

ACT Onco[®] + Report

PATIENT		
Name: 薛耀淵		Patient ID: 37798713
Date of Birth: Apr 09, 1961		Gender: Male
Diagnosis: Lung non-small cell carcinoma		
ORDERING PHYSICIAN		
Name: 江起陸醫師		Tel: 886-228712121
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SPECIMEN		
Specimen ID: S11111394		Type: FFPE tissue
Collection site: Neck lymph node		D/ID: NA
Date received: Mar 24, 2022		Lab ID: AA-22-01474

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 L861Q	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-	-

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
EGFR Amplification	Afatinib, Erlotinib, Gefitinib, Osimertinib, Necitumumab, Cetuximab, Panitumumab	-

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
<i>EGFR</i>	L861Q	93.7%
<i>LRP1B</i>	Splice acceptor	26.4%
<i>RBM10</i>	T476fs	49.0%
<i>TP53</i>	V157F	38.9%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr13	<i>BRCA2</i>	Heterozygous deletion	1
Chr17	<i>TP53</i>	Heterozygous deletion	1
Chr3	<i>ATR</i>	Heterozygous deletion	1
Chr5	<i>RAD50</i>	Heterozygous deletion	1
Chr9	<i>CDKN2A, TSC1</i>	Heterozygous deletion	1
Chr11	<i>CCND1, FGF3, VEGFB</i>	Amplification	6*
Chr7	<i>EGFR</i>	Amplification	71

* 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)	6.5 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 39% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco[®] to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is $< 30\%$.

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THERAPEUTIC IMPLICATIONS TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 1		
EGFR L861Q	Afatinib	sensitive
Level 2		
EGFR L861Q	Dacomitinib, Erlotinib, Gefitinib, Osimertinib	sensitive
Level 3B		
EGFR Amplification	Afatinib, Erlotinib, Gefitinib, Osimertinib, Necitumumab, Cetuximab, Panitumumab	sensitive

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
LRP1B loss-of-function	Likely associated with BETTER response to ICIs
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 L861Q, Amplification

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].

The L861Q mutation results in an amino acid substitution at position 861 in EGFR, from a leucine to a glutamine. This gain-of-function mutation lies within exon 21 in the EGFR kinase domain, and occurs with a frequency of approximately 2% in EGFR-mutated lung tumors^[5].

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^[6] (Annals of Oncology (2017) 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376).

The indication for afatinib has been expanded to include patients with NSCLC in the metastatic setting whose tumors harbor rare EGFR mutations such as G719X, L861Q, and S768I. Clinical studies of NSCLC patients reported that patients harboring EGFR L861Q mutation responded to EGFR TKIs, including erlotinib, gefitinib and afatinib (afatinib had an objective response rate (ORR) of 56.3% whereas gefitinib/erlotinib ORR had an ORR of 39.6% and median progression survival of 8.1 months)^{[7][8][9][10]}. NSCLC patients harboring L861Q mutation also showed clinical response to icotinib, a selective EGFR inhibitor that inhibits both wild-type and mutant forms of EGFR (J Clin Oncol 35, 2017 (suppl; abstr e14050)).

The National Comprehensive Cancer Network (NCCN) guidelines now recommend that less common mutations of EGFR-mutated NSCLC (including S768I, L861Q, G719X, exon 19 insertion) are also responsiveness to EGFR TKI therapy.

Increased EGFR copy number is associated with tumor response to panitumumab, an EGFR-targeted antibody, in colorectal cancer patients, based on data from a phase III study^[11]. A recent Phase II trial of cetuximab (another approved anti-EGFR antibody) oxaliplatin/leucovorin/5-fluorouracil therapy in first-line setting also demonstrated an association between higher EGFR copy number and better overall survival in gastric cancer patients^[12]. The addition of cetuximab to chemotherapy reduced the risk of death by 44% for advanced squamous non-small cell lung cancer (NSCLC) patients with EGFR-amplified tumor, according to clinical trial findings presented at the 2015 World Conference on Lung Cancer. Preclinical data of gastric cancer (GC)-derived xenograft also showed that EGFR amplification or overexpression is associated with response to cetuximab^[13]. Besides, a phase III study of necitumumab showed squamous cell lung cancer patients with EGFR amplification had improved overall survival (14.8 versus 7.6 months, p = 0.033) (NCT00981058)^[14].

Increased EGFR copy number has been shown to be associated with better response and survival in gefitinib or erlotinib treatment for NSCLC^{[15][16][17][18][19][20]}, esophageal cancer^[21], and mucinous urethral adenocarcinoma^[22]. Concurrent amplification of EGFR and ERBB2 is associated with response to afatinib in patients with trastuzumab-refractory esophagogastric cancer^[23]. However, dacomitinib has been reported with a limited single-agent activity in

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recurrent glioblastoma with EGFR amplification in a phase II trial^[24]. EGFR amplification has been determined as an inclusion criterion for the trials evaluating erlotinib, afatinib, and osimertinib efficacy in PDAC with co-expressing EGFR and c-Met (NCT03213626), glioblastoma (NCT03732352), urothelial tract carcinoma (NCT02780687), and brain cancer (NCT02423525).

LRP1B Splice acceptor

Biological Impact

Low-density lipoprotein receptor protein 1B (LRP1B) is a surface protein involved in the receptor-mediated endocytosis and signal transduction (UniProtKB). LRP1B is known as a tumor suppressor and was reported among the top 10 most significantly deleted genes across 3312 human cancer specimens^[25]. Besides deletions, mutations and epigenetic silencing of LRP1B have been previously reported in lung adenocarcinoma^[26], hepatocellular carcinoma^[27], renal cell carcinoma^[28], thyroid cancer^[29], gastric cancer^[30], esophageal squamous cell carcinoma^[31], and colon cancer^[32].

LRP1B c.1237-1G>T is a variant located at the splice acceptor region, which may result in the exon skipping.

Therapeutic and prognostic relevance

The prevalence of genetic alterations (mostly loss-of-function mutations) in the LRP1B gene was significantly higher in patients who responded to PD-1 blockade than that of the non-responders (11 vs. 1 mutations, 34% vs. 3%, respectively, $P = 0.008$). Moreover, an analysis of TCGA dataset showed that melanomas patients with LRP1B mutations had significantly higher tumor mutational load when compared with those without LRP1B mutations^{[33][34]}, as well as prolonged survival in response to immunotherapy. In addition, a retrospective study has shown that pathogenic and likely pathogenic alternations of LRP1B gene are associated with higher ORR, improved PFS and OS in ICI treated advanced or metastatic malignancies (DOI: 10.1200/JCO.2020.38.15_suppl.3007)^[35]. However, there were several limitations in this study, including limited sample size and unmeasured confounders. Therefore, further clinical validations are still needed.

A retrospective study has demonstrated that deletion or downregulation of LRP1B showed significant correlation with acquired chemotherapy resistance in patients with high-grade serous ovarian cancer (HGSC). Functional studies also showed that reducing LRP1B expression was sufficient to reduce the sensitivity of HGSC cell lines to liposomal doxorubicin but not to doxorubicin^[36]. Furthermore, deletion of LRP1B has been reported to be significantly associated with poor progression-free survival (6.4 m vs. 10.1 m) and overall survival (13.4 m vs. 17.8 m) in patients with glioblastoma^[37].

RBM10 T476fs

Biological Impact

RBM10 (RNA binding motif protein 10) gene encodes a nuclear protein of the RNA-binding motif gene family which plays essential roles in alternative splicing^{[38][39]}. Loss-of-function of RBM10 has been reported as the causes of TARP syndrome which results in pre- or postnatal death in affected males^{[40][41][42]}. Mutations of RBM10 have been reported in lung adenocarcinoma^{[43][44][45]}, bladder and colorectal cancer^[46].

T476fs mutation results in a change in the amino acid sequence beginning at 476, likely to cause premature truncation of the functional RBM10 protein (UniProtKB). This mutation is predicted to lead to a loss of RBM10 protein function, despite not being characterized in the literature.

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Therapeutic and prognostic relevance

Low expression of RBM10 was associated with shorter overall survival in lung adenocarcinoma patients^[47].

TP53 V157F, 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^[48]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[49].

TP53 V157F lies within the DNA-binding domain (DBD) of the p53 protein(UniProtKB). This mutation results in destabilization of the protein and decreased DNA binding activity. However, biochemical assays revealed that V157F also confers gain-of-function to the p53 protein, as demonstrated by transactivation of target genes, such as hTERT, ASNS, and GEF-H1, which are not transactivated by wild-type p53^{[50][51][52]}.

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)^[53].

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^[54]. 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^[55].

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^{[56][57][58]}. 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)^[59]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[60][61]}. 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^[62].

ATR Heterozygous deletion

Biological Impact

Ataxia Telangiectasia and Rad3-related protein (ATR) gene encodes a serine/threonine kinase that is involved in the DNA damage response. ATR plays as a central coordinator of the DNA damage response (DDR) by responding to single-stranded regions of the DNA^{[63][64]} and the maintenance of genome stability^[65]. ATR 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^{[66][67]}. Germline mutation of ATR is associated with cancer predisposition and Seckel syndrome, a condition associated with CNS disorders^{[68][69]}. Somatic mutations of ATR are associated with microsatellite instability and are found in colorectal cancer^[70], urothelial cancer^[71], gastric cancer^[72], endometrial cancer^[73] and myelomas^[74].

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Therapeutic and prognostic relevance

ATR has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in ovarian cancer^[75] and advanced solid tumors (NCT03297606; CAPTUR trial), rucaparib efficacy in ovarian cancer^[76], niraparib efficacy in pancreatic cancer (NCT03553004), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair^[77]. 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^[78]. 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^[79]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers^[80].

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^[81]; (2) in combination with bevacizumab as first-line maintenance treatment for patients with homologous recombination deficiency (HRD)-positive status^[82]; (3) maintenance treatment for patients with germline BRCA-mutated recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy^{[83][84]}; (4) treatment for patients with germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy^[85]. 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^[86] and germline BRCA-mutated metastatic pancreatic cancer^[87]. 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^[88].

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^{[76][89]}. 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^{[90][91][92]}. In addition, talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer^[93].

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CCND1 Amplification

Biological Impact

The cyclin D1 (CCND1) gene encodes a protein involved in the control of cell growth, proliferation, transcription, and DNA repair^[94]. CCND1 forms a complex with CDK4 and CDK6, leading to G1-S cell-cycle transition by inhibiting the retinoblastoma (RB) protein^[94]. Amplification or overexpression of CCND1 could be oncogenic and is associated with carcinogenesis of various cancer types^[95].

Therapeutic and prognostic relevance

Several CDK4 inhibitors, including palbociclib (PD0332991), LEE011, and LY2835219 have entered clinical trials for tumors with CCND1 amplification^{[96][97]}. In the Phase II study of palbociclib and letrozole in patients with ER-positive HER2-negative metastatic breast cancer, patient selection based on CCND1 amplification or p16 loss did not further improve patient outcome^[98]. Preclinical studies also demonstrated conflicting results regarding the correlation between high-level CCND1 and palbociclib sensitivity^{[99][100][101]}.

CCND1 amplification has been implicated in predicting poor clinical outcomes in postmenopausal breast cancer patients treated with either anastrozole or tamoxifen^[102]. In lung cancer patients, the increased CCND1 copy number is associated with poorer overall survival^[103].

A retrospective study showed that melanoma patients whose tumor harboring CCND1, cRAF or KRAS gene copy number gain had better treatment response with CPS (carboplatin, paclitaxel, and sorafenib)^[104].

Amplification of CCND1 are frequent and contributes to dedifferentiation and cellular proliferative activity of intrahepatic cholangiocarcinoma (ICC), and also indicates a poor prognosis for ICC patients^[105].

Of note, CCND1 amplification has been selected as an inclusion criterion for the trial examining CDK4/6 inhibitors in different types of malignant solid tumors (NCT02187783, NCT02896335, NCT03526250, NCT02693535, NCT01037790, NCT03454919, NCT03310879, and NCT03356223).

CDKN2A Heterozygous deletion

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53^{[106][107][108]}. 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^[109]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation^{[110][111]}.

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors^{[112][98]}. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments^{[113][114][115]}. 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^{[116][117][118]}. However, CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for

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the treatment of ER+ and HER2- breast cancer^{[98][119][120]}.

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^[114]. 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^[121].

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^[122].

FGF3 Amplification

Biological Impact

FGF3 (fibroblast growth factor 3, also known as INT2) gene encodes a protein belonging to the fibroblast growth factor family. FGF/FGFR signaling plays essential roles in embryonic development, angiogenesis, cell proliferation, differentiation, migration and survival^{[123][124][125]}. FGF3, FGF4, FGF19, and CCND1 are located at 11q13 and has been reported to co-amplify in multiple cancer types including breast cancer, lung cancer, colon cancer, bladder cancer, advanced medullary thyroid cancer, and hepatocellular carcinoma^{[126][127][128][129]}. Furthermore, recurrent amplification and overexpression of FGF3 and FGF4 are observed in Kaposi's Sarcoma^[130].

Therapeutic and prognostic relevance

A retrospective study indicated that FGF3/FGF4 amplification associates with increased response to sorafenib in hepatocellular carcinoma^[131]. However, FGF3 and FGF4 locate at chromosome 11 (11q13), the region which also contains FGF19 and CCND1, are frequently reported to exert amplifications in HCC^[129]. Further evidence is needed to clarify if FGF3/FGF4 amplification is directly associated with higher response rate to sorafenib^[132].

RAD50 Heterozygous deletion

Biological Impact

The RAD50 gene encodes a highly-conserved DNA double-strand break (DSB) repair factor. It forms MRN complex with NBS1 and MRE11 protein and is involved in sensing and early processing of DSB, cell cycle checkpoints, DNA recombination and maintenance of telomeres^{[133][134]}. Mutations in the components of the MRN complex could increase susceptibility to familial breast cancer^{[135][136]}, gastric cancer^[137], colorectal cancer^[138], and urothelial cancer^[139]. RAD50 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]. Besides, RAD50 deletion was also suggested as a marker of BRCAness, a phenotype shared between non-BRCA1/2-mutated ovarian cancers and BRCA1/2-mutated ovarian cancers^[141].

Therapeutic and prognostic relevance

Preclinical data showed that knockdown of the RAD50 gene in ovarian cancer cell lines was significantly associated with better responses to two PARP inhibitors, olaparib and rucaparib^[141]. RAD50 has been selected as an inclusion criterion for the trials examining talazoparib efficacy in HER2-negative breast cancer, olaparib efficacy in breast cancer, rucaparib efficacy in metastatic prostate cancer and niraparib efficacy in any malignancy (except prostate) (NCT02401347, NCT03207347, NCT03344965, NCT03413995).

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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^{[142][143]}. Mutations in TSC1/TSC2 tumor suppressor genes that result in inactivation of the complex are commonly found in patients with tuberous sclerosis^{[144][145][146]}, while LOH in TSC1/TSC2 has been identified in head and neck squamous cell carcinoma (HNSCC)^[147] and endometrial cancer^[148]. Loss of single TSC1 allele (haploinsufficiency) may provide a growth advantage to bladder epithelial cells, contributing to bladder cancer development^[149]. 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^[150].

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^[151], gastric, sarcoma, thyroid cancer, and HNSCC^[152]. 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^[153]. Recent studies indicate that there are mTORC1-independent signaling pathways downstream of hamartin-tuberin, which may represent new therapeutic targets^[154].

Everolimus has been approved 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).

VEGFB Amplification

Biological Impact

The VEGF gene family is constituted of VEGF-A, VEGF-B, VEGF-C, VEGF-D and placenta growth factor (PlGF)^[155]. Bindings of VEGFs with their receptors, such as Flt-1 (VEGFR-1), Flk-1/KDR (VEGFR-2) and VEGFR-3, lead to endothelial cell proliferation and new blood vessel growth and thus plays a key role in angiogenesis^{[156][157]}. VEGFs and their receptors are expressed in the vast majority of human solid tumors, including those of the lung^[158], breast^[159], gastrointestinal tract^[160], kidney^[161], bladder^[161], ovary^[162], endometrium^[162], brain^[163] and endocrine^[164] system.

In contrast to VEGFA, VEGF-B plays a relatively less pronounced role in the vascular system.

Therapeutic and prognostic relevance

Aflibercept (VEGF trap), a soluble decoy receptor that binds and inactivates members of the VEGF family, including VEGF-A, VEGF-B, and PlGF, has been shown to inhibit ascites, and causes dramatic vascular remodeling in an ovarian cancer model^[165]. Moreover, Aflibercept plus paclitaxel significantly exerted antitumor activity and inhibited ascites while prolonging survival in human ovarian cancer model^[166] and demonstrated promising antitumor activity in combination with docetaxel in patients with recurrent gynecologic malignancies, including ovarian cancer^[167].

High VEGFB expression is associated with significantly shortened survival in lung squamous cell carcinoma (LSCC) and melanoma^[168]. In ovarian cancer, overexpression of intratumoral VEGF, found to correlate with poorer prognosis^{[169][170][171]}.

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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)

monarchE NCT03155997	Breast cancer (Approved on 2021/10/12)
	HR-positive, HER2-negative Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3^[172] NCT00246621	Breast cancer (Approved on 2018/02/26)
	HR-positive, HER2-negative Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 2^[120] NCT02107703	Breast cancer (Approved on 2017/09/28)
	HR-positive, HER2-negative Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1^[173] NCT02102490	Breast cancer (Approved on 2017/09/28)
	HR-positive, HER2-negative 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^[174] 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^[175] 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^[176] 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]

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EXTREME ^[177] 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]
^[178] NCT00004227	Head and neck cancer (Approved on 2006/03/01)
	-
	Cetuximab + radiation vs. Radiation [OS(M): 49 vs. 29.3]
^[179] 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 ^[180] 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]

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 ^[181] 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 ^[182] NCT00026338	Pancreatic cancer (Approved on 2005/11/02)
	-
	Gemcitabine vs. Placebo [OS(M): 6.4 vs. 6]

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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 ^[183] NCT01524783	Lung or gastrointestinal neuroendocrine tumor (Approved on 2016/02/26)
	- Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2 ^[184] 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 ^[185] NCT00510068	Pancreatic neuroendocrine tumor (Approved on 2011/05/05)
	- Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1 ^[186] NCT00789828	Subependymal giant cell astrocytoma (Approved on 2010/10/29)
	- Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1 ^[187] 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 ^[188] NCT01203917	Non-small cell lung carcinoma (Approved on 2015/07/13)
	Exon 19 Del/Exon 21 substitution (L858R) Gefitinib [ORR(%): 50.0]

Necitumumab (PORTRAZZA)

Necitumumab is a recombinant human IgG1 monoclonal antibody against the human epidermal growth factor receptor (EGFR) and blocks the binding of EGFR to its ligands. Necitumumab is developed and marketed by Eli Lilly under the trade name PORTRAZZA.

- FDA Approval Summary of Necitumumab (PORTRAZZA)

SQUIRE ^[189] NCT00981058	Lung squamous cell carcinoma (Approved on 2015/11/14)
	- Gemcitabine + cisplatin vs. Placebo [OS(M): 11.5 vs. 9.9]

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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 ^[92] 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 ^[91] 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 ^[88] 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 ^[82] 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]
POLO ^[87] 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 ^[81] 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 ^[86] 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 ^[190] NCT01874353	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	gBRCA+ Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]

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Study 19 ^[191] 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 ^[192] 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 ^[193] 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 ^[194] NCT02151981	Non-small cell lung carcinoma (Approved on 2017/03/30)
	EGFR T790M+
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA ^[195] NCT01802632	Non-small cell lung carcinoma (Approved on 2015/11/13)
	EGFR T790M+
	Osimertinib [ORR(%): 59.0]

Palbociclib (IBRANCE)

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

- FDA Approval Summary of Palbociclib (IBRANCE)

PALOMA-2 ^[196] NCT01740427	Breast cancer (Approved on 2017/03/31)
	ER+, HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3 ^[197] NCT01942135	Breast cancer (Approved on 2016/02/19)
	ER+, HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

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Panitumumab (VECTIBIX)

Panitumumab is a fully human monoclonal antibody against the human epidermal growth factor receptor (EGFR) and binds to the extracellular domain to prevent its activation. Panitumumab is developed by Abgenix and Amgen, and marketed by the latter under the trade name VECTIBIX.

- FDA Approval Summary of Panitumumab (VECTIBIX)

Study 20050203 ^[198] NCT01412957	Colorectal cancer (Approved on 2017/06/29)
	-
	Panitumumab + bsc vs. Bsc [OS(M): 10 vs. 6.9]
PRIME ^[199] NCT00364013	Colorectal cancer (Approved on 2014/05/23)
	-
	Panitumumab + folfox vs. Folfox [PFS(M): 9.6 vs. 8]
ASPECCT ^[200] NCT01001377	Colorectal cancer (Approved on 2014/05/23)
	-
	Panitumumab vs. Cetuximab [OS(M): 10.4 vs. 10]
Study 20080763 ^[201] NCT00113763	Colorectal cancer (Approved on 2006/09/27)
	-
	Panitumumab + bsc vs. Bsc [PFS(M): 3.2 vs. 2]

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 ^[119] 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+, sBRCA
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3 ^[76] 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]

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ARIEL2 ^[202] 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 ^[93] 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)

^[203] 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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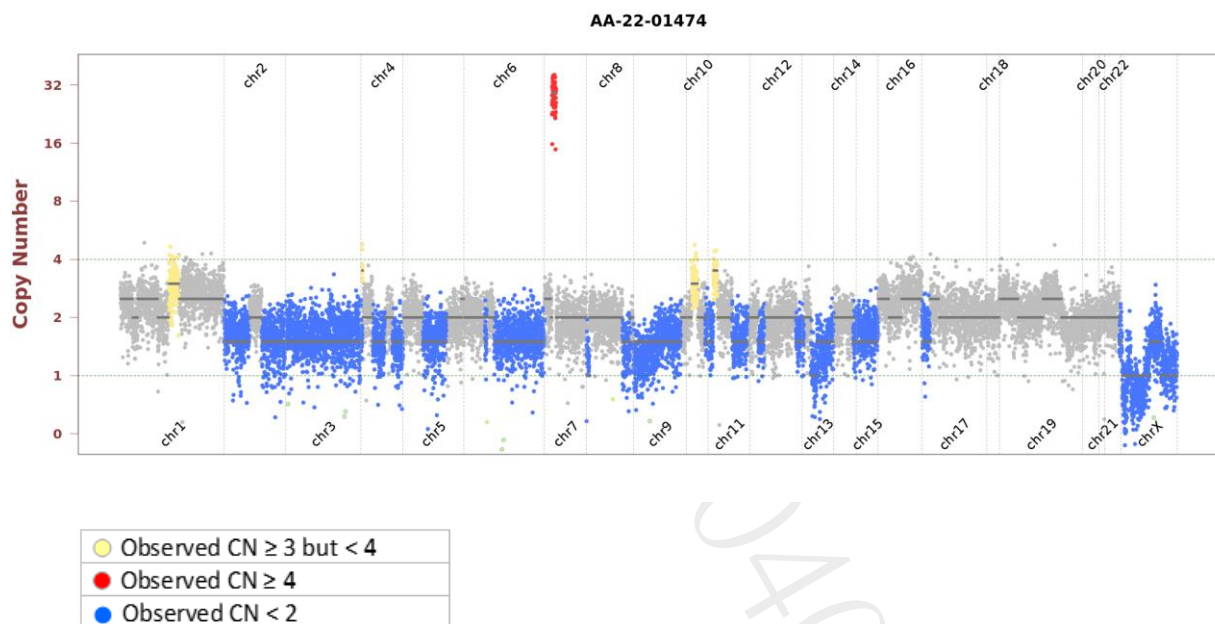
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
EGFR	L861Q	21	c.2582T>A	NM_005228	COSM6213	93.7%	3997
LRP1B	Splice acceptor	-	c.1237-1G>T	NM_018557	-	26.4%	125
RBM10	T476fs	13	c.1425del	NM_005676	-	49.0%	145
TP53	V157F	5	c.469G>T	NM_000546	COSM10670	38.9%	807

- 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
ADAMTS13	R190Q	6	c.569G>A	NM_139025	-	73.6%	888
ATRX	Splice region	-	c.5567-3C>G	NM_000489	COSM85991	28.4%	208
CALR	G259E	6	c.776G>A	NM_004343	-	12.6%	989
CBL	V200D	4	c.599T>A	NM_005188	-	13.8%	247
CD79A	P87R	2	c.260C>G	NM_001783	-	17.9%	1405
DNMT3A	G543C	14	c.1627G>T	NM_175629	COSM87002	10.3%	543
ERCC5	L999V	15	c.2995T>G	NM_000123	COSM5619887	72.0%	1132
FANCA	G811D	26	c.2432G>A	NM_000135	-	70.7%	2880
FANCF	R122W	1	c.364C>T	NM_022725	-	43.6%	1256
FLT3	T325N	8	c.974C>A	NM_004119	-	20.5%	1077
IGF1R	G1328S	21	c.3982G>A	NM_000875	-	44.2%	579
IL7R	R140W	4	c.418C>T	NM_002185	COSM1695578	45.4%	1340
JAK2	N193K	6	c.579C>A	NM_004972	-	22.0%	663
MAP3K1	S1039P	14	c.3115T>C	NM_005921	-	67.4%	438
MSH6	E1163V	6	c.3488A>T	NM_000179	COSM4416035	50.0%	1249
NOTCH2	Splice region	-	c.2480-4C>G	NM_024408	-	32.4%	867
NOTCH2	D1533Y	26	c.4597G>T	NM_024408	-	48.7%	2531
NTRK1	R33W	2	c.97C>T	NM_001007792	COSM1984395	13.5%	1376
SYNE1	S289T	10	c.866G>C	NM_182961	-	55.8%	898

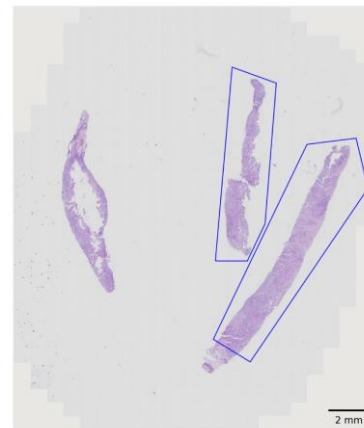
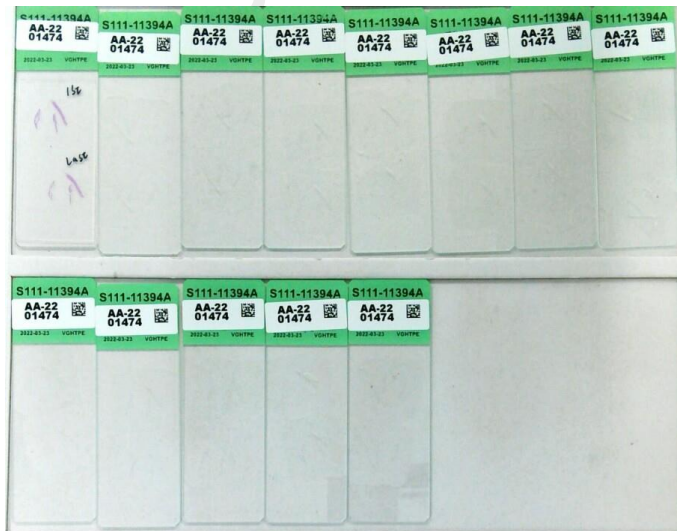
Note:

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

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TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Mar 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11111394
- Collection site: Neck lymph node
- Examined by: Dr. Chien-Ta Chiang
 1. The percentage of viable tumor cells in total cells in the whole slide (%): 30%
 2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 35%
 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: 1083x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 68

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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 ≥ 25 , 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).

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 .

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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:

醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

Sign Off

醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
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Yun Yu Chen

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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*	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*	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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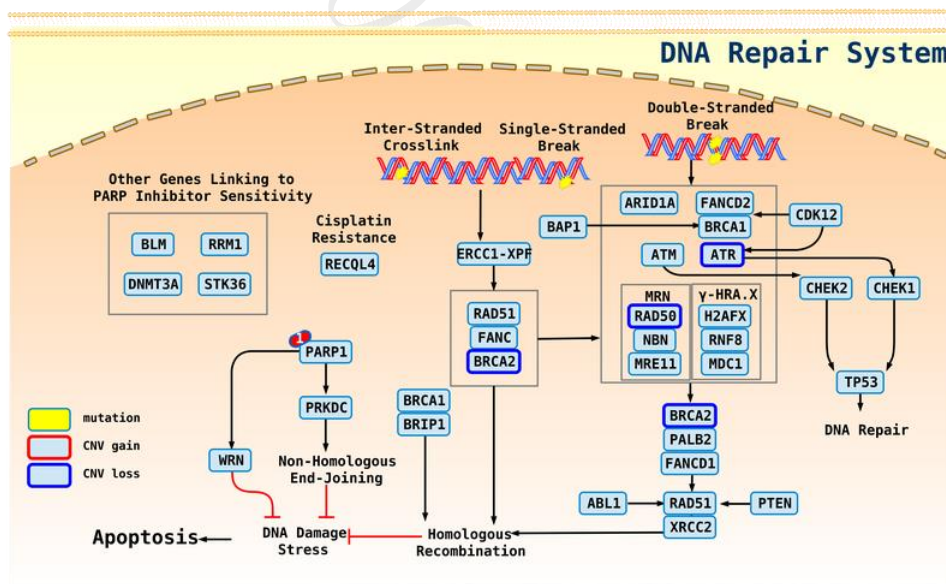
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

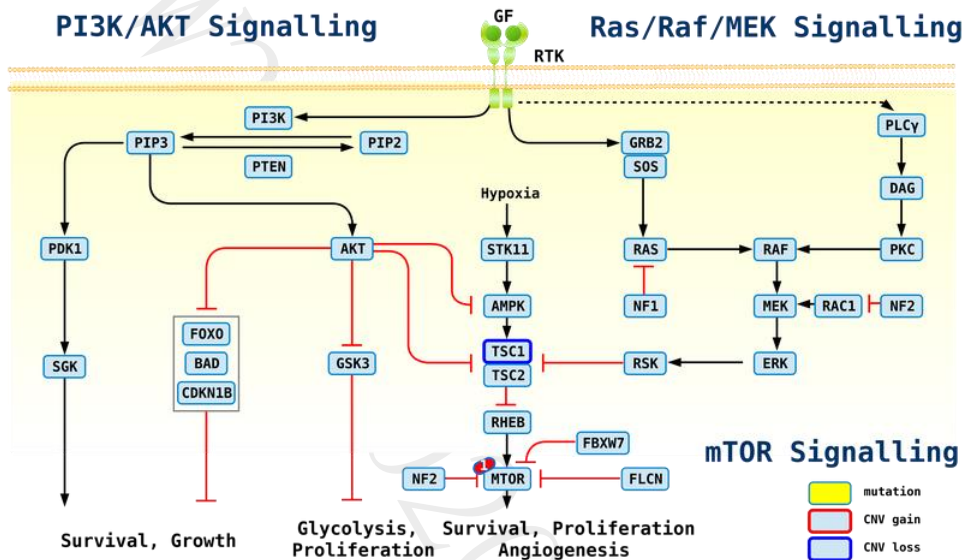
Gene	Therapies	Possible effect
CDKN2A	Abemaciclib, Palbociclib, Ribociclib	sensitive
TSC1	Everolimus, Temsirolimus	sensitive
ATR	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
RAD50	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

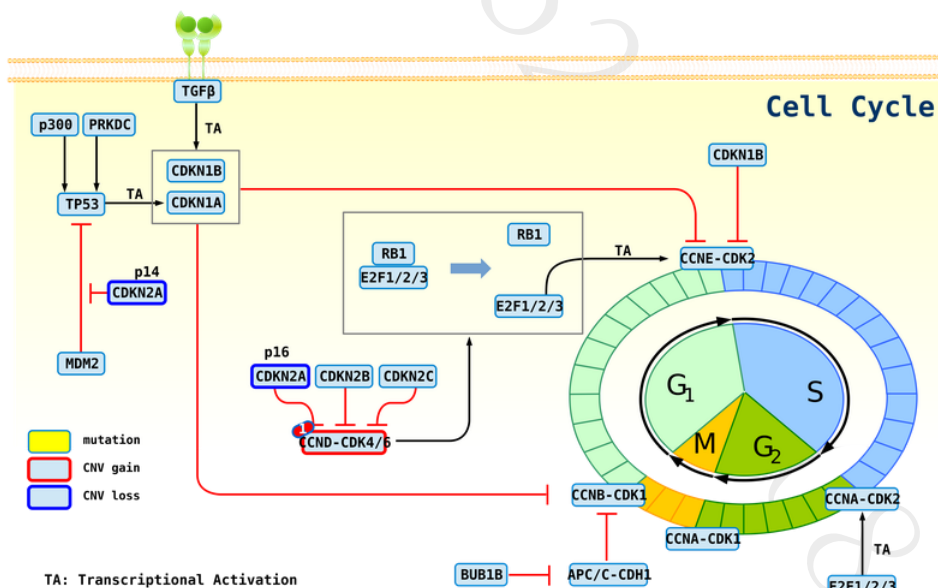


1: Olaparib, Niraparib, Rucaparib, Talazoparib

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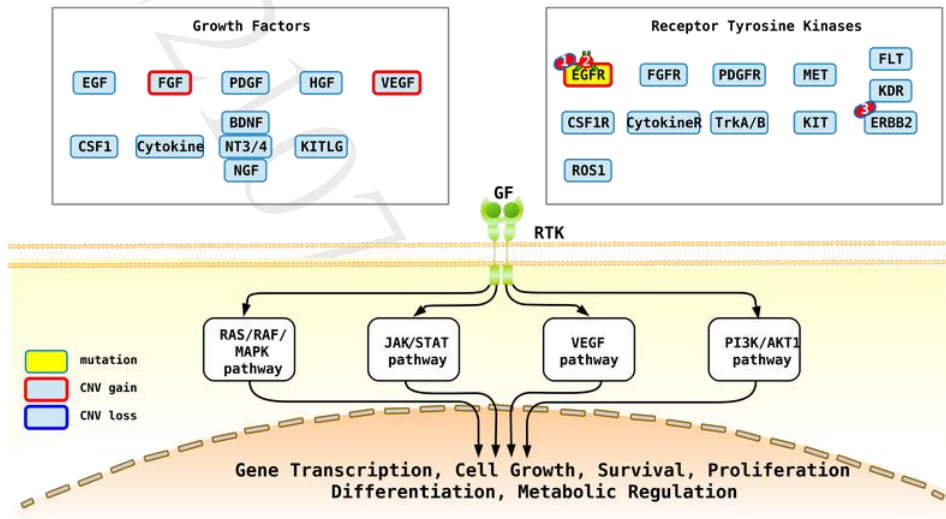
1: Everolimus, Temsirolimus



1: Abemaciclib, Palbociclib, Ribociclib

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Receptor Tyrosine Kinase/Growth Factor Signalling



1: Gefitinib, Afatinib, Erlotinib, Osimertinib, Dacomitinib; 2: Cetuximab, Panitumumab, Necitumumab; 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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