of benign but often progressive neoplasms^[233].

Therapeutic and prognostic relevance

Genomic alterations with activating effects of the mTOR signaling pathway (including deletion/inactivation of TSC1/TSC2) have been shown to confer sensitivity to everolimus across multiple neoplasms, such as bladder tumors^[234], gastric, sarcoma, thyroid cancer, and HNSCC^[235]. There were case reports demonstrated the efficacy of sirolimus in malignant uterine perivascular epithelioid cell tumors (PEComa) patients harboring mutations/deletions in TSC1 and TSC2 genes, and temsirolimus in PEComa patients with hyperactivated mTOR pathway. Genomic profiling analysis of GOG248, a Phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer showed that mutations in AKT1, TSC1 and TSC2 may predict clinical benefit from temsirolimus^[236]. Recent studies indicate that there are mTORC1-independent signaling pathways downstream of hamartin-tuberin, which may represent new therapeutic targets^[237].

Everolimus has been approval by the U.S. FDA for Tuberous Sclerosis Complex (TSC)-associated renal angiomyolipoma and Tuberous Sclerosis Complex (TSC)-associated subependymal giant cell astrocytoma (SEGA). This approval is based on the results from EXIST-1, EXIST-2, and Study 2485 trials (NCT00789828, NCT00790400, and NCT00411619).

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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 ^[238] NCT01523587	Non-small cell lung carcinoma (Approved on 2016/04/15)
	EGFR Del19/L858R
	Afatinib vs. Erlotinib [PFS(M): 2.4 vs. 1.9]
LUX-Lung 3 ^[239] NCT00949650	Non-small cell lung carcinoma (Approved on 2013/07/13)
	EGFR Del19/L858R
	Afatinib vs. Pemetrexed + cisplatin [PFS(M): 11.1 vs. 6.9]

Cetuximab (ERBITUX)

Cetuximab is a recombinant, chimeric (human/mouse) monoclonal antibody that binds to the extracellular domain and inhibits epidermal growth factor receptor (EGFR). Cetuximab is developed by ImClone and marketed by Eli Lilly under the trade name ERBITUX.

- FDA Approval Summary of Cetuximab (ERBITUX)

CRYSTAL ^[240] NCT00154102	Colorectal cancer (Approved on 2012/07/06)
	EGFR-expressing, K-Ras Wild-type
	Cetuximab + 5-fluorouracil + folinic acid + irinotecan vs. 5-fluorouracil + folinic acid + irinotecan [PFS(M): 8.9 vs. 8.1]
EXTREME ^[241] NCT00122460	Head and neck cancer (Approved on 2011/11/07)
	-
	Cetuximab + cisplatin/carboplatin + 5-fu vs. Cisplatin/carboplatin + 5-fu [OS(M): 10.1 vs. 7.4]
[242] NCT00004227	Head and neck cancer (Approved on 2006/03/01)
	-
	Cetuximab + radiation vs. Radiation [OS(M): 49 vs. 29.3]
[243] NCT00063141	Colorectal cancer (Approved on 2004/02/12)
	EGFR-expressing
	Cetuximab + irinotecan vs. Irinotecan [DOR(M): 5.7 vs. 4.2]

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 ^[10] NCT01774721	Non-small cell lung carcinoma (Approved on 2018/09/27)
	EGFR Del 19/ L858R
	Dacomitinib vs. Gefitinib [PFS(M): 14.7 vs. 9.2]

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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 exon 19 deletion or exon 21 (L858R)
	Erlotinib + ramucirumab vs. Erlotinib + placebo [PFS(M): 19.4 vs. 12.4]
EURTAC ^[244] NCT00446225	Non-small cell lung carcinoma (Approved on 2013/05/14)
	Exon 19 Del/Exon 21 substitution (L858R)
	Erlotinib vs. Cisplatin + gemcitabine or cisplatin + docetaxel or carboplatin + gemcitabine or carboplatin + docetaxel [PFS(M): 10.4 vs. 5.2]
PA.3 ^[245] 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 ^[246] NCT01524783	Lung or gastrointestinal neuroendocrine tumor (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2 ^[247] 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 ^[49] NCT00510068	Pancreatic neuroendocrine tumor (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1 ^[248] NCT00789828	Subependymal giant cell astrocytoma (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1 ^[249] NCT00410124	Renal cell carcinoma (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

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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 ^[250] NCT01203917	Non-small cell lung carcinoma (Approved on 2015/07/13)
	Exon 19 Del/Exon 21 substitution (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]
QUADRA ^[98] NCT02354586	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2019/10/23)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Niraparib [ORR(%): 24.0, DOR(M): 8.3]
NOVA ^[97] 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)
	gBRCA
	Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound ^[93] NCT02987543	Prostate cancer (Approved on 2020/05/19)
	ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm, RAD54Lm
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1 ^[87] NCT02477644	Ovarian cancer (Approved on 2020/05/08)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]

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POLO ^[92] NCT02184195	Pancreatic adenocarcinoma (Approved on 2019/12/27)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1 ^[86] NCT01844986	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2018/12/19)
	Germline or somatic BRCA-mutated (gBRCAm or sBRCAm)
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD ^[91] NCT02000622	Breast cancer (Approved on 2018/02/06)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21 ^[251] NCT01874353	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	gBRCA+
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19 ^[252] NCT00753545	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]
Study 42 ^[253] NCT01078662	Ovarian cancer (Approved on 2014/12/19)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

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 exon 19 deletions or exon 21 L858R mutations
	Osimertinib vs. Placebo + adjuvant chemotherapy [DFS(M): NR vs. 19.6]
FLAURA ^[20] NCT02296125	Non-small cell lung carcinoma (Approved on 2018/04/18)
	EGFR Del19/L858R
	Osimertinib vs. Gefitinib or erlotinib [PFS(M): 18.9 vs. 10.2]
AURA3 ^[254] NCT02151981	Non-small cell lung carcinoma (Approved on 2017/03/30)
	EGFR T790M+
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA ^[19] NCT01802632	Non-small cell lung carcinoma (Approved on 2015/11/13)
	EGFR T790M+
	Osimertinib [ORR(%): 59.0]

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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+, sBRCA Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3 ^[94] NCT01968213	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2018/04/06)
	All HRD tBRCA 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]
ARIEL2 ^[255] NCT01482715, NCT01891344	Ovarian cancer (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation Rucaparib [ORR(%): 54.0]

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 ^[99] NCT01945775	Breast cancer (Approved on 2018/10/16)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative 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)

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

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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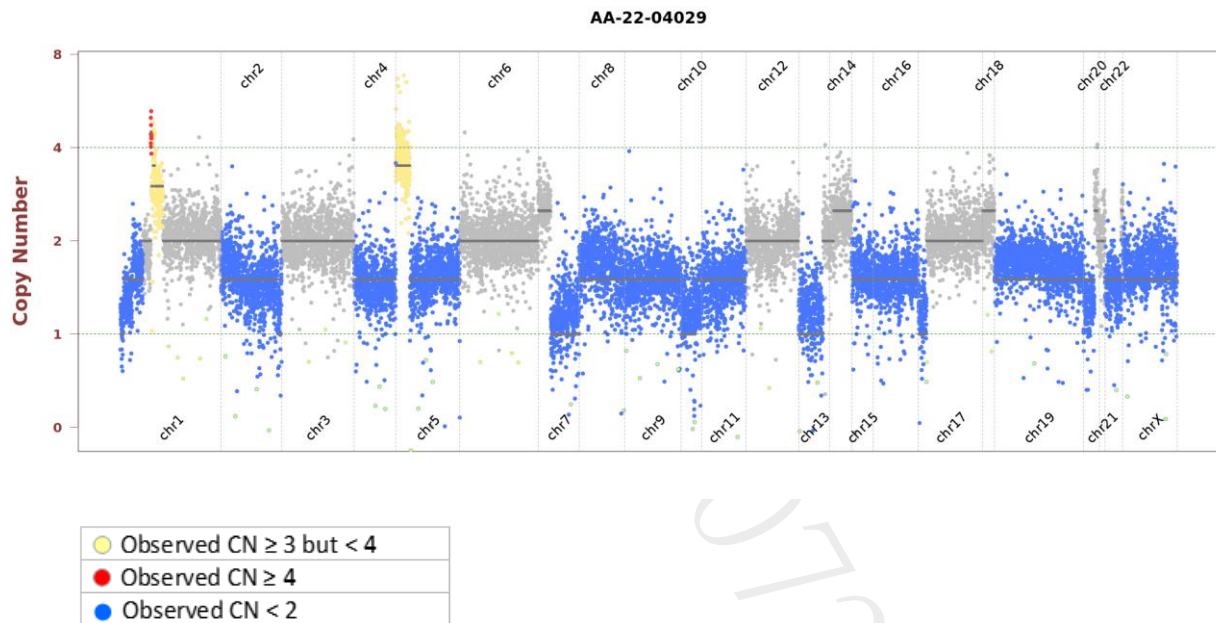
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
EGFR	R776H	20	c.2327G>A	NM_005228	COSM22940	70.0%	2593
EGFR	L858R	21	c.2573T>G	NM_005228	COSM6224	72.7%	3146
PTEN	Q110*	5	c.328C>T	NM_000314	COSM5161	93.1%	1144
TP53	R110L	4	c.329G>T	NM_000546	COSM10716	93.3%	615

- 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
FANCD2	L234*	10	c.700_703del	NM_001018115	-	5.9%	1172
FAT1	N3055D	12	c.9163A>G	NM_005245	-	60.8%	663
FBXW7	Splice region	-	c.1644+6A>C	NM_033632	-	56.3%	931
KDM5C	S451N	10	c.1352G>A	NM_004187	-	55.8%	2086
MUC16	G1950A	1	c.5849G>C	NM_024690	-	60.6%	954
MUC16	T2202A	1	c.6604A>G	NM_024690	-	63.8%	898
NOTCH4	M1592K	27	c.4775T>A	NM_004557	-	52.5%	1413
PDGFRB	A789S	17	c.2365G>T	NM_002609	-	70.6%	1131
PDIA3	A112T	3	c.334G>A	NM_005313	-	27.8%	367
RECQL4	E711K	13	c.2131G>A	NM_004260	COSM3670381	51.5%	1329
SYNE1	E7706Q	127	c.23116G>C	NM_182961	-	46.9%	1446

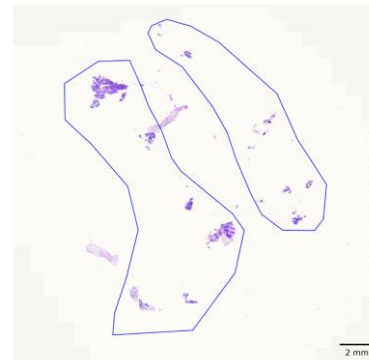
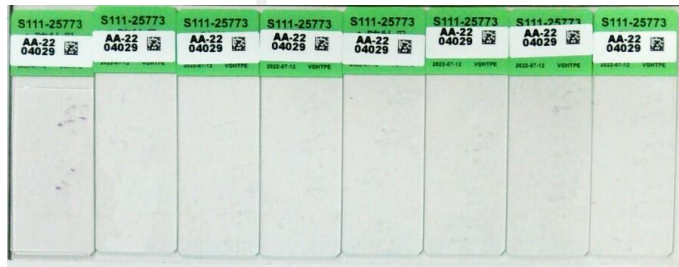
Note:

- 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: Jul 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11125773
- Collection site: Lung
- Examined by: Dr. Chien-Ta Chiang
 1. The percentage of viable tumor cells in total cells in the whole slide (%): 25%
 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: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco[®]+

DNA test

- Mean Depth: 981x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 164

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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 $\geq 5\%$ and actionable variants with allele frequency $\geq 2\%$ were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at $100\times \geq 85\%$ with a mean coverage $\geq 500\times$.

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 $\geq 10\%$; (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:

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Sign Off

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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	BMP1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2*	BTB	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*	SLC1B1*
SLC1B3*	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOC1*	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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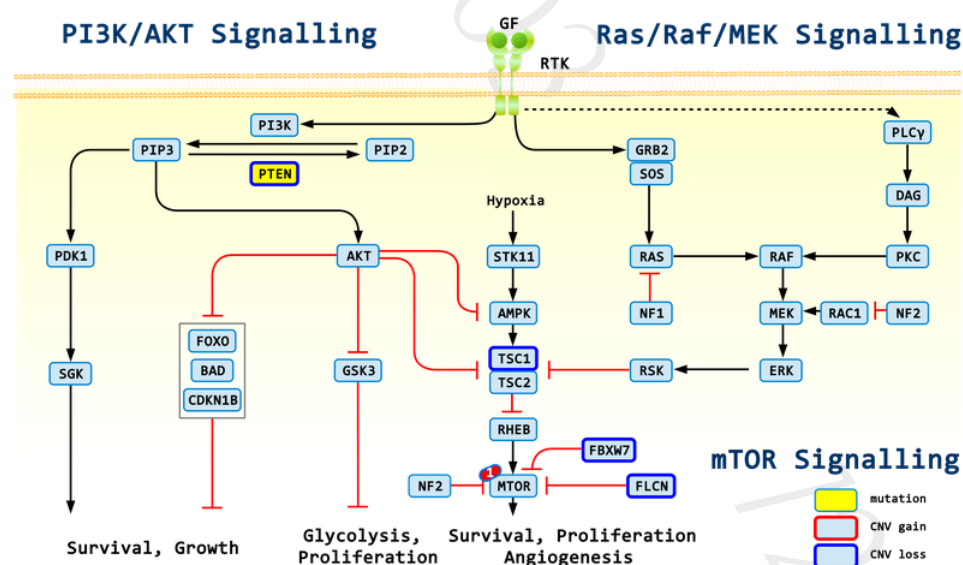
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

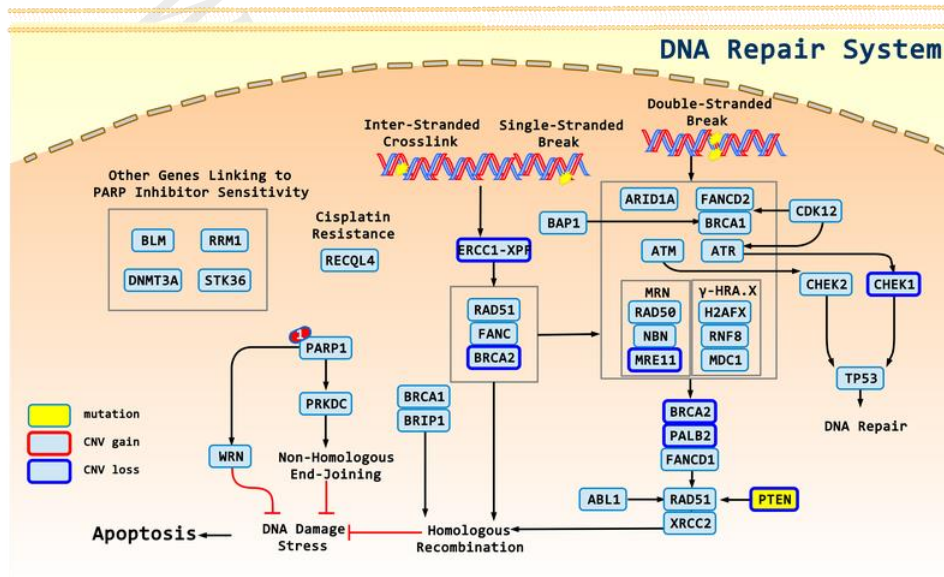
Gene	Therapies	Possible effect
<i>FBXW7</i>	Everolimus, Temsirolimus	sensitive
<i>FLCN</i>	Everolimus, Temsirolimus	sensitive
<i>TSC1</i>	Everolimus, Temsirolimus	sensitive
<i>BRCA2</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<i>CHEK1</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<i>ERCC1</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<i>KMT2C</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<i>MRE11</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<i>PALB2</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<i>RB1</i>	Abemaciclib, Palbociclib, Ribociclib	resistant
<i>FBXW7</i>	Gefitinib, Regorafenib	resistant

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



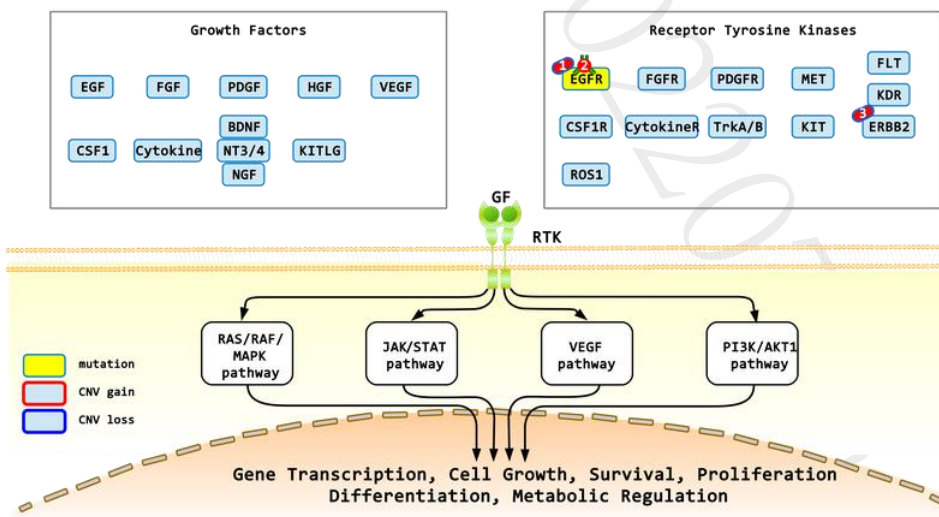
1: Everolimus, Temsirolimus

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1: Olaparib, Niraparib, Rucaparib, Talazoparib

Receptor Tyrosine Kinase/Growth Factor Signalling



1: Gefitinib, Erlotinib, Afatinib, Osimertinib, Dacomitinib; 2: Cetuximab; 3: Afatinib

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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。

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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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