ACT Onco® + Report

PATIENT		
Identifier: 陳慧吟		Patient ID: 42951724
Date of Birth: Sep 17, 1960		Gender: Female
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11132487A	Collection site: Adrenal gland	Type: FFPE tissue
Date received: Dec 14, 2022	Lab ID: AA-22-07619	D/ID: NA

ABOUT ACTOnco®+

The test is a next-generation sequencing (NGS)-based assay developed for efficient and comprehensive genomic profiling of cancers. This test interrogates coding regions of 440 genes associated with cancer treatment, prognosis and diagnosis. Genetic mutations detected by this test include small-scale mutations like single nucleotide variants (SNVs), small insertions and deletions (InDels) (≤ 15 nucleotides) and large-scale genomic alterations like copy number alterations (CNAs). The test also includes an RNA test, detecting fusion transcripts of 13 genes.

SUMMARY FOR ACTIONABLE VARIANTS

VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Probable Effects in Patient's Cancer Type		Probable Sensitive in Other Cancer Types
	Sensitive	Resistant	
EGFR L858R	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-	-
EGFR S768I	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-	-

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
EGFR S768I	Mobocertinib	Cetuximab
FGFR1 Amplification	Erdafitinib, Infigratinib, Lenvatinib, Pazopanib, Ponatinib, Regorafenib, Sunitinib	Palbociclib, Ribociclib

Note:

- The above summary tables present genomic variants and biomarkers based on the three-tiered approach proposed by US FDA for reporting tumor profiling NGS testing. "Variants/biomarkers with evidence of clinical significance" refers to mutations that are widely recognized as standard-of-care biomarkers (FDA level 2/AMP tier 1). "Variants/biomarkers with potential clinical significance" refers to mutations that are not included in the standard of care but are informational for clinicians, which are commonly biomarkers used as inclusion criterial for clinical trials (FDA level 3/AMP tier 2).
- The therapeutic agents and possible effects to a given drug are based on mapping the variants/biomarkers with ACT Genomics clinical knowledge database. The mapping results only provide information for reference, but not medical recommendation.
- Please refer to corresponding sections for more detailed information about genomic alteration and clinical relevance listed above.

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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
EGFR	L858R	50.4%
EGFR	S768I	49.1%
TP53	R273C	43.9%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr13	*BRCA2, RB1*	Heterozygous deletion	1
Chr17	*BRCA1, FLCN, NF1, RAD51C, TP53*	Heterozygous deletion	1
Chr18	*SMAD4*	Heterozygous deletion	1
Chr19	*STK11*	Heterozygous deletion	1
Chr8	*FGFR1, KAT6A*	Amplification	6

- 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)	2.6 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 48% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is < 30%.

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 1		
EGFR L858R	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	**sensitive**
EGFR S768I	Afatinib	**sensitive**
Level 2		
EGFR S768I	Dacomitinib, Erlotinib, Gefitinib, Osimertinib	**sensitive**
Level 3B		
FGFR1 Amplification	Erdafitinib, Infigratinib, Ponatinib, Regorafenib, Sunitinib	**sensitive**
Level 4		
EGFR S768I	Mobocertinib	**sensitive**
FGFR1 Amplification	Lenvatinib, Pazopanib	**sensitive**
EGFR S768I	Cetuximab	**resistant**
FGFR1 Amplification	Palbociclib, Ribociclib	**resistant**

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

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

- Other Biomarkers with Potential Clinical Effects for ICIs

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

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

CHEMOTHERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
TP53 R273C	Platinum- and taxane-based regimens	**Less sensitive**	Clinical	Ovarian cancer

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
FGFR1 Amplification	Letrozole	**Resistant**	Clinical	Estrogen-receptor positive breast cancer
	Tamoxifen	**Resistant**	Preclinical	Breast cancer

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OTHERS

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AA	Irinotecan-based regimens	Level 1B

Clinical Interpretation:
Patients with the AA genotype and cancer who are treated with irinotecan-based regimens may have an increased risk of diarrhea and neutropenia as compared to patients with the AG or GG genotype. Other genetic and clinical factors may also influence a patient's risk of diarrhea and neutropenia.

* Level of evidence was defined by PharmGKB (https://www.pharmgkb.org/page/clinAnnLevels)

Level 1A: Clinical annotations describe variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation.
Level 1B: Clinical annotations describe variant-drug combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label.
Level 2A: Variants in Level 2A clinical annotations are found in PharmGKB's Tier 1 Very Important Pharmacogenes (VIPs). These variants are in known pharmacogenes, implying causation of drug phenotype is more likely.

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.

VARIANT INTERPRETATION

EGFR L858R, S768I

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 S768I lies within the protein kinase domain of the EGFR protein (UniProt.org). EGFR S768I is an oncogenic mutant that results in constitutive phosphorylation of EGFR protein, increased downstream signaling and transforming ability when overexpressed in cells[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].

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. 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 responsive to EGFR TKI therapy.

The responsiveness of patients carrying S768I to first generation EGFR TKIs is still controversial. A retrospective

analysis of patients with non-small cell carcinoma (NSCLC) indicated that S768I is associated with an unfavourable response to oral TKI, particularly erlotinib[21]. However, there are case reports showed that EGFR S768I mutant lung carcinoma is sensitive to erlotinib and gefitinib[22][23].

The cell-based assay also revealed that compared with L858R and DelL747-753insS, S768I mutation is less sensitive to both gefitinib, erlotinib, and osimertinib, but were sensitive to afatinib[7][24]. In line with this, a patient with NSCLC carrying S768I had benefit from afatinib after showing no response to gefitinib[25].

In preclinical studies, transformed cells expressing S768I were sensitive to mobocertinib but resistant to cetuximab and gefitinib treatment in vitro[26][27].

TP53 R273C, 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[28]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[29].

R273C is a hotspot mutation occurred at the DNA-binding domain (DBD) of the p53 protein[30]. This is a gain-of-function mutation that has been shown to cause aberrant activation of gene expression, increased cell proliferation, migration and increase the HER2 promoter activity and mRNA expression in vitro[31][32][33].

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)[34].

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[35]. 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[36].

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[37][38][39]. 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)[40]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[41][42]. 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[43].

TP53 oncomorphic mutations, including P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L, and R282W have been shown to predict resistance to platinum- and taxane-based chemotherapy in advanced serous ovarian carcinoma patients[44].

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BRCA1 Heterozygous deletion

Biological Impact

The breast cancer 1, early onset (BRCA1) gene encodes for a multifunctional ubiquitin E3 ligase, a tumor suppressor that has diverse cellular functions, including transcription, protein ubiquitination, cell cycle regulation and DNA damage response, with a particularly important role in homologous recombination, a DNA double-strand break repair pathway. BRCA1 germline mutations confer an increased lifetime risk of developing breast, ovarian and prostate cancer[45][46]. BRCA1 is also a Fanconi anemia susceptibility gene in FANCS, a rare Fanconi anemia subtype[47]. Prevalence of BRCA1 somatic mutation is in non-small cell lung cancer (NSCLC), pancreatic cancer, and colon cancer[48]. Deletion of BRCA1 gene has been correlated to significantly lower expression levels of the BRCA1 mRNA and reduced BRCA1 protein dosage, leading to a reduction in the efficiency of homologous recombination repair of DNA double-strand breaks[49][50][51]. Deleterious BRCA1 mutations have been detected in 8.5% of patients with triple-negative breast cancer (TNBC) (n=1824) unselected for family history and TNBC patients with mutations in BRCA1/2 and genes involved in homologous recombination (including PALB2, BARD1, RAD51D, RAD51C and BRIP1) were diagnosed at an earlier age and had higher-grade tumors than those without mutations[52].

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[53]; (2) in combination with bevacizumab as first-line maintenance treatment for patients who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status[54]; (3) maintenance treatment for patients with recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy[55][56]. In addition, olaparib has also been approved in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative breast cancer who have been treated with chemotherapy in either neoadjuvant, adjuvant, or metastatic setting[57]and germline BRCA-mutated metastatic pancreatic cancer[58]. 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(NCT02987543)[59].

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[60]. NCCN guidelines recommend rucaparib as recurrence therapy for patients with BRCA-mutated ovarian cancer, who have been treated with two or more lines of chemotherapies[61]. 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). Moreover, NCCN guidelines recommend rucaparib as maintenance therapy following prior platinum-based therapy for patients with metastatic pancreatic cancer harboring germline or somatic BRCA mutation.

The U.S. FDA has approved niraparib for the maintenance treatment of patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to first-line platinum-based chemotherapy and patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy[62][63]. Besides, NCCN guidelines recommend niraparib as maintenance therapy for ovarian cancer patients with BRCA mutations. The U.S. FDA also approved talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer[64].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[65]. 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[66]. 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[46]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[48].

Therapeutic and prognostic relevance

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FGFR1 Amplification

Biological Impact

The fibroblast growth factor receptor 1 (FGFR1) gene encodes a receptor tyrosine kinase that plays crucial roles in cellular proliferation, survival, migration and angiogenesis[67][68]. Several studies have demonstrated that FGFR1 amplification correlates with FGFR1 overexpression[69][70][71][72][73][74]. Overexpression of FGFR1 has also been shown to enhance both ligand-dependent, and independent activation of downstream signaling pathways such as the phosphoinositide-3 kinase (PI3K) and the extracellular signal-regulated kinase 1/2 (ERK1/2) cascades[75][76][77].

Amplification of FGFR1 has been associated with early relapse, and poor survival, specifically in ER+ breast cancer[75][78], and may be associated with progression of breast cancer from in situ-to-invasive transition[79].

FGFR1 amplifications have been reported in various types of cancer, including lung cancer[80], breast cancer[75], oral squamous cell carcinoma (OSCC)[81], prostate cancer[82], and esophageal cell carcinoma[83]. Besides, activating mutations (C381R and N330I) have been identified in giant cell lesions of the jaw[84].

Therapeutic and prognostic relevance

Non-selective TKI-targeting inhibitors such as pazopanib, regorafenib, and ponatinib are multi-kinase inhibitors with inhibitory activities towards FGFR1[85][86].FGFR1 mutations, amplifications, and fusions, have been determined as an inclusion criteria for a trial examining pemigatinib efficacies in advanced malignancies including solid tumor, endometrial carcinoma, gastric carcinoma, multiple myeloma, myeloproliferative neoplasm, squamous cell lung carcinoma, and urothelial carcinoma (FIGHT-101; NCT02393248).

To date, Erdafitinib (BALVERSATM), is the first and only pan-FGFR kinase inhibitor approved by U.S. FDA, for the treatment of patients with locally advanced or metastatic bladder cancer with FGFR3 mutations or FGFR2/FGFR3 fusions. Addition of the erdafitinib to palbociclib/fulvestrant induced complete responses of FGFR1-amplified/ER+ patient-derived-xenografts[87].

In a phase II clinical trial (TAPUR; NCT02693535), heavily pre-treated patients with metastatic breast cancer harboring FGFR1 amplification and/or mutation were treated with sunitinib, resulting in two partial responses (ORR=7%) and five stable diseases at 16+ weeks, with a disease control rate of 29% (Cancer Res (2021) 81 (13_Supplement): CT173.).

A case report of a patient with HR+, HER2- breast cancer harboring FGFR1 amplification responded well to pazopanib[88]. Another clinical study demonstrated that three patients with metastatic colorectal cancer achieved partial responses to regorafenib treatment, and all of them harbored FGFR1 amplification[89].

FGFR1 amplification has been selected as an inclusion criteria for the trial examining erdafitinib, ponatinib, regorafenib, sunitinib, and infigratinib efficacies in multiple tumor types (NCT03390504, NCT03473743, NCT03238196, NCT02272998, NCT02795156, NCT02693535, NCT04233567, NCT02150967).

Several small molecule FGFR inhibitors such as AZD-4547 and NVP-BGJ398 (Infigratinib) are under clinical evaluation, although mainly in the early stages of trials[90]. Infigratinib has shown antitumor activity and manageable safety profile in patients with a variety of solid tumors, including FGFR1-amplified squamous cell lung cancer (sqNSCLC) and FGFR3-mutant bladder/urothelial cancers[91]. Meanwhile, Dovitinib, a potent FGFR inhibitor, in combination with fulvestrant showed promising clinical activity in the FGF pathway-amplified postmenopausal patients with HR+, HER2- advanced breast cancer[92].

In ER-positive breast cancer, FGFR1 amplification has been implicated as an acquired mechanism of resistance to endocrine therapies[93], such as letrozole, 4-hydroxytamoxifen, and anastrozole-containing regimen[94][75][95]. Besides, FGFR1/2 amplification or activating mutations were detected in ctDNA from post-progression ER-positive breast cancer patients after the fulvestrant plus palbociclib treatment. According to the subgroup analysis from MONALEESA-2 clinical trial, ER-positive breast cancer patients with FGFR1 amplification exhibited a shorter progression-free survival when treated with letrozole plus ribociclib[87].

Meanwhile, in non-small cell lung carcinoma (NSCLC), FGFR1 is considered as an alternative acquired mechanism of resistance to EGFR tyrosine kinase inhibitors[96]. For example, upregulated FGFR1-FGF2 autocrine loop was identified in a gefitinib-resistant cell model[97], and focal FGFR1 amplification was observed in an NSCLC patient who developed resistance to osimertinib treatment[98].

The BOLERO-2 clinical trial (everolimus plus exemestane) suggested that FGFR1 amplification and CCND1 amplification may be correlated with lessened progression-free survival (PFS) with the mTOR inhibitor everolimus[99][100].

In preclinical study, thyroid cancer cell with FGFR1 amplification is sensitive to lenvatinib treatment[101][102]. Ponatinib, a multi-targeted tyrosine kinase inhibitor, demonstrated anti-proliferative activity in lung cancer, breast cancer, and Ewing's sarcoma cells overexpressing FGFR1[103][85][104].

FLCN Heterozygous deletion

Biological Impact

The FLCN gene encodes the tumor suppressor, Folliculin, a GTPase activating protein (GAP) for RagC/D GTPase proteins involved in amino acid sensing and signaling to mTORC1[105]. FLCN has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[106][107]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[108][109]. Germline mutation of the FLCN gene causes the Birt-Hogg-Dubé syndrome, a rare disorder that is characterized by benign hamartomatous skin lesions and an increased risk of pneumothorax and renal tumors[110].

Therapeutic and prognostic relevance

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTC) patients who had PI3K/mTOR/AKT alterations, including TSC2, FLCN or NF1, showed impressive progression-free survival (PFS) of 15.2 months after receiving everolimus[111]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[112].

KAT6A Amplification

Biological Impact

The KAT6A (Lysine Acetyltransferase 6A) gene encodes for a member of the MOZ, YBFR2, SAS2, TIP60 family of histone acetyltransferases. KAT6A is a HAT enzyme that controls fundamental cellular processes, including gene transcription and maintenance of normal hematopoietic stem cell[113]. Analysis of the genomic dataset from The Cancer Genome Atlas (TCGA) showed that KAT6A is amplified in at least 11% of breast tumors, at a higher frequency (22%) in the Luminal B subtype (HER2-)[114].

Therapeutic and prognostic relevance

A study of the TCGA data demonstrated a strong correlation between KAT6A copy number and mRNA expression levels. Besides, high level of KAT6A expression was associated with significant reduction in overall survival[115].

Preclinical study of gliomas showed that overexpression of KAT6A promotes PI3K/AKT signaling pathway activation by upregulating PIK3CA expression. Besides, the pan-PI3K inhibitor LY294002 is capable of abrogating the growth-promoting effect of KAT6A[116].

NF1 Heterozygous deletion

Biological Impact

The neurofibromin 1 (NF1) gene encodes a GTPase activating protein (GAP) which is an important negative regulator of the Ras cellular proliferation pathways[117][118][119][120]. Besides, NF1 also physically interacts with the N-terminal domain of focal adhesion kinase (FAK) and involves in the regulation of cell adhesion, growth, and other pathways[121][122]. NF1 is considered a classical haploinsufficient tumor suppressor gene with loss of one allele through inherited or acquired mutation may lead to reduced protein expression and is insufficient to execute normal cellular functions contributing to tumor development[123][124][125][126][127]. NF1 syndrome is a germline condition resulting in a predisposition to several types of cancer such as neurofibromas, melanoma, lung cancer, ovarian cancer, breast cancer,

colorectal cancer, hematological malignancies[128][129][130]. Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types[131], including myelodysplastic syndromes, melanomas, colon cancer[132], glioblastomas[133], lung cancer[134], ovarian cancer, and breast cancer[128].

Therapeutic and prognostic relevance

In April 2020, the U.S. FDA has approved selumetinib for pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN). A phase II trial (NCT02664935, NLMT) demonstrated that selumetinib in combination with docetaxel resulted in a confirmed ORR of 28.5% (4/14), durable clinical benefit (DCB) rate of 50% (7/14), and mPFS of 5.3 months in lung adenocarcinoma patients harboring NF1 loss[135]. NF1 loss has been determined as an inclusion criterion for the trials evaluating selumetinib efficacies in lung cancer (NCT02664935) and NF1-associated tumors (NCT03326388).

NF1 depletion has been associated with drug resistance to RAF and EGFR inhibitors, tamoxifen, and retinoic acid[131][136]. For example, loss of NF1 was identified in patients with lung adenocarcinomas or colorectal cancer who presented resistance to anti-EGFR treatment, including erlotinib, gefitinib, afatinib, and cetuximab, respectively[137][138][139]. Loss of NF1 in patients with BRAF-mutated melanomas was also suggested conferring resistance to BRAF inhibitors[140][141][142][143].

Notably, preclinical studies further revealed that the addition of a MEK inhibitor could restore the sensitivity to erlotinib[137]. Also, in a liquid biopsy-based ctDNA profiling study of HER2-positive metastatic gastric cancer, NF1 loss (either induced by mutation or deletion) was suggested as a novel mechanism contributes to trastuzumab resistance. The cell-based study also showed that the trastuzumab and lapatinib resistance could be overcome with a combination of HER2 and MEK/ERK inhibitors[144].A case study had reported that MEK inhibitor, trametinib, was effective in a treatment-refractory neurofibromatosis type I-associated glioblastoma[145]. Various preclinical data had also supported the activity of MEK and mTOR inhibitors in NF1-deficient tumors[146][147][148][149][150][151]. In an NGS-based study, patients harboring mutations in the mTOR pathway, including mTOR, TSC1, TSC2, NF1, PIK3CA, and PIK3CG responded to everolimus[152].

RAD51C Heterozygous deletion

Biological Impact

The RAD51C (RAD51 paralog C) encodes a member of the RAD51 protein family involved in the late phase of homologous recombination DNA repair. Germline mutations in RAD51C have been shown to confer increased susceptibility to ovarian cancer and head and neck squamous cell carcinoma (HNSCC)[153][154][155][156][157]. Amplification of RAD51C has been implicated in tumor progression[158][159]. RAD51C is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function[160].

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[59].

A preclinical study using gastric cancer xenograft model showed that RAD51C deficiency caused sensitivity to PARP inhibitor olaparib[161].

RAD51C loss of function mutation has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer[60][162]; talazoparib efficacy in HER2-negative breast cancer (NCT02401347) or prostate cancer (NCT03148795), and niraparib efficacies in pancreatic cancer (NCT03553004).

RB1 Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[163]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[164]. RB1 has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[165][166][167]. Deletion or inactivating mutation of RB1 is found in a number of tumors, including lung, prostate, bladder, breast cancers and sarcomas. RB1 mutations are found in approximately half of all retinoblastoma cases[168].

Therapeutic and prognostic relevance

A deleterious mutation in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response and better overall survival to cisplatin-based chemotherapy for muscle-invasive bladder cancer patients[169]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytoxan (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy[170].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[171][172].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[173]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[174].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[175][176]. Analyses of repeat biopsy samples from patients with EGFR-mutant adenocarcinoma that had transformed to the SCLC subtype have revealed that 100% of these patients have loss of RB1 and may be the alteration that induces this non-small-cell to small-cell transformation[172][177].

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[178]. 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[179]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)[180][181][182][183]. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer[184], colorectal cancer (CRC)[182][185][186], and less frequently seen in other cancers such as lung adenocarcinoma[187], head and neck cancer[188][189], and cutaneous squamous cell carcinoma[190].

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[138]. 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[191].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)[192][193]. 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[194].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis[195][196][197][198][199][200][201][202]. 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[203].

STK11 Heterozygous deletion

Biological Impact

The serine/threonine kinase 11 (STK11, also known as LKB1) gene encodes the multifunctional serine/threonine kinase, a tumor suppressor that functions as an inhibitor for the mTOR signaling pathway[204][205]. STK11 is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[206][207]. In the mouse model, loss of STK11 promotes aggressive endometrial and squamous cell carcinomas[208][209]. Mutations in STK11 have been found in lung, breast, cervical, testicular, and liver cancers, as well as malignant melanoma, pancreatic and biliary carcinoma[210]. Germline mutations in STK11 are found in 30-70% of Peutz-Jeghers syndrome[211].

Therapeutic and prognostic relevance

A clinical study in a pancreatic cancer patient with Peutz-Jeghers syndrome whose tumor harboring an STK11 D194E mutation coupled with the loss of heterozygosity of the other STK11 allele displayed partial response to the everolimus treatment[212]. In another clinical case study, an adrenocorticotropic pituitary carcinoma patient whose tumor bearing an STK11 inactivating mutation responded to a combination of everolimus and radiotherapy[213].

Preclinical data suggested that lung cancer cell lines with STK11 inactivating mutations may confer increased sensitivity to the MEK-1 and MEK-2 inhibitor, trametinib[214].

Inactivating mutations of STK11 was shown to be associated with resistance to immune checkpoint blockade in KRAS-mutant lung adenocarcinoma (LUAC) and NSCLC (DOI: 10.1200/JCO.2017.35.15_suppl.9016)[215][216][217]. It was proposed that loss of STK11 negatively impacts the number and function of tumor-infiltrating T cells (TILs) and PD-L1 expression on tumor cells and therefore results in an ineffective response to PD-1-targeting antibodies[218].

US FDA-APPROVED DRUG(S)

Afatinib (GILOTRIF)

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

- FDA Approval Summary of Afatinib (GILOTRIF)

LUX-Lung 8[219] NCT01523587	**Non-small cell lung carcinoma** (Approved on 2016/04/15)
	EGFR ex19del or L858R
	Afatinib vs. Erlotinib [PFS(M): 2.4 vs. 1.9]
LUX-Lung 3[220] NCT00949650	**Non-small cell lung carcinoma** (Approved on 2013/07/13)
	EGFR ex19del or L858R
	Afatinib vs. Pemetrexed + cisplatin [PFS(M): 11.1 vs. 6.9]

Binimetinib (MEKTOVI)

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

- FDA Approval Summary of Binimetinib (MEKTOVI)

MEKTOVI[221] NCT01909453	**Melanoma** (Approved on 2018/06/27)
	BRAF V600E/K
	Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3]

Cobimetinib (COTELLIC)

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

- FDA Approval Summary of Cobimetinib (COTELLIC)

coBRIM[222] NCT01689519	**Melanoma** (Approved on 2015/11/10)
	BRAF V600E/K
	Cobimetinib + vemurafenib vs. Placebo + vemurafenib [PFS(M): 12.3 vs. 7.2]

Dacomitinib (VIZIMPRO)

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

- FDA Approval Summary of Dacomitinib (VIZIMPRO)

ARCHER 1050[10] NCT01774721	**Non-small cell lung carcinoma** (Approved on 2018/09/27)
	EGFR ex19del or L858R
	Dacomitinib vs. Gefitinib [PFS(M): 14.7 vs. 9.2]

ACT Onco® + Report

Erdafitinib (BALVERSA)

Erdafitinib is a kinase inhibitor that binds to and inhibits enzymatic activity of FGFR1, FGFR2, FGFR3 and FGFR4 based on in vitro data. Erdafitinib also binds to RET, CSF1R, PDGFRA, PDGFRB, FLT4, KIT, and VEGFR2. Erdafitinib is developed and marketed by Janssen under the trade name BALVERSA.

- FDA Approval Summary of Erdafitinib (BALVERSA)

Study BLC2001 NCT02365597	**Bladder urothelial carcinoma** (Approved on 2019/04/12)
	FGFR2/3 fusion or FGFR3 mutation
	Erdafitinib [ORR(%): 32.2]

Erlotinib (TARCEVA)

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

- FDA Approval Summary of Erlotinib (TARCEVA)

RELAY NCT02411448	**Non-small cell lung carcinoma** (Approved on 2020/05/29)
	EGFR ex19del or L858R
	Erlotinib + ramucirumab vs. Erlotinib + placebo [PFS(M): 19.4 vs. 12.4]
EURTAC[223] NCT00446225	**Non-small cell lung carcinoma** (Approved on 2013/05/14)
	EGFR ex19del or L858R
	Erlotinib vs. Cisplatin + gemcitabine or cisplatin + docetaxel or carboplatin + gemcitabine or carboplatin + docetaxel [PFS(M): 10.4 vs. 5.2]
PA.3[224] 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[225] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[226] 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[227] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[228] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[229] 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[230] NCT01203917	**Non-small cell lung carcinoma** (Approved on 2015/07/13)
	EGFR ex19del or L858R
	Gefitinib [ORR(%): 50.0]

Infigratinib (TRUSELTIQ)

Infigratinib a kinase inhibitor. Infigratinib is developed and marketed by QED Therapeutics, Inc. under the trade name TRUSELTIQ.

- FDA Approval Summary of Infigratinib (TRUSELTIQ)

CBGJ398X2204 NCT02150967	**Cholangiocarcinoma** (Approved on 2021/05/28)
	FGFR2 fusion
	Infigratinib [ORR(%): 23.0, DOR(M): 5]

Lenvatinib (LENVIMA)

Lenvatinib is a multiple kinase inhibitor against the VEGFR1, VEGFR2 and VEGFR3. Lenvatinib is marketed by Eisai Inc. under the trade name LENVIMA.

- FDA Approval Summary of Lenvatinib (LENVIMA)

KEYNOTE-775 (Study 309) NCT03517449	**Endometrial carcinoma** (Approved on 2021/07/22)
	MSS/pMMR
	Pembrolizumab + lenvatinib vs. Investigator's choice of doxorubicin or paclitaxel [PFS(M): 6.6 vs. 3.8, OS(M): 17.4 vs. 12]
KEYNOTE-146 NCT02501096	**Endometrial carcinoma** (Approved on 2019/09/17)
	MSS/pMMR
	Pembrolizumab + lenvatinib [ORR(%): 38.3, DOR(M): NR]
REFLECT[231] NCT01761266	**Hepatocellular carcinoma** (Approved on 2018/08/16)
	-
	Lenvatinib vs. Sorafenib [OS(M): 13.6 vs. 12.3]

SELECT[232] NCT01136733	**Renal cell carcinoma** (Approved on 2016/05/13) - Lenvatinib+ everolimus vs. Everolimus [PFS(M): 14.6 vs. 5.5]
SELECT[233] NCT01321554	**Thyroid cancer** (Approved on 2015/02/13) - Lenvatinib vs. Placebo [PFS(M): 18.3 vs. 3.6]

Mobocertinib (EXKIVITY)

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

- FDA Approval Summary of Mobocertinib (EXKIVITY)

Study 101[234] NCT02716116	**Non-small cell lung carcinoma** (Approved on 2021/09/15) **EGFR ex20ins** Mobocertinib [ORR(%): 28.0, DOR(M): 17.5]

Niraparib (ZEJULA)

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

- FDA Approval Summary of Niraparib (ZEJULA)

PRIMA NCT02655016	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2020/04/29) - Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
NOVA[63] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27) - Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

Olaparib (LYNPARZA)

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

- FDA Approval Summary of Olaparib (LYNPARZA)

OlympiA NCT02032823	**Her2-negative high-risk early breast cancer** (Approved on 2022/03/11) **HER2-/gBRCA mutation** Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound[59] NCT02987543	**Prostate cancer** (Approved on 2020/05/19) **HRR genes mutation** Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1[54] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08) **HRD+** Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]

POLO[58] NCT02184195	**Pancreatic adenocarcinoma** (Approved on 2019/12/27)
	gBRCA mutation
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1[53] NCT01844986	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19)
	gBRCA mutation or sBRCA mutation
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD[57] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[235] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA mutation
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19[236] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

Osimertinib (TAGRISSO)

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

- FDA Approval Summary of Osimertinib (TAGRISSO)

ADAURA NCT02511106	**Non-small cell lung carcinoma** (Approved on 2020/12/18)
	EGFR ex19del or L858R
	Osimertinib vs. Placebo + adjuvant chemotherapy [DFS(M): NR vs. 19.6]
FLAURA[20] NCT02296125	**Non-small cell lung carcinoma** (Approved on 2018/04/18)
	EGFR ex19del or L858R
	Osimertinib vs. Gefitinib or erlotinib [PFS(M): 18.9 vs. 10.2]
AURA3[237] NCT02151981	**Non-small cell lung carcinoma** (Approved on 2017/03/30)
	EGFR T790M
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA[19] NCT01802632	**Non-small cell lung carcinoma** (Approved on 2015/11/13)
	EGFR T790M
	Osimertinib [ORR(%): 59.0]

Pazopanib (VOTRIENT)

Pazopanib is an oral, small molecule, multi-kinase inhibitor that targets receptor tyrosine kinase including vascular endothelial growth factor receptor-1, -2, -3 (VEGFR-1, -2, -3), platelet-derived growth factor receptor-α, -β (PDGFR-α, -β), c-kit, fibroblast growth factor-1 and -3 (FGFR-1, -3), thereby inhibiting angiogenesis. Pazopanib is developed and marketed by GlaxoSmithKline under the trade name VOTRIENT.

- FDA Approval Summary of Pazopanib (VOTRIENT)

PALETTE[238] NCT00753688	**Sarcoma** (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]

VEG105192[239] NCT00334282	**Renal cell carcinoma** (Approved on 2009/10/19) - Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]

Ponatinib (ICLUSIG)

Ponatinib is an oral, small molecule, multi-kinase inhibitor designed to inhibit the activity of the tyrosine kinase ABL, including the T315I mutated ABL as well. Ponatinib is developed and marketed by ARIAD under the trade name ICLUSIG.

- FDA Approval Summary of Ponatinib (ICLUSIG)

PACE[240] NCT01207440	**Chronic phase chronic myeloid leukemia** (Approved on 2014/03/12) - Ponatinib [MCyR(%): 55]
PACE[240] NCT01207440	**Accelerated phase chronic myeloid leukemia** (Approved on 2014/03/12) - Ponatinib [MaHR(%): 57]
PACE[240] NCT01207440	**Blast phase chronic myeloid leukemia** (Approved on 2014/03/12) - Ponatinib [MaHR(%): 31]
PACE[240] NCT01207440	**Philadelphia-positive acute lymphoblastic leukemia** (Approved on 2014/03/12) - Ponatinib [MaHR(%): 41]

Regorafenib (STIVARGA)

Regorafenib is a multi-kinase inhibitor which targets angiogenic, stromal and oncogenic receptor tyrosine kinases (RTKs). Regorafenib is developed and marketed by Bayer HealthCare Pharmaceuticals under the trade name STIVARGA.

- FDA Approval Summary of Regorafenib (STIVARGA)

RESORCE[241] NCT01774344	**Hepatocellular carcinoma, Hepatocellular carcinoma** (Approved on 2017/04/27) - Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]
GRID[242] NCT01271712	**Gastrointestinal stromal tumor** (Approved on 2013/02/25) - Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]
CORRECT[243] NCT01103323	**Colorectal cancer** (Approved on 2012/09/27) - Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

Rucaparib (RUBRACA)

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

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[60] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	-
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]

Selumetinib (KOSELUGO)

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

- FDA Approval Summary of Selumetinib (KOSELUGO)

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

Sunitinib (SUTENT)

Sunitinib is an oral, small molecule, multi-kinase inhibitor that targets receptor tyrosine kinase including platelet-derived growth factor receptor-α, -β (PDGFR-α, -β), vascular endothelial growth factor receptors-1, -2, -3 (VEGFR-1, -2, -3), c-kit, Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET), thereby inhibiting angiogenesis. Sunitinib is developed and marketed by Pfizer under the trade name SUTENT.

- FDA Approval Summary of Sunitinib (SUTENT)

[244][245][246] NCT00428597	**Pancreatic cancer** (Approved on 2011/05/20)
	-
	Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]
[247][248] NCT00083889	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib vs. Ifn-α [PFS(W): 47.3 vs. 22]
[249][250][248] NCT00077974	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 34.0]
[250][248] NCT00054886	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 36.5]
[251] NCT00075218	**Gastrointestinal stromal tumor** (Approved on 2006/01/26)
	-
	Sunitinib vs. Placebo [TTP(W): 27.3 vs. 6.4]

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

Temsirolimus (TORISEL)

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

- FDA Approval Summary of Temsirolimus (TORISEL)

[252] 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[253] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[254] 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[255] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[256] 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

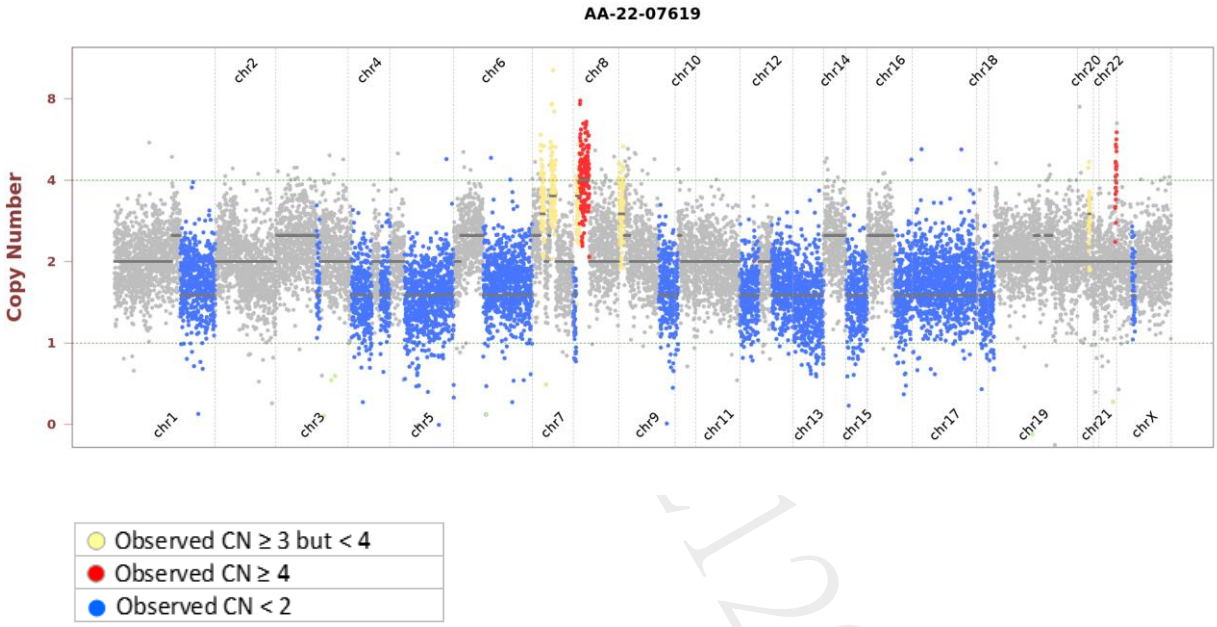
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
EGFR	L858R	21	c.2572_2573inv	NM_005228	COSM13553	50.4%	3966
EGFR	S768I	20	c.2303G>T	NM_005228	COSM6241	49.1%	709
TP53	R273C	8	c.817C>T	NM_000546	COSM10659	43.9%	1766

- 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
BMPR1A	Q117*	6	c.349C>T	NM_004329	-	51.0%	2118
CCNB2	V301G	7	c.902T>G	NM_004701	-	30.2%	1868
FANCA	G811D	26	c.2432G>A	NM_000135	-	31.4%	2542
FANCL	Splice region	-	c.541-3C>T	NM_018062	-	20.3%	408
FGF10	K103del	1	c.307_309del	NM_004465	-	8.3%	876
IDH2	R149W	4	c.445C>T	NM_002168	COSM6851659	61.5%	3989
KMT2C	N4686S	54	c.14057A>G	NM_170606	-	38.9%	2176
KMT2C	V2322A	36	c.6965T>C	NM_170606	COSM1581245	56.0%	1625
LRP1B	P3589S	69	c.10765C>T	NM_018557	-	30.4%	1118
MAP3K1	G616W	10	c.1846G>T	NM_005921	-	48.3%	1277
NFKB1	E600A	17	c.1799A>C	NM_003998	-	32.7%	428
PIK3R3	R383C	9	c.1147C>T	NM_003629	COSM170368	50.7%	899
PTCH1	A741V	14	c.2222C>T	NM_000264	-	43.4%	2656
TNFAIP3	G456V	7	c.1367G>T	NM_006290	COSM303677	46.9%	1085
USH2A	A3438T	52	c.10312G>A	NM_206933	-	40.6%	1973

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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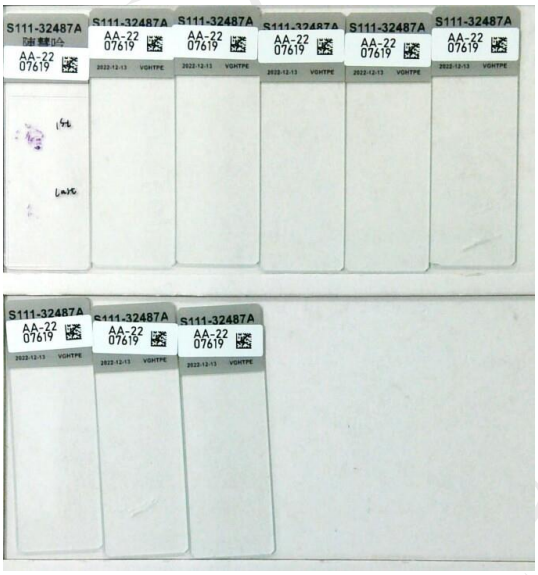
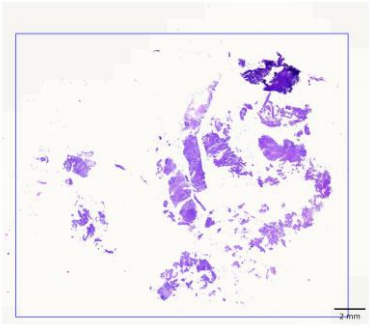
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: Aug 19, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11132487A
- Collection site: Adrenal gland
- Examined by: Dr. Yun-An Chen
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 70%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 70%
    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: N/A
- Manual macrodissection: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 1599x
- Target Base Coverage at 100x: 97%

RNA test

- Average unique RNA Start Sites per control GSP2: 119

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LIMITATIONS

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

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RNA test

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

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

DATABASE USED

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

Variant Analysis:
醫檢師張筑芃 博士
Chu-Yuan Chang Ph.D.
檢字第 020115 號

Sign Off
解剖病理專科醫師王業翰
Yeh-Han Wang M.D.
病解字第 000545 號

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GENE LIST

SNV & CNV

ABCB1*	ABCC2*	ABCG2*	ABL1	ABL2	ADAMTS1	ADAMTS13	ADAMTS15	ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9
ADAMTSL1	ADGRA2	ADH1C*	AKT1	AKT2	AKT3	ALDH1A1*	ALK	AMER1	APC	AR	ARAF
ARID1A	ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2	AXL
B2M	BAP1	BARD1	BCL10	BCL2*	BCL2L1	BCL2L2*	BCL6	BCL9	BCOR	BIRC2	BIRC3
BLM	BMPR1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2*	BTK	BUB1B	CALR
CANX	CARD11	CASP8	CBFB	CBL	CCNA1	CCNA	CCNB1	CCNB2	CCNB3	CCND1	CCND2
CCND3	CCNE1	CCNE2	CCNH	CD19	CD274	CD58	CD70*	CD79A	CD79B	CDC73	CDH1
CDK1	CDK12	CDK2	CDK4	CDK5	CDK6	CDK7	CDK8	CDK9	CDKN1A	CDKN1B	CDKN2A
CDKN2B	CDKN2C	CEBPA*	CHEK1	CHEK2	CIC	CREBBP	CRKL	CRLF2	CSF1R	CTCF	CTLA4
CTNNA1	CTNNB1	CUL3	CYLD	CYP1A1*	CYP2B6*	CYP2C19*	CYP2C8*	CYP2D6	CYP2E1*	CYP3A4*	CYP3A5*
DAXX	DCUN1D1	DDR2	DICER1	DNMT3A	DOT1L	DPYD	DTX1	E2F3	EGFR	EP300	EPCAM
EPHA2	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2	ERBB3	ERBB4	ERCC1	ERCC2	ERCC3	ERCC4
ERCC5	ERG	ESR1	ESR2	ETV1	ETV4	EZH2	FAM46C	FANCA	FANCC	FANCD2	FANCE
FANCF	FANCG	FANCL	FAS	FAT1	FBXW7	FCGR2B	FGF1*	FGF10	FGF14	FGF19*	FGF23
FGF3	FGF4*	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLT1	FLT3	FLT4
FOXL2*	FOXP1	FRG1	FUBP1	GATA1	GATA2	GATA3	GNA11	GNA13	GNAQ	GNAS	GREM1
GRIN2A	GSK3B	GSTP1*	GSTT1*	HGF	HIF1A	HIST1H1C*	HIST1H1E*	HNF1A	HR	HRAS*	HSP90AA1
HSP90AB1	HSPA4	HSPA5	IDH1	IDH2	IFNL3*	IGF1	IGF1R	IGF2	IKBKB	IKBKE	IKZF1
IL6	IL7R	INPP4B	INSR	IRF4	IRS1	IRS2*	JAK1	JAK2	JAK3	JUN*	KAT6A
KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT	KMT2A	KMT2C	KMT2D	KRAS	LCK	LIG1
LIG3	LMO1	LRP1B	LYN	MALT1	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAP3K7	MAPK1	MAPK3
MAX	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MPL	MRE11
MSH2	MSH6	MTHFR*	MTOR	MUC16	MUC4	MUC6	MUTYH	MYC	MYCL	MYCN	MYD88
NAT2*	NBN	NEFH	NF1	NF2	NFE2L2	NFKB1	NFKBIA	NKX2-1*	NOTCH1	NOTCH2	NOTCH3
NOTCH4	NPM1	NQO1*	NRAS	NSD1	NTRK1	NTRK2	NTRK3	PAK3	PALB2	PARP1	PAX5
PAX8	PBRM1	PDCD1	PDCD1LG2	PDGFRA	PDGFRB	PDIA3	PGF	PHOX2B*	PIK3C2B	PIK3C2G	PIK3C3
PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1	PIK3R2	PIK3R3	PIM1	PMS1	PMS2	POLB	POLD1
POLE	PPARG	PPP2R1A	PRDM1	PRKAR1A	PRKCA	PRKCB	PRKCG	PRKCI	PRKCQ	PRKDC	PRKN
PSMB8	PSMB9	PSME1	PSME2	PSME3	PTCH1	PTEN	PTGS2	PTPN11	PTPRD	PTPRT	RAC1
RAD50	RAD51	RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10	RECQL4
REL	RET	RHOA	RICTOR	RNF43	ROS1	RPPH1	RPTOR	RUNX1	RUNX1T1	RXRA	SDHA
SDHB	SDHC	SDHD	SERPINB3	SERPINB4	SETD2	SF3B1	SGK1	SH2D1A*	SLC19A1*	SLC22A2*	SLCO1B1*
SLCO1B3*	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1*	SOX2*	SOX9	SPEN	SPOP
SRC	STAG2	STAT3	STK11	SUFU	SYK	SYNE1	TAF1	TAP1	TAP2	TAPBP	TBX3
TEK	TERT	TET1	TET2	TGFBR2	TMSB4X*	TNF	TNFAIP3	TNFRSF14	TNFSF11	TOP1	TP53
TPMT*	TSC1	TSC2	TSHR	TYMS	U2AF1	UBE2A*	UBE2K	UBR5	UGT1A1*	USH2A	VDR*
VEGFA	VEGFB	VHL	WT1	XIAP	XPO1	XRCC2	ZNF217				

*Analysis of copy number alterations NOT available.

FUSION

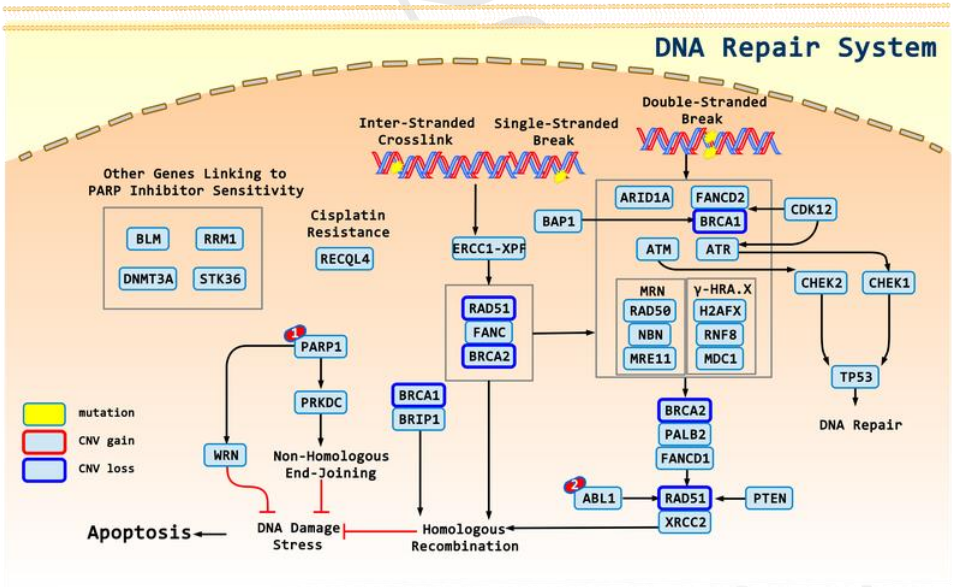
ALK	BRAF	EGFR	FGFR1	FGFR2	FGFR3	MET	NRG1	NTRK1	NTRK2	NTRK3	RET	ROS1

APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
NF1	Binimetinib, Cobimetinib, Trametinib, Selumetinib, Everolimus, Temsirolimus	**sensitive**
STK11	Binimetinib, Cobimetinib, Trametinib, Everolimus, Temsirolimus	**sensitive**
FLCN	Everolimus, Temsirolimus	**sensitive**
BRCA1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RAD51C	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RB1	Abemaciclib, Palbociclib, Ribociclib	**resistant**
NF1	Afatinib, Erlotinib, Gefitinib, Lapatinib, Cetuximab, Trastuzumab, Vemurafenib	**resistant**
SMAD4	Cetuximab	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib; 2: Ponatinib

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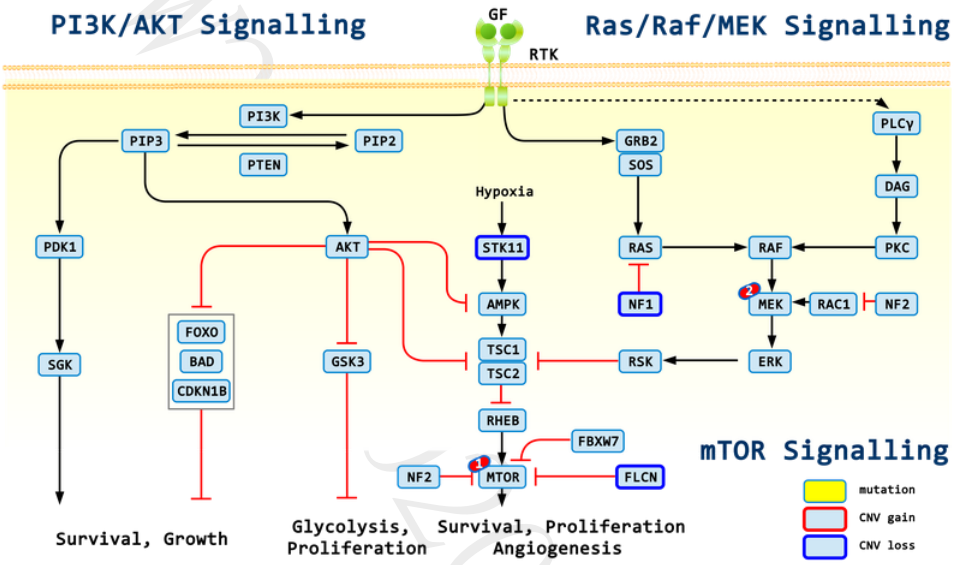
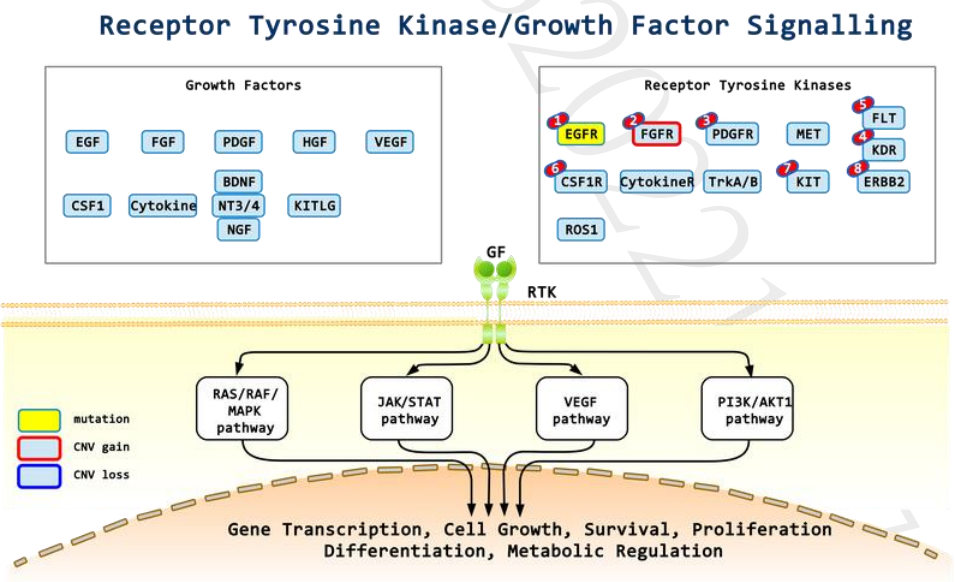


1: Everolimus, Temsirolimus; 2: Trametinib, Selumetinib, Binimetinib, Cobimetinib



1: Gefitinib, Erlotinib, Osimertinib, Dacomitinib, Afatinib, Mobocertinib; 2: Ponatinib, Lenvatinib, Erdafitinib, Infigratinib, Pazopanib; 3: Ponatinib, Pazopanib, Erdafitinib, Sunitinib, Regorafenib; 4: Ponatinib, Lenvatinib, Pazopanib, Erdafitinib, Sunitinib; 5: Lenvatinib, Pazopanib, Erdafitinib, Sunitinib, Ponatinib; 6: Sunitinib; 7: Ponatinib, Regorafenib, Lenvatinib, Pazopanib, Erdafitinib, Sunitinib; 8: 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。
本檢驗報告非經本公司許可，不得私自變造、塗改，或以任何方式作為廣告及其他宣傳之用途。
本公司於提供檢驗報告後，即已完成本次契約義務，後續之報告解釋、判讀及用藥、治療，應自行尋求相關專業醫師協助，若需將報告移件其他醫師，本人應取得該醫師同意並填寫移件申請書，主動告知行動基因，行動基因僅能配合該醫師意願與時間提供醫師解說。

醫療決策需由醫師決定

任何治療與用藥需經由醫師在考慮病患所有健康狀況相關資訊包含健檢、其他檢測報告和病患意願後，依照該地區醫療照護標準由醫師獨立判斷。醫師不應僅依據單一報告結果(例如本檢測或本報告書內容)做決策。

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

藥物潛在臨床效益(或缺乏潛在臨床效益)的實證證據是依據至少一篇臨床療效個案報告或臨床前試驗做為評估。本公司盡力提供適時及準確之資料，但由於醫學科技之發展日新月異，本公司不就本報告提供的資料是否為準確、適宜或最新作保證。

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