

ACT Onco[®] + Report

PATIENT		
Name: 李志銳		Patient ID: 46192329
Date of Birth: Feb 17, 1956		Gender: Male
Diagnosis: Lung adenocarcinoma metastatic		
ORDERING PHYSICIAN		
Name: 沈佳儀醫師		Tel: 886-228712121
Facility: 臺北榮總		
Address: 臺北市北投區石牌路二段 201 號		
SPECIMEN		
Specimen ID: S11126343A	Collection site: Bone	Type: FFPE tissue
Date received: Jul 21, 2022	Lab ID: AA-22-04215	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	-	-
PIK3CA E545K	-	-	Alpelisib

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
EGFR R776H	Afatinib, Erlotinib, Gefitinib, Osimertinib, Cetuximab	-
PIK3CA E545K	Everolimus, Temsirolimus, Trametinib, Trastuzumab†, Lapatinib†	-
PTPRD Homozygous deletion	-	Bevacizumab

[†]Based on published evidence, this alteration may confer less benefit from the indicated drug.

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>	R776H	34.2%
<i>EGFR</i>	L858R	30.1%
<i>JAK1</i>	V310I	42.6%
<i>PIK3C2G</i>	Y1103fs	46.3%
<i>PIK3CA</i>	E545K	3.0%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr9	<i>PTPRD</i>	Homozygous deletion	0
Chr13	<i>BRCA2</i>	Heterozygous deletion	1
Chr18	<i>SMAD4</i>	Heterozygous deletion	1
Chr22	<i>CHEK2</i>	Heterozygous deletion	1
Chr4	<i>FBXW7</i>	Heterozygous deletion	1
Chr9	<i>CDKN2A</i>	Heterozygous deletion	1
Chr3	<i>BCL6</i>	Amplification	12
Chr3	<i>PRKCI</i>	Amplification	21

- 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 37% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco[®] + to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is $< 30\%$.

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THERAPEUTIC IMPLICATIONS TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 1		
EGFR L858R	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	sensitive
Level 3A		
PIK3CA E545K	Alpelisib	sensitive
Level 3B		
PIK3CA E545K	Everolimus, Temsirolimus	sensitive
Level 4		
EGFR R776H	Afatinib, Erlotinib, Gefitinib, Osimertinib, Cetuximab	sensitive
PIK3CA E545K	Trametinib	sensitive
PIK3CA E545K	Lapatinib, Trastuzumab	less sensitive
PTPRD Homozygous deletion	Bevacizumab	resistant

Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence in professional guidelines or peer-reviewed journals.

Level	Description
1	FDA-recognized biomarkers predictive of response or resistance to FDA approved drugs in this indication
2	Standard care biomarkers (recommended by the NCCN guideline) predictive of response or resistance to FDA approved drugs in this indication
3A	Biomarkers predictive of response or resistance to therapies approved by the FDA or NCCN guideline in a different cancer type
3B	Biomarkers that serve as inclusion criteria for clinical trials (minimal supportive data required)
4	Biomarkers that show plausible therapeutic significance based on small studies, few case reports, or preclinical studies

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

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

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
EGFR aberration	Likely associated with WORSE response to ICIs

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

CHEMOTHERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
PIK3C2G Y1103fs	Oxaliplatin	Resistant	Clinical	Colorectal cancer

HORMONAL THERAPIES

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

OTHERS

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

Note:

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

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VARIANT INTERPRETATION

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 (UniProtKB). 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].

JAK1 V310I

Biological Impact

Janus kinase 1 (JAK1) gene encodes a protein tyrosine kinase of the JAK family^{[26][27]}, which plays essential roles in several cellular functions including proliferation, differentiation and antigen presentation via JAK/STAT signaling^{[28][26]}. Activating mutations of JAK1 have been reported in acute lymphoblastic leukemia (ALL) and other hematological malignancies^[29]. Of note, recurrent loss-of-function mutations of JAK1 have been reported in multiple tumor types including gynecologic tumors, colorectal, stomach and prostate carcinomas. Besides, JAK1 loss-of-function mutations were suggested representing a potential pan-cancer adaption to immune responses against tumor with microsatellite instability, possibly by loss of the JAK1-mediated interferon response^{[30][31]}.

V310I is a missense mutation lies within the FERM (4.1/ezrin/radixin/moesin) domain of the JAK1 protein (UniProtKB). This mutant has been proposed as a gain-of-function mutation with the conformational change to be more readily activated by ligand-induced gp130 dimerization and resulting in hyper-responsiveness to normal levels of cytokines^[32].

Therapeutic and prognostic relevance

Biallelic inactivation of JAK1/2 was associated with primary and acquired resistance to PD-1 blockade due to defects in the pathways involved in interferon-receptor signaling^{[33][34]}. In MSI+ colorectal cancer, patients carrying loss-of-function mutations of JAK1 were found to have favorable overall survival^[35].

In a study of 142 NSCLC patients, activation and expression of JAK1 was correlated with NSCLC and predicted a poorer overall survival^[36].

JAK1 V310I has been reported in a patient with cutaneous Castleman disease (CD) who attained a complete response for seven years when treated with siltuximab^[32].

PIK3C2G Y1103fs

Biological Impact

The PIK3C2G gene encodes a protein contains a lipid kinase catalytic domain as well as a C-terminal C2 domain, a characteristic of the class II phosphoinositide 3-kinases (PI3Ks). C2 domains act as calcium-dependent phospholipid binding motifs that mediate translocation of proteins to membranes, and may also mediate protein-protein interactions^{[37][38]}. PIK3C2G plays roles in the regulation of protein trafficking signaling pathways and glycogen synthase^[39]. Inactivating mutations of PIK3C2G are found in melanomas^[40].

Y1103fs mutation results in a change in the amino acid sequence beginning at 1103, likely to cause premature truncation of the functional PIK3C2G protein (UniProtKB). This mutation is predicted to lead to a loss of PIK3C2G protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

Low copy number of PIK3C2G has been reported to associate with shorter overall survival and recurrence-free survival in stage III colorectal cancer patients treated with oxaliplatin-based chemotherapy^[41].

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PIK3CA E545K

Biological Impact

The PIK3CA gene encodes the catalytic subunit (p110 α) of phosphatidylinositol 3-kinase (PI3K) that plays a key role in the PI3K/AKT signaling pathway and is involved in the regulation of cellular functions such as proliferation, metabolism and protein synthesis, angiogenesis and apoptosis. PIK3CA has long been described as an oncogene and the PIK3CA gene amplification, deletion, and mutations have been reported in a wide range of cancers, including colorectal, breast, brain, liver, ovarian, stomach and lung cancers^{[42][43][44][45]}. Mutations located in the exon 9 that encodes the PI3K helical (like E542K, E545K) and the exon 20 that encodes the catalytic/kinase domain (like H1047R, H1047L, H1047Y) have been shown to result in the constitutively activated mutant, which could enhance downstream signaling and oncogenic transformation in vitro and in vivo^{[43][46][47][48]}.

The PIK3CA E545K/E542K is the second most prevalent activating mutations in breast cancer and are also highly recurrent in other cancer types.

Therapeutic and prognostic relevance

In a preclinical study, cells harbored different activating PIK3CA mutations (H1047R, E545K, G1049R, Q546K, N345K, H1047L, E542K) were significantly more sensitive to PIK3 pathway inhibitors (dactolisib, MK2206, alpelisib), and MEK1/2 inhibitor trametinib, compared to wild-type^[49]. According to ExteNET trial, PIK3CA activating mutation was not an appropriate predictive biomarker of response to neratinib in HER2-positive early breast cancer^[50].

In 2019 May, alpelisib, the PI3K inhibitor, in combination with fulvestrant received U.S. FDA approval for the treatment of postmenopausal women and men, with HR+, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced breast cancer following progression on or after an endocrine-based regimen. The approval is based on the results of the SOLAR-1 trial (NCT02437318), a randomized phase III trial of 572 patients with breast cancers showed that addition of alpelisib to fulvestrant significantly prolonged progression-free survival (median of 11 months vs. 5.7 months) in patients whose tumors had a PIK3CA mutation including C420R, E542K, E545A, E545D, E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y^[51].

An early phase study demonstrated that alpelisib has potential treatment benefits in a subset of PIK3CA-mutated tumors. Of the 114 patients with PIK3CA-mutated tumors, one patient with endometrial cancer achieved a complete response and seven had partial responses (including cervical, breast, endometrial, colon and rectal cancers). Besides, stable disease was observed in 70 patients and disease control rate was 58.2%^[52].

Given that compared to patients with wild-type PIK3CA, those carrying PIK3CA mutations have a favorable response to mTOR inhibitors-containing monotherapy like everolimus and temsirolimus in several clinical studies of advanced malignancies or temsirolimus in combination with doxorubicin and bevacizumab^{[53][54][55][56][57][58][59]}, combining PI3K-targeted agent with endocrine therapy was suggested.

Meanwhile, clinical benefit and response were observed when everolimus, an mTOR kinase inhibitor, was added to trastuzumab for the treatment of patients with HER2-overexpressing metastatic breast cancer, who progressed on trastuzumab-based therapy^[60]. BOLERO-1 and BOLERO-3 (Breast Cancer Trials of Oral Everolimus) also suggested that patients with HER2-positive advanced breast cancer carrying PIK3CA mutations, PTEN loss, or hyperactive PI3K pathway could derive progression-free survival (PFS) benefit from everolimus^[61]. In addition, BOLERO-3 study also showed that the addition of everolimus to trastuzumab plus vinorelbine significantly prolonged PFS in patients with trastuzumab-resistant and taxane-pretreated, HER2-positive, advanced breast cancer. However, the clinical benefit should be considered in the context of the adverse event profile in this population^[62]. According to ExteNET trial, PIK3CA activating mutation was not an appropriate predictive biomarker of response to neratinib in HER2-positive early breast cancer^[50].

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PIK3CA mutations have been determined as an inclusion criterion for the trials evaluating everolimus efficacy in patients with malignant glioma and different types of tumors (NCT03834740, NCT01827384) and trials examining temsirolimus in malignant solid tumors, multiple myeloma, B-cell non-Hodgkin lymphoma and malignant uterine neoplasm (NCT03297606, NCT02693535). On the other hand, there are several investigational PI3K inhibitors, including taselisib and buparlisib, which are currently in clinical development^{[63][64]}.

Hyperactivation of the PI3K signaling pathway is common and has been implicated in resistance to endocrine therapy and HER2-targeting neoadjuvant therapies such as trastuzumab and lapatinib in patients with advanced breast cancer^{[65][63][66][67][68][69][70][71]}.

Results from a clinical study showed that PIK3CA mutations occur in approximately 5% (2/37) of EGFR-mutated lung cancers who developed acquired resistance to EGFR TKI therapy^[72]. Preclinical data also showed that PI3K/AKT/mTOR signaling was implicated in gefitinib resistance in EGFR-mutated lung cancer cell lines^[73]. Although preclinical data suggested that addition of everolimus restored gefitinib sensitivity in NSCLC cancer cell lines^{[74][75]}, the efficacy was not evidenced in the clinical settings^{[76][77]}.

A retrospective study indicated that CRC patients with PIK3CA mutation and wild-type KRAS/BRAF showed fair responses to anti-EGFR therapies^[78]. Two meta-analyses involving five studies demonstrated a significant correlation of PIK3CA mutations with better recurrence-free survival (RFS) in patients with unsorted breast cancer^{[79][80][69]}. In patients with advanced EGFR- or KRAS-mutant lung adenocarcinoma, a concurrent PIK3CA mutation has been reported as a poor prognostic factor^[81].

BCL6 Amplification

Biological Impact

BCL6 (B-cell CLL/lymphoma 6) gene encodes a zinc-finger transcriptional repressor which plays essential roles in lymphocyte differentiation, cell cycle progression and apoptosis^{[82][83][84][85]}. BCL6 amplification and/or rearrangement were frequently observed in diffuse large B-cell Lymphoma (DLBCL)^{[86][85]}, non-Hodgkin's lymphoma^[87], and nodular lymphocyte-predominant Hodgkin Lymphoma^[88]. Besides, overexpression of BCL6 has been identified in gallbladder carcinoma^[89], and ovarian cancer^{[90][91]}.

Therapeutic and prognostic relevance

In a retrospective study, BCL6 gene amplification could cause BCL6 mRNA upregulation and overexpression of BCL6 protein in muscle-invasive urinary bladder urothelial carcinoma (UBUC) patients. BCL6 gene amplification and overexpression of BCL6 protein were associated with poor prognosis in UBUC. The UBUC patients with high BCL6 expression level had poor disease-specific and metastasis-free survivals^[92].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair^[93]. 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^[94]. 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^[95]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers^[96].

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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^[97]; (2) in combination with bevacizumab as first-line maintenance treatment for patients with homologous recombination deficiency (HRD)-positive status^[98]; (3) maintenance treatment for patients with germline BRCA-mutated recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy^{[99][100]}; (4) treatment for patients with germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy^[101]. 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^[102] and germline BRCA-mutated metastatic pancreatic cancer^[103]. 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^[104].

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^{[105][106]}. 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^{[107][108][109]}. In addition, talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer^[110].

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^{[111][112][113]}. 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^[114]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation^{[115][116]}.

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors^{[117][118]}. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments^{[119][120][121]}. 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^{[122][123][124]}. 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).

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Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for the treatment of ER+ and HER2- breast cancer^{[118][125][126]}.

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^[120]. 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^[127].

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^[128].

CHEK2 Heterozygous deletion

Biological Impact

The checkpoint kinase 2 (CHEK2 or CHK2) gene encodes a serine/threonine protein kinase involved in transducing DNA damage signals that are required for both the intra-S phase and G2/M checkpoints^[129]. CHEK2 heterozygosity has been shown to cause haploinsufficient phenotypes that can contribute to tumorigenesis through inappropriate S phase entry, accumulation of DNA damage during replication, and failure to restrain mitotic entry^{[130][131]}. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers^{[132][133][134][135][136]}.

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^[104].

In addition, CHEK2 has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer (NCT03533946)^{[105][137]}, niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

In a phase 2 trial, two prostate cancer patients harboring CHEK2 homozygous deletion was enrolled. One of the two patients had a response to olaparib^[138].

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^{[139][140]}, c-Jun^[141], cyclin E^[142], Notch family members^{[143][144]}, Aurora-A^[145], mTOR^[146], KLF5^[147], and MCL-1^[148]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation^[149]. 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^{[147][148][150]}.

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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)^{[151][152]}. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor^[146].

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^{[153][154][155][156]}.

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^{[157][155]}.

PRKCI Amplification

Biological Impact

The PRKCI gene encodes a member of the atypical protein kinase C (PKC). PKCs are a family of lipid-dependent serine/threonine kinases that represent a branch of the AGC kinase group which are central components of many signaling pathways that regulate diverse cellular functions including proliferation, cell cycle, differentiation, survival, cell migration, and polarity^{[158][159][160]}. PRKCI resides on chromosome 3q26, one of the most frequently amplified genomic regions in human cancers, including cervical, head and neck, lung squamous and serous ovarian cancers^{[161][162][163][164]}. PKCi is frequently overexpressed in the majority of tumor types^[165]. As reviewed in^{[166][165][167]}, PKCi is required for multiple aspects of the transformed phenotype and appears to participate in the initiation, progression and metastatic stages of cancer.

Therapeutic and prognostic relevance

In NSCLC, the PB1-PB1 interaction between PKCi and Par6 is required for the transformed phenotype and Rac1 activation^[168]. A high throughput screen for small molecular weight compounds identified gold-containing compounds such as aurothioglucose (ATG), aurothiomalate (ATM) (FDA-approved for treatment of rheumatoid arthritis patients), and auranofin (ANF) as selective and potent inhibitors of PKCi and Par6 binding^[169]. Phase I studies suggested that ATM is well tolerated in patients with NSCLC and ovarian cancer (NCT00575393). However, currently, there is no FDA-approved PKCi inhibitor for patients with cancer.

Increased PRKCI gene copy number and/or increased PKCi protein expression level are associated with decreased progression-free survival and overall survival in various cancer types, including lung^[162], pancreatic cancer^[170], cholangiocarcinoma^[171], ovarian cancer^{[163][172]}. Moreover, a correlation between PKCi expression and prostate cancer recurrence was reported^[173].

PTPRD Homozygous deletion

Biological Impact

PTPRD encodes the enzyme Receptor-type tyrosine-protein phosphatase delta (PTPδ), which is involved in various cellular processes and cell-cell adhesion^{[174][175]}. PTPRD is inactivated in a large number of glioblastomas and is mutated, deleted or promoter methylated in multiple other human cancers, ranging from neuroblastomas to endometrial, lung and colon cancers and has a putative tumor suppressor function^{[176][177]}.

Therapeutic and prognostic relevance

Deleterious PTPRD/PTPRT alternations, including PTPRD copy number loss, PTPRD/PTPRT missense variants and truncating variants, have been shown associated with bevacizumab-resistance in metastatic colorectal cancer and lead to shortened survival in bevacizumab-treated patients compared to those without deleterious PTPRT/PTPRD alternations (Median PFS: 8.6 v.s. 13.1 months)^[178]. Reduced expression of PTPRD was shown correlated with poor

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prognosis in gastric adenocarcinoma^[179]. Moreover, a clinical study suggested that PTPRD/PTPRT mutations were associated with increased TMB and longer OS and PFS in ICI-treated NSCLC patients (doi: 10.1200/JCO.2020.38.15_suppl.e15112).

SMAD4 Heterozygous deletion

Biological Impact

The SMAD family member 4 (SMAD4) gene encodes a transcription factor that acts as a downstream effector in the TGF- β signaling pathway. Upon phosphorylated and activated by serine-threonine receptor kinase, Smad4 is the Co-Smad which recruits other activated R-Smad proteins to the Smad transcriptional complex and regulate TGF- β -targeted genes^[180]. Smad4 has been identified as a haploinsufficient gene with one copy loss may lead to a weak protein expression and is insufficient to execute its original physiological function^[181]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)^{[182][183][184][185]}. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer^[186], colorectal cancer (CRC)^{[184][187][188]}, and less frequently seen in other cancers such as lung adenocarcinoma^[189], head and neck cancer^{[190][191]}, and cutaneous squamous cell carcinoma^[192].

Therapeutic and prognostic relevance

In Chinese patients with metastatic colorectal cancer, SMAD4 or NF1 mutations are suggested as a potential biomarker for poor prognosis to cetuximab-based therapy^[193]. Preclinical data demonstrated that depletion of SMAD4 by shRNA knockdown increased clonogenic survival and cetuximab resistance in HPV-negative head and neck squamous cell carcinoma cells^[194].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)^{[195][196]}. CRC patients with normal SMAD4 diploidy exhibited three-fold higher benefit of 5-FU/mitomycin-based adjuvant therapy when compared with those with SMAD4 deletion^[197].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis^{[198][199][200][201][202][203][204][205]}. In cervical cancer patients, weak cytoplasmic SMAD4 expression and absent nuclear SMAD4 expression were shown to be significantly associated with poor disease-free and overall 5-year survival^[206].

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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 ^[207] NCT02246621	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 ^[126] 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 ^[208] NCT02102490	Breast cancer (Approved on 2017/09/28)
	HR-positive, HER2-negative Abemaciclib [ORR(%): 19.7 vs. 17.4]

Afatinib (GILTRIF)

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 GILTRIF (United States) and GIOTRIF (Europe).

- FDA Approval Summary of Afatinib (GILTRIF)

LUX-Lung 8 ^[209] 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 ^[210] 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]

Alpelisib (PIQRAY)

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3K α . Gain-of-function mutations in the gene encoding the catalytic α -subunit of PI3K (PIK3CA) lead to activation of PI3K α and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models. Alpelisib is developed and marketed by Novartis under the trade name PIQRAY.

- FDA Approval Summary of Alpelisib (PIQRAY)

SOLAR-1 ^[51] NCT02437318	Hr-positive, her2-negative breast cancer (Approved on 2019/05/24)
	PIK3CA mutation Alpelisib plus fulvestrant vs. Placebo plus fulvestrant [PFS(M): 11 vs. 5.7]

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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 ^[211] 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 ^[212] 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]
^[213] NCT00004227	Head and neck cancer (Approved on 2006/03/01)
	- Cetuximab + radiation vs. Radiation [OS(M): 49 vs. 29.3]
^[214] 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]

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 ^[215] 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]

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PA.3 ^[216] 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 ^[217] NCT01524783	Lung or gastrointestinal neuroendocrine tumor (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2 ^[218] 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 ^[219] NCT00510068	Pancreatic neuroendocrine tumor (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1 ^[220] NCT00789828	Subependymal giant cell astrocytoma (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1 ^[221] 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 ^[222] NCT01203917	Non-small cell lung carcinoma (Approved on 2015/07/13)
	Exon 19 Del/Exon 21 substitution (L858R)
	Gefitinib [ORR(%): 50.0]

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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 ^[109] 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 ^[108] 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 ^[104] 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 ^[98] 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 ^[103] 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 ^[97] 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 ^[102] 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 ^[223] 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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Study19 ^[224] 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 ^[225] 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 ^[226] 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]

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 ^[227] NCT01740427	Breast cancer (Approved on 2017/03/31)
	ER+, HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3 ^[228] 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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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 ^[125] 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 ^[105] 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 ^[229] 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 ^[110] 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]

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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)

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

Trametinib (MEKINIST)

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

- FDA Approval Summary of Trametinib (MEKINIST)

BRF117019, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060, NCT02124772	Cancer (Approved on 2022/06/22)
	BRAF V600E
	Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0]
BRF117019 ^[231] NCT02034110	Anaplastic thyroid cancer (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928 ^[232] NCT01336634	Non-small cell lung cancer (Approved on 2017/06/22)
	BRAF V600E
	Trametinib + dabrafenib vs. Dabrafenib [ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9]
COMBI-d ^[233] NCT01584648	Melanoma (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC ^[234] NCT01245062	Melanoma (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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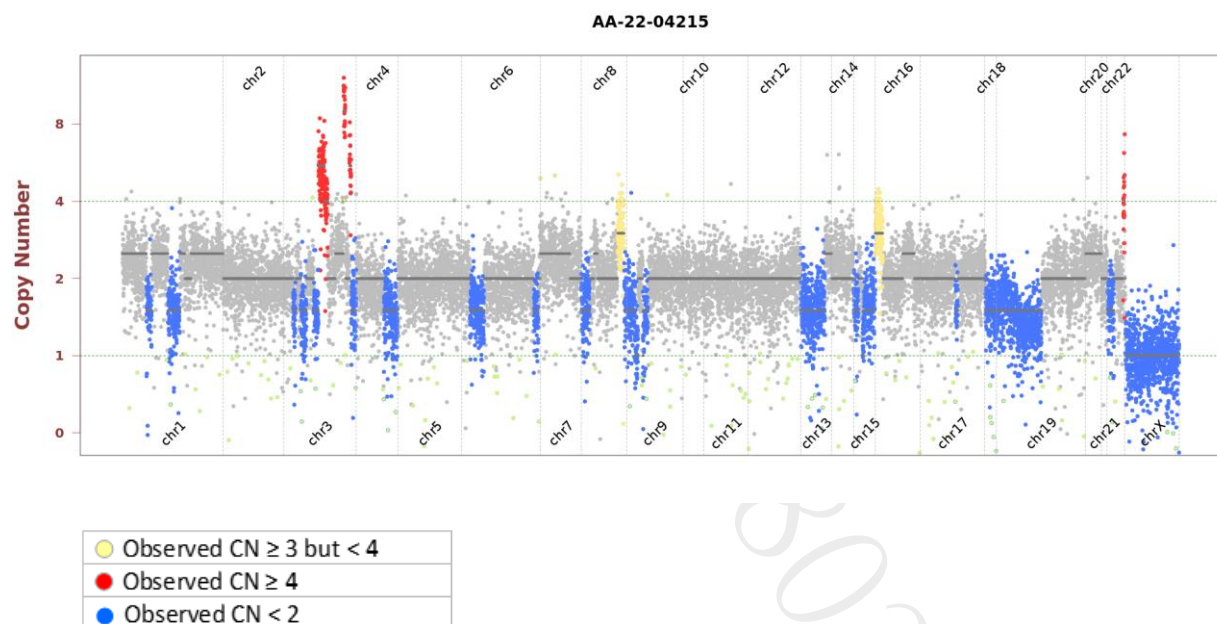
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
EGFR	R776H	20	c.2327G>A	NM_005228	COSM22940	34.2%	2390
EGFR	L858R	21	c.2573T>G	NM_005228	COSM6224	30.1%	2709
JAK1	V310I	7	c.928G>A	NM_002227	COSM194241	42.6%	1050
PIK3C2G	Y1103fs	24	c.3299_3306dup	NM_004570	COSM2003816	46.3%	326
PIK3CA	E545K	10	c.1633G>A	NM_006218	COSM763	3.0%	896

- 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
APC	M1211T	16	c.3632T>C	NM_000038	-	47.5%	836
AXL	R71W	2	c.211C>T	NM_021913	COSM996949	54.3%	1037
CCNA1	Frameshift	1	c.108+1del	NM_001111045	-	37.5%	602
EPHA5	K148T	3	c.443A>C	NM_001281765	COSM1056658	18.8%	1125
ESR1	G145S	1	c.433G>A	NM_000125	-	47.8%	425
KMT2D	R3110H	34	c.9329G>A	NM_003482	COSM9113805	53.9%	670
MSH2	I169V	3	c.505A>G	NM_000251	COSM1684714	50.2%	904
MUC16	P14112L	74	c.42335C>T	NM_024690	COSM3541793	63.3%	999
NTRK3	V502A	13	c.1505T>C	NM_001012338	-	16.4%	955
PTCH1	Splice region	-	c.2560+7C>T	NM_000264	-	46.6%	1521
ROS1	V1732F	31	c.5194G>T	NM_002944	-	22.6%	421
SETD2	E972Q	3	c.2914G>C	NM_014159	-	39.1%	276

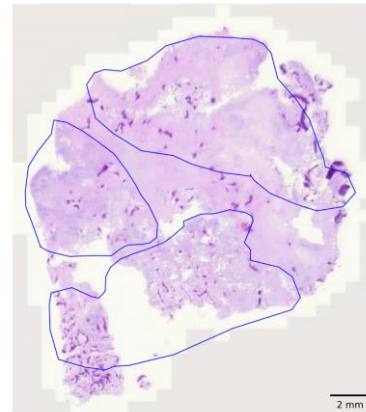
Note:

- 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.: S11126343A
- Collection site: Bone
- 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: 829x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 132

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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:

醫檢師張筑芻 博士
Chu-Yuan Chang Ph.D.
檢字第 020115 號



Sign Off

醫檢師張筑芻 博士
Chu-Yuan Chang Ph.D.
檢字第 020115 號



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GENE LIST SNV & CNV

ABCB1*	ABCC2*	ABCG2*	ABL1	ABL2	ADAMTS1	ADAMTS13	ADAMTS15	ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9
ADAMTSL1	ADGRA2	ADH1C*	AKT1	AKT2	AKT3	ALDH1A1*	ALK	AMER1	APC	AR	ARAF
ARID1A	ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2	AXL
B2M	BAP1	BARD1	BCL10	BCL2*	BCL2L1	BCL2L2*	BCL6	BCL9	BCOR	BIRC2	BIRC3
BLM	BMPR1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2*	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	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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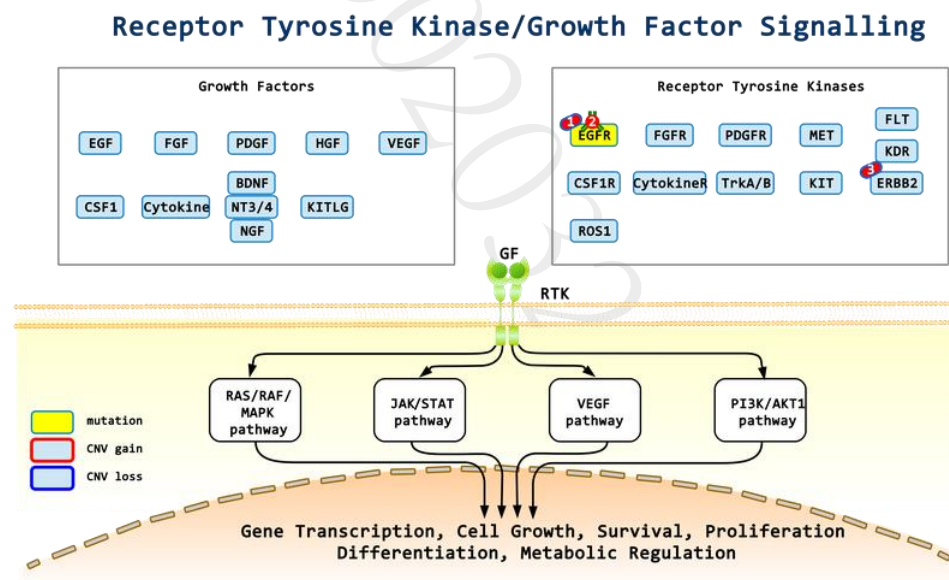
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

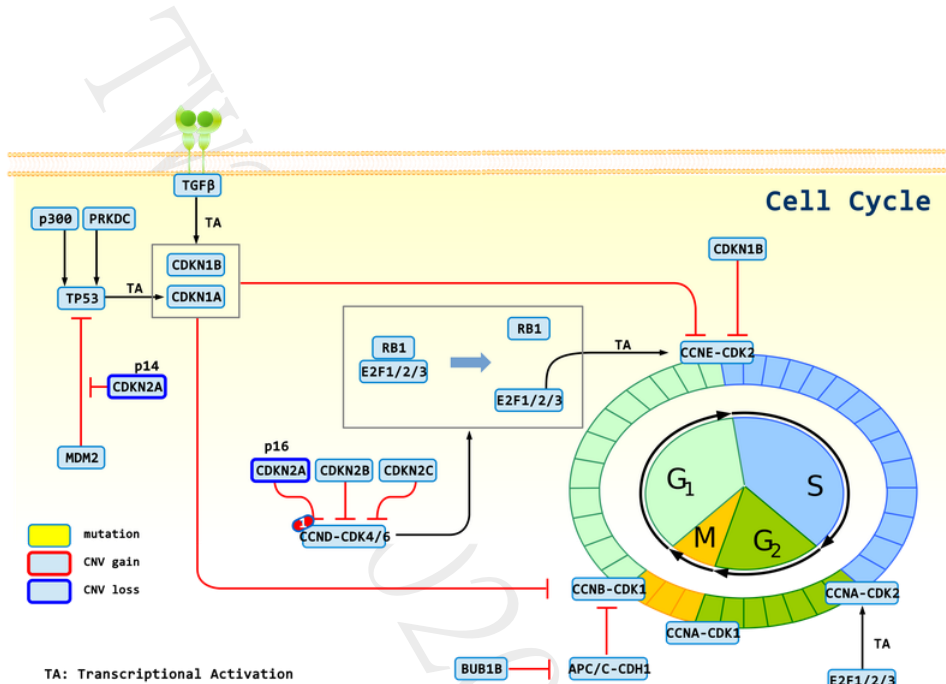
Gene	Therapies	Possible effect
CDKN2A	Abemaciclib, Palbociclib, Ribociclib	sensitive
FBXW7	Everolimus, Temsirolimus	sensitive
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
CHEK2	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
SMAD4	Cetuximab	resistant
FBXW7	Gefitinib, Regorafenib	resistant

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

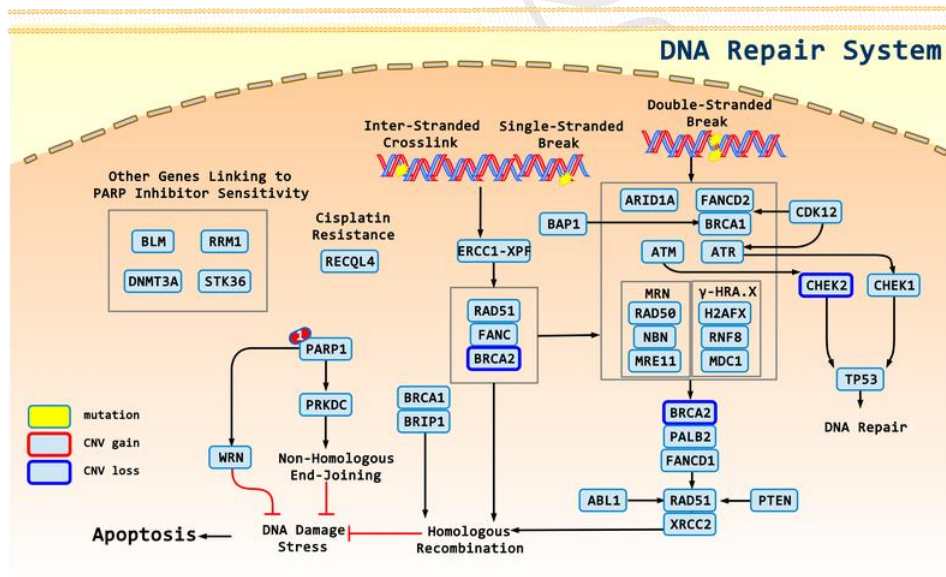


1: Gefitinib, Erlotinib, Afatinib, Osimertinib, Dacomitinib; 2: Cetuximab; 3: Afatinib

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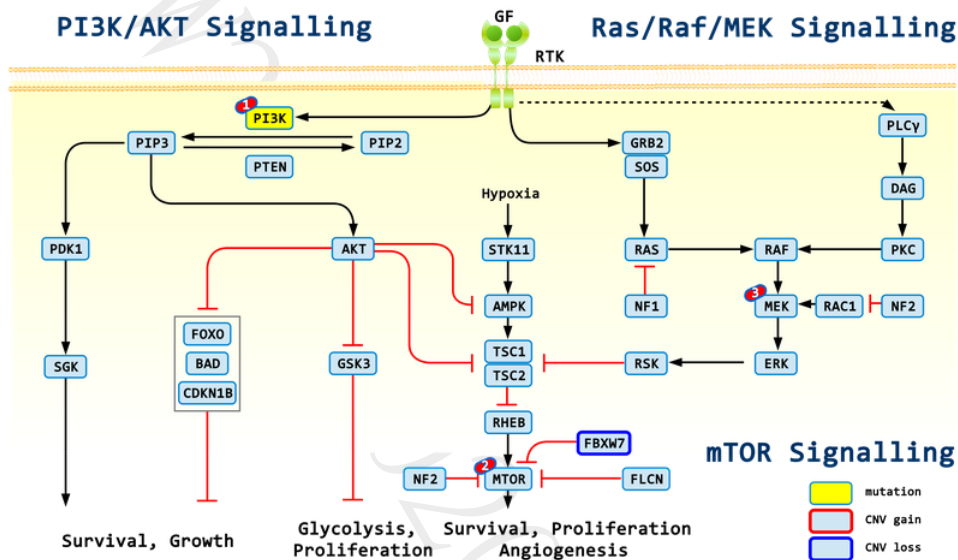


1: Abemaciclib, Palbociclib, Ribociclib



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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1: Alpelisib; 2: Everolimus, Temsirolimus; 3: Trametinib

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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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