施貴英
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ACT Onco® + Report

PATIENT		
Identifier: 施貴英		Patient ID: 47678411
Date of Birth: Sep 05, 1969		Gender: Female
Diagnosis: Gastric cancer		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11168422S	Collection site: Uterus	Type: FFPE tissue
Date received: Oct 18, 2022	Lab ID: AA-22-06266	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	
TMB-High	Dostarlimab-gxly, Nivolumab, Pembrolizumab	-	Atezolizumab, Avelumab, Cemiplimab-rwlc, Durvalumab, Ipilimumab, Tremelimumab

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
EGFR Amplification	Afatinib, Cetuximab, Erlotinib, Gefitinib, Necitumumab, Osimertinib, Panitumumab	-
IL6 Amplification	-	Erlotinib, Gefitinib, Trastuzumab

Note:

- The above summary tables present genomic variants and biomarkers based on the three-tiered approach proposed by US FDA for reporting tumor profiling NGS testing. "Variants/biomarkers with evidence of clinical significance" refers to mutations that are widely recognized as standard-of-care biomarkers (FDA level 2/AMP tier 1). "Variants/biomarkers with potential clinical significance" refers to mutations that are not included in the standard of care but are informational for clinicians, which are commonly biomarkers used as inclusion 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
PBRM1	K277*	77.9%
TP53	G244S	74.5%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr17	*BRCA1, NF1, RAD51C*	Heterozygous deletion	1
Chr22	*CHEK2, NF2*	Heterozygous deletion	1
Chr4	*FBXW7*	Heterozygous deletion	1
Chr7	*CARD11, EGFR, IL6*	Amplification	7

- 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)	7.5 muts/Mb (TMB-High)
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 64% 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 3B		
EGFR Amplification	Afatinib, Cetuximab, Erlotinib, Gefitinib, Necitumumab, Osimertinib, Panitumumab	**sensitive**
Level 4		
IL6 Amplification	Erlotinib, Gefitinib, Trastuzumab	**resistant**

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

Genomic Alterations	Approved for Patient's Cancer Type	Approved for Other Cancer Type
TMB-High (7.5 muts/Mb)	Dostarlimab-gxly, Nivolumab, Pembrolizumab	Atezolizumab, Avelumab, Cemiplimab-rwlc, Durvalumab, Ipilimumab, Tremelimumab

TMB, Tumor Mutational Burden; Muts/Mb, mutations per megabase

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
Not detected	

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

CHEMOTHERAPIES

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

HORMONAL THERAPIES

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

OTHERS

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AG	Irinotecan-based regimens	Level 1B
Clinical Interpretation: Patients with the AG 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 GG genotype, or a decreased risk of diarrhea and neutropenia compared to patients with the AA 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

Tumor mutational burden (TMB): High (7.5 mutations / Mb)

High TMB is a potential biomarker that predicts response to immune checkpoint inhibitors, including anti-CTLA-4 and anti-PD-1 in melanoma, anti-PD-1 in non-small cell lung cancer (NSCLC) and colorectal cancer (CRC), cutaneous squamous cell carcinoma (CSCC), and anti-PD-L1 therapy in bladder cancer[1][2][3][3][4][5][6][7][8]. Of note, the U.S. FDA has approved tumor mutational burden-high (TMB-H) as a predictive biomarker for pembrolizumab in adult and pediatric patients with unresectable or metastatic solid tumor who have progressed following prior treatment and have no satisfactory alternative treatment options. CRCs with defects in mismatch-repair (MMR) are more susceptible to PD-1 blockade[6]. High mutation load is associated with shorter overall survival in lung cancer and breast cancer patients[9][10].

PBRM1 K277*

Biological Impact

The PBRM1 gene encodes the protein BAF180 tumor suppressor, which is a component of the nucleosome-remodeling complex switching defective/sucrose non-fermenting (SWI/SNF)[11]. Loss of PBRM1 activity is associated with chromosomal instability[12]. PBRM1, BAP1 and SETD2 are three frequently altered tumor suppressor genes on chromosome 3p in a region that is deleted in over 90% of clear cell renal cell carcinoma (ccRCC)[13][14].

K277* mutation results in a premature truncation of the PBRM1 protein at amino acid 277 (UniProtKB). This mutation is predicted to lead to a loss of PBRM1 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

Biallelic loss or loss-of-function mutation of PBRM1 has been shown to correlate with clinical benefit in clear cell renal cell carcinoma (ccRCC), melanoma, lung cancer, bladder cancer, and head and neck squamous carcinoma (HNSCC) patients treated with immune checkpoint inhibitors[15][16].

Decreased expression of PBRM1 has been shown to predict unfavorable clinical outcome in patients with ccRCC[17].

TP53 G244S

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[18]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[19].

TP53 G244S is a missense mutation lies within the DNA-binding domain (DBD) of the p53 protein (UniProtKB). G244S is demonstrated as a loss-of-function mutation with decreased transcriptional activity in vitro[20].

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)[21].

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[22]. 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[23].

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[24][25][26]. 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)[27]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[28][29]. 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[30].

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[31][32]. BRCA1 is also a Fanconi anemia susceptibility gene in FANCS, a rare Fanconi anemia subtype[33]. Prevalence of BRCA1 somatic mutation is in non-small cell lung cancer (NSCLC), pancreatic cancer, and colon cancer[34]. 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[35][36][37]. 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[38].

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[39]; (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[40]; (3) maintenance treatment for patients with recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy[41][42]. 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[43]and germline BRCA-mutated metastatic pancreatic cancer[44]. 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)[45].

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[46]. 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[47]. 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[48][49]. 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[50].

CARD11 Amplification

Biological Impact

CARD11 (caspase recruitment domain 11) gene encodes a cytoplasmic scaffold protein of the CARD11/BCL10/MALT1 (CBM) complex which plays essential roles in regulating apoptosis and NF-κB activation in response to upstream stimuli[51][52]. CARD11 gain-of-function mutations are frequently detected in human diffuse large B-cell lymphoma (DLBCL)[53]and cutaneous squamous cell carcinoma[54]. Moreover, CARD11 gene amplification has been observed in a significant proportion of DLBCL[55]. Biochemical assays revealed that enforced expression of CARD11/BCL10/MALT1 is essential for transformation of B-cell and survival of DLBCL cell[56].

Therapeutic and prognostic relevance

Retrospective studies have shown that high CARD11 expression or CARD11 gene amplification was associated with poor survival in diffuse large B cell lymphoma (DLBCL)[57][55].

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[58]. 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[59][60]. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers[61][62][63][64][65].

Therapeutic and prognostic relevance

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate (NCT02987543)[45].

In a phase II trial (TBCRC 048; NCT03344965), 7 metastatic breast cancer patients harboring only germline mutations in CHEK2 were not responded to olaparib treatment (SD: n=3, PD: n=4)[66]. Furthermore, in another phase II trial (TRITON2; NCT02952534), 12 mCRPC patients harboring CHEK2 alteration had limited response to rucaparib treatment. One patient with co-occurring ATM alteration had a radiographic partial response (n=1/9 evaluable patients). The prostate-specific antigen response rate was 16.7% (n=2/12), and the 6-month clinical benefit rate was 37.5% (n=3/8)[67].

In addition, CHEK2 has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in advanced solid tumors (NCT03297606; CAPTUR trial), rucaparib efficacy in ovarian cancer (NCT01968213)[46], and prostate cancer (NCT02952534, NCT03533946)[67], niraparib efficacy in metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma (NCT03840967), melanoma (NCT03925350), pancreatic cancer (NCT03553004, NCT03601923), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative solid tumors (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

EGFR Amplification

Biological Impact

The EGFR gene encodes for the Epidermal Growth Factor Receptor, a receptor tyrosine kinase which binds to its ligands, including Epidermal Growth Factor (EGF) and Transforming Growth Factor-alpha (TGF-alpha), activates downstream signaling pathways, including the canonical oncogenic MAPK and PI3K/AKT/mTOR signaling cascades[68]. 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[69]. 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[70]. On the other hand, in the brain and colorectal cancers, the most prevalent EGFR alteration is copy number amplification that results in receptor overexpression[71].

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

Increased EGFR copy number is associated with tumor response to panitumumab, an EGFR-targeted antibody, in colorectal cancer patients, based on data from a phase III study[73]. A recent Phase II trial of cetuximab (another approved anti-EGFR antibody) oxaliplatin/leucovorin/5-fluorouracil therapy in first-line setting also demonstrated an association between higher EGFR copy number and better overall survival in gastric cancer patients[74]. The addition of cetuximab to chemotherapy reduced the risk of death by 44% for advanced squamous non–small cell lung cancer (NSCLC) patients with EGFR-amplified tumor, according to clinical trial findings presented at the 2015 World Conference on Lung Cancer. Preclinical data of gastric cancer (GC)-derived xenograft also showed that EGFR amplification or overexpression is associated with response to cetuximab[75]. Besides, a phase III study of necitumumab showed squamous cell lung cancer patients with EGFR amplification had improved overall survival (14.8 versus 7.6 months, p = 0.033) (NCT00981058)[76].

Increased EGFR copy number has been shown to be associated with better response and survival in gefitinib or erlotinib treatment for NSCLC[77][78][79][80][81][82], esophageal cancer[83], and mucinous urethral adenocarcinoma[84]. Concurrent amplification of EGFR and ERBB2 is associated with response to afatinib in patients with trastuzumab-refractory esophagogastric cancer[85]. However, dacomitinib has been reported with a limited single-agent activity in recurrent glioblastoma with EGFR amplification in a phase II trial[86]. EGFR amplification has been determined as an inclusion criterion for the trials evaluating erlotinib, afatinib, and osimertinib efficacy in PDAC with co-expressing EGFR and c-Met (NCT03213626), glioblastoma (NCT03732352), urothelial tract carcinoma (NCT02780687), and brain cancer (NCT02423525).

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[87][88], c-Jun[89], cyclin E[90], Notch family members[91][92], Aurora-A[93], mTOR[94], KLF5[95], and MCL-1[96]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation[97]. 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[95][96][98].

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)[99][100]. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor[94].

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[101][102][103][104].

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[105][103].

IL6 Amplification

Biological Impact

The Interleukin 6 (IL6) gene encodes a key cytokine produced by various cell types including monocytes, macrophages, fibroblasts, keratinocytes, endothelial cells, B cells, T cells, and also several tumor cells during infection and inflammation. It is a pleiotropic cytokine that regulates the immune response, tissue regeneration, and promoting tumor growth and survival[106][107][108][109]. In cancers, IL6 is implicated in inflammation to malignant transformation by activating the NF-κB pathway, and the induction of an epithelial-mesenchymal transition (EMT)[110].

Therapeutic and prognostic relevance

Preclinical studies showed that IL6 is sufficient to modify the sensitivity of EGFR mutant non-small cell lung cancer (NSCLC) cell line to erlotinib treatment[111]. Inhibition of IL6 signaling by metformin can potentiate gefitinib-induced antitumor activity[112].

A preclinical study showed that increased expression of the cytokines IL6 was associated with trastuzumab resistance in HER2+ breast cancer[113].

Amplification of IL6 was associated with shortened survival in glioblastoma patients[114].

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[115][116][117][118]. 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[119][120]. 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[121][122][123][124][125]. 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[126][127][128]. Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types[129], including myelodysplastic syndromes, melanomas, colon cancer[130], glioblastomas[131], lung cancer[132], ovarian cancer, and breast cancer[126].

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[133]. 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[129][134]. 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[135][136][137]. Loss of NF1 in patients with BRAF-mutated melanomas was also suggested conferring resistance to BRAF inhibitors[138][139][140][141].

Notably, preclinical studies further revealed that the addition of a MEK inhibitor could restore the sensitivity to erlotinib[135]. 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[142].A case study had reported that MEK inhibitor, trametinib, was effective in a treatment-refractory neurofibromatosis type I-associated glioblastoma[143]. Various preclinical data had also supported the activity of MEK and mTOR inhibitors in NF1-deficient tumors[144][145][146][147][148][149]. In an NGS-based study, patients harboring mutations in the mTOR pathway, including mTOR, TSC1, TSC2, NF1, PIK3CA, and PIK3CG responded to everolimus[150].

NF2 Heterozygous deletion

Biological Impact

The neurofibromin (NF2) gene encodes the protein Merlin, a tumor suppressor that functions as a negative regulator of the PI3K/AKT/mTOR pathway[151][152][153]. NF2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[154]. Inactivation germline mutations in the NF2 are associated with the hereditary neurofibromatosis type 2, a disorder characterized by the growth of noncancerous tumors in the nervous system[151][155]. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas[156], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers[157].

Therapeutic and prognostic relevance

Genomic alterations with activating effects on the mTOR signaling pathway have been identified to confer sensitivity to everolimus across multiple cancer types[158][159][160][150]. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer and urothelial carcinoma[161][162], both harboring NF2 truncating mutations. Preclinical evidence has shown the efficacy of MEK1/2 inhibitor selumetinib in KRAS-mutant thyroid cancer model with NF2 loss[163].

Analysis of afatinib-plus-cetuximab-resistant biopsy specimens revealed a loss-of-function alteration in genes that modulate mTOR signaling pathway, including NF2 and TSC1[164].

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)[165][166][167][168][169]. Amplification of RAD51C has been implicated in tumor progression[170][171]. RAD51C is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function[172].

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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[45].

A preclinical study using gastric cancer xenograft model showed that RAD51C deficiency caused sensitivity to PARP inhibitor olaparib[173].

RAD51C loss of function mutation has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer[46][67]; talazoparib efficacy in HER2-negative breast cancer (NCT02401347) or prostate cancer (NCT03148795), and niraparib efficacies in pancreatic cancer (NCT03553004).

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[174] 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[175] 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]

Atezolizumab (TECENTRIQ)

Atezolizumab is a humanized, anti-programmed cell death-ligand 1 (PD-L1) monoclonal antibody of the IgG1 isotype, which can lead to the reactivation of immune cells that might recognize and attack tumor cells. Atezolizumab is developed and marketed by Genentech/Roche under the trade name TECENTRIQ.

- FDA Approval Summary of Atezolizumab (TECENTRIQ)

IMpower010 NCT02486718	**Non-small cell lung carcinoma** (Approved on 2021/10/15) **PD-L1** Atezolizumab vs. Best supportive care (BSC) [DFS (PD-L1 TC≥1%)(M): not reached vs. 35.3]
IMbrave150 NCT03434379	**Hepatocellular carcinoma** (Approved on 2020/05/29) - Atezolizumab plus bevacizumab vs. Sorafenib [PFS(M): 6.8 vs. 4.3, OS(M): NR vs. 13.2]
IMpower133[176] NCT02763579	**Small cell lung cancer** (Approved on 2019/03/18) - Atezolizumab plus carboplatin and etoposide vs. Carboplatin and etoposide [PFS(M): 5.2 vs. 4.3, OS(M): 12.3 vs. 10.3]
OAK[177] NCT02008227	**Non-small cell lung carcinoma** (Approved on 2016/10/18) **PD-L1** Atezolizumab vs. Docetaxel [OS(M): 13.8 vs. 9.6]
POPLAR[178] NCT01903993	**Non-small cell lung carcinoma** (Approved on 2016/10/18) **PD-L1** Atezolizumab vs. Docetaxel [OS(M): 12.6 vs. 9.7]
IMvigor210[179] NCT02951767	**Bladder urothelial carcinoma** (Approved on 2016/05/18) - Atezolizumab [ORR (PD-L1 < 5%)(%): 21.8, ORR (PD-L1 ≥ 5%)(%): 28.1]

Avelumab (BAVENCIO)

Avelumab is fully human monoclonal programmed death ligand-1 (PD-L1) antibody, belonging to the group of immune checkpoint blockade cancer therapies. Avelumab is developed and marketed by Merck KGaA and Pfizer under the trade name BAVENCIO.

- FDA Approval Summary of Avelumab (BAVENCIO)

JAVELIN Renal 101[180] NCT02684006	**Renal cell carcinoma** (Approved on 2019/05/14)
	-
	Avelumab plus axitinib vs. Sunitinib [ORR(%): 51.4 vs. 25.7, PFS(M): 13.8 vs. 8.4]
JAVELIN Solid Tumor NCT01772004	**Bladder urothelial carcinoma** (Approved on 2017/05/09)
	-
	Avelumab [ORR(13W)(%): 13.6, ORR(6M)(%): 16.1]
JAVELIN Merkel 200[181] NCT02155647	**Merkel cell carcinoma** (Approved on 2017/03/23)
	-
	Avelumab [ORR(%): 33.0, DOR(M): 2.8 to 23.3+]

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

Cemiplimab-rwlc (LIBTAYO)

Cemiplimab-rwlc is a recombinant human IgG4 monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2. Cemiplimab-rwlc is developed and marketed by Sanofi and Regeneron under the trade name LIBTAYO.

- FDA Approval Summary of Cemiplimab-rwlc (LIBTAYO)

Study 1624 NCT03088540	**Non-small lung cancer** (Approved on 2021/02/22)
	PD-L1
	Cemiplimab-rwlc vs. Platinum-based chemotherapy [PFS(M): 6.2 vs. 5.6, OS(M): 22.1 vs. 14.3]
Study 1620 NCT03132636	**Locally advanced basal cell carcinoma (labcc)** (Approved on 2021/02/09)
	-
	Cemiplimab-rwlc [ORR(%): 29.0, DOR(M): NR]
Study 1620 NCT03132636	**Metastatic basal cell carcinoma (mbcc)** (Approved on 2021/02/09)
	-
	Cemiplimab-rwlc [ORR(%): 21.0, DOR(M): NR]
Study 1423, Study 1540 [7] NCT02383212, NCT02760498	**cutaneous squamous cell carcinoma** (Approved on 2018/09/28)
	-
	Cemiplimab-rwlc [ORR(%): 47.2]

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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)

BEACON CRC[183] NCT02928224	**Colorectal cancer** (Approved on 2020/04/08)
	BRAF V600E
	Encorafenib in combination with cetuximab vs. Irinotecan or folfiri with cetuximab [OS(M): 8.4 vs. 5.4]
CRYSTAL[184] NCT00154102	**Colorectal cancer** (Approved on 2012/07/06)
	KRAS Wild-type/EGFR-expressing
	Cetuximab + 5-fluorouracil + folinic acid + irinotecan vs. 5-fluorouracil + folinic acid + irinotecan [PFS(M): 8.9 vs. 8.1]
EXTREME[185] 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]
[186] NCT00004227	**Head and neck cancer** (Approved on 2006/03/01)
	-
	Cetuximab + radiation vs. Radiation [OS(M): 49 vs. 29.3]
[187] NCT00063141	**Colorectal cancer** (Approved on 2004/02/12)
	KRAS Wild-type/EGFR-expressing
	Cetuximab + irinotecan vs. Irinotecan [DOR(M): 5.7 vs. 4.2]

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

Dostarlimab-gxly (JEMPERLI)

Dostarlimab-gxly is a programmed death receptor-1 (PD-1)-blocking antibody. Dostarlimab-gxly is developed and marketed by GlaxoSmithKline LLC under the trade name JEMPERLI.

- FDA Approval Summary of Dostarlimab-gxly (JEMPERLI)

GARNET NCT02715284	**Cancer** (Approved on 2021/08/17)
	dMMR
	Dostarlimab [ORR(%): 41.6, DoR(M): 34.7]

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GARNET (Cohort A) NCT02715284	**Endometrial carcinoma** (Approved on 2021/04/22)
	dMMR
	Dostarlimab-gxly [ORR(%): 42.3, DOR(M): NR]

Durvalumab (IMFINZI)

Durvalumab is a programmed death ligand-1 (PD-L1)-blocking antibody. Durvalumab is developed and marketed by AstraZeneca under the trade name IMFINZI.

- FDA Approval Summary of Durvalumab (IMFINZI)

HIMALAYA NCT03298451	**Hepatocellular carcinoma** (Approved on 2022/10/21)
	-
	Durvalumab + tremelimumab vs. Durvalumab + sorafenib [OS(M): 16.4 vs. 13.9]
TOPAZ-1 NCT03875235	**Biliary tract cancer** (Approved on 2022/09/02)
	-
	Durvalumab [OS(M): 12.8 vs. 11.5]
CASPIAN[189] NCT03043872	**Extensive-stage small cell lung cancer** (Approved on 2020/03/27)
	-
	Durvalumab + etoposide + carboplatin or durvalumab + etoposide + cisplatin vs. Etoposide + carboplatin or etoposide + cisplatin [OS(M): 13 vs. 10.3]
PACIFIC[190] NCT02125461	**Non-small cell lung carcinoma** (Approved on 2018/02/16)
	-
	Durvalumab vs. Placebo [PFS(M): 16.8 vs. 5.6]

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[191] 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[192] NCT00026338	**Pancreatic cancer** (Approved on 2005/11/02)
	-
	Gemcitabine vs. Placebo [OS(M): 6.4 vs. 6]

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Everolimus (AFINITOR)

Everolimus, a derivative of sirolimus, works as an inhibitor of mammalian target of rapamycin complex 1 (mTORC1) and blocks mTORC1-mediated downstream signals for cell growth, proliferation, and survival. Everolimus is developed and marketed by Novartis under the trade name AFINITOR.

- FDA Approval Summary of Everolimus (AFINITOR)

RADIANT-4[193] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[194] 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[195] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[196] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[197] 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[198] NCT01203917	**Non-small cell lung carcinoma** (Approved on 2015/07/13)
	EGFR ex19del or L858R
	Gefitinib [ORR(%): 50.0]

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Ipilimumab (YERVOY)

Ipilimumab is a fully human monoclonal antibody against the cytotoxic T-lymphocyte associated protein 4 (CTLA-4), an immune checkpoint protein receptor, to reactivate the immune responses. Ipilimumab is developed by Medarex and Bristol-Myers Squibb, and marketed by the latter under the trade name YERVOY.

- FDA Approval Summary of Ipilimumab (YERVOY)

CHECKMATE-648 NCT03143153	**Esophagus squamous cell carcinoma** (Approved on 2022/05/27)
	-
	Nivolumab and ipilimumab vs. Chemotherapy [OS(M): 12.8 vs. 10.7]
CHECKMATE-743 NCT02899299	**Pleural mesothelioma** (Approved on 2020/10/02)
	-
	Nivolumab + ipilimumab vs. Pemetrexed + cisplatin [OS(M): 18.1 vs. 14.1]
CHECKMATE-9LA NCT03215706	**Non-small cell lung carcinoma** (Approved on 2020/05/26)
	-
	Nivolumab + ipilimumab + platinum-doublet chemotherapy vs. Platinum-doublet chemotherapy [OS(M): 14.1 vs. 10.7]
CHECKMATE-227 NCT02477826	**Non-small cell lung carcinoma** (Approved on 2020/05/15)
	PD-L1
	Nivolumab + ipilimumab vs. Platinum-doublet chemotherapy [OS(M): 17.1 vs. 14.9]
CHECKMATE-040 NCT01658878	**Hepatocellular carcinoma** (Approved on 2020/03/10)
	-
	Nivolumab + ipilimumab [ORR(%): 33.0]
CHECKMATE-142[199] NCT02060188	**Colorectal cancer** (Approved on 2018/07/10)
	MSI-H or dMMR
	Ipilimumab plus nivolumab vs. Nivolumab [ORR(%): 49.0 vs. 32.0]
CHECKMATE-214[200] NCT02231749	**Renal cell carcinoma** (Approved on 2018/04/16)
	-
	Nivolumab plus ipilimumab vs. Sunitinib [OS(M): 67.1 vs. 55.5]
EORTC 18071[201] NCT00636168	**Melanoma** (Approved on 2015/10/28)
	-
	Ipilimumab vs. Placebo [RFS(M): 26 vs. 17]
MDX010-20[202] NCT00094653	**Melanoma** (Approved on 2011/03/25)
	-
	Ipilimumab vs. Peptide vaccine with incomplete freund's adjuvant (gp100) [OS(M): 10 vs. 6]

Necitumumab (PORTRAZZA)

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

- FDA Approval Summary of Necitumumab (PORTRAZZA)

SQUIRE[203] NCT00981058	**Lung squamous cell carcinoma** (Approved on 2015/11/14)
	-
	Gemcitabine + cisplatin vs. Placebo [OS(M): 11.5 vs. 9.9]

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[49] 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]

Nivolumab (OPDIVO)

Nivolumab is a programmed death receptor-1 (PD-1)-blocking antibody. Nivolumab is developed and marketed by Bristol-Myers Squibb under the trade name OPDIVO.

- FDA Approval Summary of Nivolumab (OPDIVO)

CHECKMATE-648 NCT03143153	**Esophagus squamous cell carcinoma** (Approved on 2022/05/27)
	-
	Nivolumab and ipilimumab vs. Chemotherapy [OS(M): 12.8 vs. 10.7]
CHECKMATE-648 NCT03143153	**Esophagus squamous cell carcinoma** (Approved on 2022/05/27)
	-
	Nivolumab, fluorouracil, and cisplatin vs. Chemotherapy [OS(M): 13.2 vs. 10.7]
CHECKMATE-816 NCT02998528	**Non-small cell lung cancer (NSCLC)** (Approved on 2022/03/04)
	-
	Nivolumab plus platinum-doublet chemotherapy vs. Platinum-chemotherapy [EFS(M): 31.6 vs. 20.8]
CHECKMATE-274 NCT02632409	**Bladder urothelial carcinoma** (Approved on 2021/08/19)
	-
	Nivolumab [DFS (all randomized)(M): 20.8 vs. 10.8, DFS (PD-L1 ≥ 1%)(M): NR vs. 8.4]
CHECKMATE-577 NCT02743494	**Gastroesophageal junction adenocarcinoma** (Approved on 2021/05/20)
	-
	Nivolumab vs. Placebo every 4 weeks beginning at week 17 for up to one year of treatment [DFS(M): 22.4 vs. 11]
CHECKMATE-649 NCT02872116	**Gastroesophageal junction adenocarcinoma, Gastric adenocarcinoma** (Approved on 2021/04/16)
	-
	Nivolumab + chemotherapy (XELOX or FOLFOX) vs. Chemotherapy (XELOX or FOLFOX) [PFS(M): 7.7 vs. 6, OS(M): 14.4 vs. 11.1]
CHECKMATE-9ER NCT03141177	**Renal cell carcinoma** (Approved on 2021/01/22)
	-
	Nivolumab + cabozantinib vs. Sunitinib [ORR(%): 55.7 vs. 27.1, PFS(M): 16.6 vs. 8.3, OS(M): NR vs. NR]

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CHECKMATE-743 NCT02899299	**Pleural mesothelioma** (Approved on 2020/10/02)
	-
	Nivolumab + ipilimumab vs. Pemetrexed + cisplatin [OS(M): 18.1 vs. 14.1]
CHECKMATE-9LA NCT03215706	**Non-small cell lung carcinoma** (Approved on 2020/05/26)
	-
	Nivolumab + ipilimumab + platinum-doublet chemotherapy vs. Platinum-doublet chemotherapy [OS(M): 14.1 vs. 10.7]
CHECKMATE-227 NCT02477826	**Non-small cell lung carcinoma** (Approved on 2020/05/15)
	PD-L1
	Nivolumab + ipilimumab vs. Platinum-doublet chemotherapy [OS(M): 17.1 vs. 14.9]
CheckMate 040 NCT01658878	**Hepatocellular carcinoma** (Approved on 2020/03/10)
	-
	Nivolumab + ipilimumab [ORR(%): 33.0]
CheckMate 142 NCT02060188	**Colorectal cancer** (Approved on 2017/07/31)
	MSI-H or dMMR
	Nivolumab [ORR(%): 32.0]
CheckMate 141[204] NCT02105636	**Squamous cell carcinoma of the head and neck cancer** (Approved on 2016/11/10)
	-
	Nivolumab vs. Investigator's choice of cetuximab, methotrexate or docetaxel [OS(M): 7.5 vs. 5.1]
CheckMate 205[205] NCT02181738	**Hodgkin's lymphoma** (Approved on 2016/05/17)
	-
	Nivolumab [ORR(%): 66.0]
CheckMate 039[206] NCT01592370	**Hodgkin's lymphoma** (Approved on 2016/05/17)
	-
	Nivolumab [ORR(%): 66.0]
CheckMate 067[207] NCT01844505	**Melanoma** (Approved on 2016/01/23)
	-
	Ipilimumab vs. Placebo [PFS(M): 11.5 vs. 2.9]
CheckMate 066[208] NCT01721772	**Melanoma** (Approved on 2015/11/24)
	BRAF V600 wild-type
	Nivolumab vs. Dacarbazine [OS(M): Not Reached vs. 10.8]
CheckMate 025[209] NCT01668784	**Renal cell carcinoma** (Approved on 2015/11/23)
	-
	Nivolumab vs. Everolimus [OS(M): 25 vs. 19.6]
CheckMate 057[210] NCT01673867	**Non-small cell lung carcinoma** (Approved on 2015/10/09)
	-
	Nivolumab vs. Docetaxel [OS(M): 12.2 vs. 9.4]
CheckMate 017[211] NCT01642004	**Non-small cell lung carcinoma** (Approved on 2015/03/04)
	-
	Nivolumab vs. Docetaxel [OS(M): 9.2 vs. 6]
CheckMate 037[212] NCT01721746	**Melanoma** (Approved on 2014/12/22)
	-
	Nivolumab vs. Dacarbazine or carboplatin + paclitaxel [ORR(%): 32.0]

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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[45] 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[40] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[44] 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[39] 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[43] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[213] 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[214] 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[215] 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[216] NCT02151981	**Non-small cell lung carcinoma** (Approved on 2017/03/30)
	EGFR T790M
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA[217] NCT01802632	**Non-small cell lung carcinoma** (Approved on 2015/11/13)
	EGFR T790M
	Osimertinib [ORR(%): 59.0]

Panitumumab (VECTIBIX)

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

- FDA Approval Summary of Panitumumab (VECTIBIX)

Study 20050203[218] NCT01412957	**Colorectal cancer** (Approved on 2017/06/29)
	KRAS Wild-type
	Panitumumab + BSC vs. BSC [OS(M): 10 vs. 6.9]
PRIME[219] NCT00364013	**Colorectal cancer** (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab + FOLFOX vs. FOLFOX [PFS(M): 9.6 vs. 8]
ASPECCT[220] NCT01001377	**Colorectal cancer** (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab vs. Cetuximab [OS(M): 10.4 vs. 10]
Study 20080763[221] NCT00113763	**Colorectal cancer** (Approved on 2006/09/27)
	KRAS Wild-type
	Panitumumab + BSC vs. BSC [PFS(M): 3.2 vs. 2]

Pembrolizumab (KEYTRUDA)

Pembrolizumab is a programmed death receptor-1 (PD-1)-blocking antibody. Pembrolizumab is developed and marketed by Merck under the trade name KEYTRUDA.

- FDA Approval Summary of Pembrolizumab (KEYTRUDA)

KEYNOTE-158 NCT02628067	**Endometrial carcinoma** (Approved on 2022/03/21)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 46.0, DoR(M): NR]
KEYNOTE-716 NCT03553836	**Melanoma** (Approved on 2021/12/03)
	-
	Pembrolizumab [RFS(M): Not reached vs. Not reached]
KEYNOTE-564 NCT03142334	**Renal cell carcinoma** (Approved on 2021/11/17)
	-
	Pembrolizumab vs. Placebo [DFS(M): NR vs. NR, OS(M): NR vs. NR]

KEYNOTE-826 NCT03635567	**Cervical cancer** (Approved on 2021/10/13)
	PD-L1
	Pembrolizumab + paclitaxel + cisplatin with or without bevacizumab vs. Placebo + paclitaxel + cisplatin with or without bevacizumab [OS (PD-L1, CPS ≥1)(M): Not reached vs. 16.3, PFS(M): 10.4 vs. 8.2]
CLEAR (Study 307/KEYNOTE-581) NCT02811861	**renal cell carcinoma** (Approved on 2021/08/11)
	-
	Pembrolizumab + lenvatinib vs. Sunitinib [PFS(M): 23.9 vs. 9.2, OS(M): NR vs. NR, ORR(%): 71.0 vs. 36.0]
KEYNOTE-522 NCT03036488	**Triple-receptor negative breast cancer** (Approved on 2021/07/26)
	-
	Pembrolizumab + chemotherapy as neoadjuvant treatment vs. Placebo in combination with chemotherapy [pCR(%): 63.0 vs. 56.0, EFS(): 123 vs. 93]
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-811 NCT03615326	**Gastroesophageal junction adenocarcinoma** (Approved on 2021/05/05)
	HER2+
	Pembrolizumab 200 mg every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin vs. Placebo every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin [ORR(%): 74.0 vs. 52.0, DOR(M): 10.6 vs. 9.5]
KEYNOTE-590 NCT03189719	**Esophageal cancer, Gastroesophageal junction adenocarcinoma** (Approved on 2021/03/22)
	-
	Pembrolizumab in combination with cisplatin and fluorouracil vs. Placebo with cisplatin and fluorouracil [PFS(M): 6.3 vs. 5.8, OS(M): 12.4 vs. 9.8]
KEYNOTE-355 NCT02819518	**Triple-receptor negative breast cancer** (Approved on 2020/11/13)
	PD-L1
	Pembrolizumab + paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin vs. Placebo + paclitaxel protein-bound, or paclitaxel, or gemcitabine plus carboplatin [PFS(M): 9.7 vs. 5.6]
KEYNOTE-204 NCT02684292	**Hodgkin's lymphoma** (Approved on 2020/10/14)
	-
	Pembrolizumab vs. Brentuximab vedotin [PFS(M): 13.2 vs. 8.3]
KEYNOTE-158 NCT02628067	**Cancer** (Approved on 2020/06/17)
	TMB-H
	Pembrolizumab (TMB-H) vs. Pembrolizumab (non-TMB-H) [ORR(%): 29.0 vs. 6.0]
KEYNOTE-146 NCT02501096	**Endometrial carcinoma** (Approved on 2019/09/17)
	MSS/pMMR
	Pembrolizumab + lenvatinib [ORR(%): 38.3, DOR(M): NR]
KEYNOTE-426[222] NCT02853331	**Renal cell carcinoma** (Approved on 2019/04/19)
	-
	Pembrolizumab + axitinib vs. Sunitinib [ORR(%): 59.3 vs. 35.7, PFS(M): 15.1 vs. 11.1]
KEYNOTE-017[223] NCT02267603	**Merkel cell carcinoma** (Approved on 2018/12/19)
	-
	Pembrolizumab [ORR(%): 56.0]

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KEYNOTE-224[224] NCT02702414	**Hepatocellular carcinoma** (Approved on 2018/11/09)
	-
	Pembrolizumab [ORR(%): 17.0]
KEYNOTE-407[225] NCT02775435	**Squamous non-small cell lung carcinoma** (Approved on 2018/10/30)
	-
	Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. Carboplatin + paclitaxel/nab-paclitaxel [ORR(%): 58.0 vs. 35.0, PFS(M): 6.4 vs. 4.8]
KEYNOTE-189[225] NCT02578680	**Nonsquamous non-small cell lung carcinoma** (Approved on 2018/08/20)
	-
	Pembrolizumab + pemetrexed + platinum vs. Pemetrexed + platinum [PFS(M): 8.8 vs. 4.9, OS(M): NR vs. 11.3]
KEYNOTE-158 NCT02628067	**Cervical cancer** (Approved on 2018/06/13)
	-
	Pembrolizumab [ORR(%): 14.3]
KEYNOTE-170 NCT02576990	**Mediastinal large b-cell lymphoma** (Approved on 2018/06/13)
	-
	Pembrolizumab [ORR(%): 45.0]
KEYNOTE-059 NCT02335411	**Gastric adenocarcinoma, Gastroesophageal junction adenocarcinoma** (Approved on 2017/09/22)
	-
	Pembrolizumab [ORR(%): 13.3]
KEYNOTE-164 NCT02460198	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-016[6] NCT01876511	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-158 NCT02628067	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-028[226][227] NCT02054806	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-012[228][229][230][231] NCT01848834	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-045[232] NCT02256436	**Urinary bladder urothelial carcinoma** (Approved on 2017/05/18)
	-
	Pembrolizumab vs. Chemotherapy [ORR(%): 21.0 vs. 11.0]
KEYNOTE-052 NCT02335424	**Urinary bladder urothelial carcinoma** (Approved on 2017/05/18)
	-
	Pembrolizumab [ORR(%): 29.0]
KEYNOTE-087[233] NCT02453594	**Hodgkin's lymphoma** (Approved on 2017/03/14)
	-
	Pembrolizumab [ORR(%): 69.0]
KEYNOTE-024[234] NCT02142738	**Non-small cell lung carcinoma** (Approved on 2016/10/24)
	PD-L1
	Pembrolizumab vs. Chemotherapy [PFS(M): 10.3 vs. 6]

KEYNOTE-012[229] NCT01848834	**Head and neck squamous cell carcinoma** (Approved on 2016/08/05)
	-
	Pembrolizumab [ORR(%): 16.0]
KEYNOTE-006[235] NCT01866319	**Melanoma** (Approved on 2015/12/18)
	-
	Pembrolizumab vs. Ipilimumab (3mg/kg every 3 weeks) [OS(M): NR vs. 16]
KEYNOTE-010[236] NCT01905657	**Non-small cell lung carcinoma** (Approved on 2015/10/02)
	PD-L1
	Pembrolizumab [OS(M): 10.4 vs. 8.5]
KEYNOTE-002[237] NCT01704287	**Melanoma** (Approved on 2014/09/24)
	-
	Pembrolizumab vs. Chemotherapy [PFS(M): 2.9 vs. 2.7]

Rucaparib (RUBRACA)

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

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[46] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	-
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]

Selumetinib (KOSELUGO)

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

- FDA Approval Summary of Selumetinib (KOSELUGO)

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

Talazoparib (TALZENNA)

Talazoparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2. Talazoparib is developed and marketed by Pfizer under the trade name TALZENNA.

- FDA Approval Summary of Talazoparib (TALZENNA)

EMBRACA[50] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	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)

[238] 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[239] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[240] 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[241] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[242] NCT01245062	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

Tremelimumab (IMJUDO)

Tremelimumab a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody.Tremelimumab is developed and marketed by AstraZeneca under the trade name IMJUDO.

- FDA Approval Summary of Tremelimumab (IMJUDO)

HIMALAYA NCT03298451	**Hepatocellular carcinoma** (Approved on 2022/10/21)
	-
	Tremelimumab + durvalumab vs. Tremelimumab + sorafenib [OS(M): 16.4 vs. 13.9]

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.

IMMUNE CHECKPOINT INHIBITORS

Pembrolizumab

(NCT02628067, Phase 2)

In this study, participants with multiple types of advanced (unresectable and/or metastatic) solid tumors who have progressed on standard of care therapy will be treated with pembrolizumab (MK-3475).

- Contact

Name: Toll Free Number
Phone: 1-888-577-8839
Email: NA

- Location

Status: Recruiting Country: Taiwan City: Taipei Name: Merck Sharp & Dohme (I.A.) Corp.	

Atezolizumab

(NCT04589845, Phase 2)

TAPISTRY is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in participants with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations or who are tumor mutational burden (TMB)-high as identified by a validated next-generation sequencing (NGS) assay. Participants with solid tumors will be treated with a drug or drug regimen tailored to their NGS assay results at screening. Participants will be assigned to the appropriate cohort based on their genetic alteration(s). Treatment will be assigned on the basis of relevant oncogenotype, will have cohort-specific inclusion/exclusion criteria, and, unless otherwise specified, will continue until disease progression, loss of clinical benefit, unacceptable toxicity, participant or physician decision to discontinue, or death, whichever occurs first.

- Contact

Name: Reference Study ID Number: BO41932 https://forpatients.roche.com/
Phone: 888-662-6728 (U.S. and Canada)
Email: Global-Roche-Genentech-Trials@gene.com

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- Location

Status: Recruiting Country: Taiwan City: Tainan Name: National Cheng Kung University Hospital; Oncology	Status: Recruiting Country: Taiwan City: Taipei City Name: Taipei Veterans General Hospital; Department of Oncology
Status: Recruiting Country: Taiwan City: Taoyuan County Name: Chang Gung Memorial Hospital-Linkou; Dept of Oncology	Status: Active, not recruiting Country: Taiwan City: Zhongzheng Dist. Name: National Taiwan University Hospital; Oncology

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

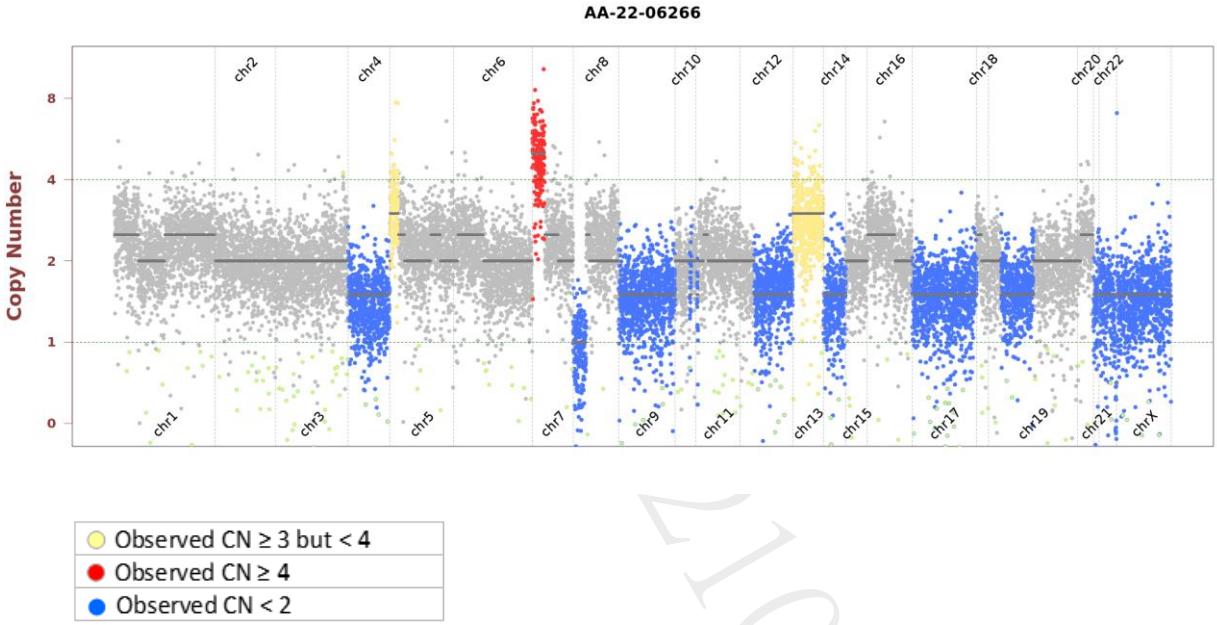
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
PBRM1	K277*	9	c.829A>T	NM_018313	COSM1424551	77.9%	399
TP53	G244S	7	c.730G>A	NM_000546	COSM10941	74.5%	993

- 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
ADAMTS16	P966L	19	c.2897C>T	NM_139056	-	5.2%	388
BIRC3	V386M	6	c.1156G>A	NM_001165	-	8.7%	508
CCNB2	A215T	6	c.643G>A	NM_004701	-	41.5%	537
EPHA5	V61M	1	c.181G>A	NM_001281765	-	12.7%	300
ERBB2	A270S	7	c.808G>T	NM_004448	COSM5574359	14.2%	648
FANCF	P117T	1	c.349C>A	NM_022725	-	10.7%	672
GATA2	V70F	2	c.208G>T	NM_032638	-	10.7%	531
KMT2C	R380L	8	c.1139G>T	NM_170606	COSM225885	5.0%	3990
LIG3	R942Q	20	c.2825G>A	NM_013975	-	100.0%	674
NOTCH2	R1260H	23	c.3779G>A	NM_024408	COSM6947255	49.7%	1198
NTRK1	T400A	10	c.1198A>G	NM_002529	-	48.5%	749
NTRK3	V687D	16	c.2060T>A	NM_001012338	-	50.8%	994
PRKCI	D204G	7	c.611A>G	NM_002740	-	8.6%	677
RHOA	F39C	2	c.116T>G	NM_001664	COSM4118494	76.7%	954
RICTOR	R910H	28	c.2729G>A	NM_001285439	COSM4430879	34.2%	427
RXRA	N114S	3	c.341A>G	NM_002957	-	51.2%	320
SYNE1	A8116V	135	c.24347C>T	NM_182961	COSM3859206	40.1%	1222
SYNE1	V2217I	45	c.6649G>A	NM_182961	COSM3020939	61.8%	1845
TAF1	Splice region	-	c.1663-8A>G	NM_138923	-	87.6%	653
TOP1	H38L	3	c.113A>T	NM_003286	-	49.9%	980
TSC1	S457R	14	c.1369A>C	NM_000368	-	50.6%	387
UBR5	Splice region	36	c.4824C>T	NM_015902	-	93.1%	347

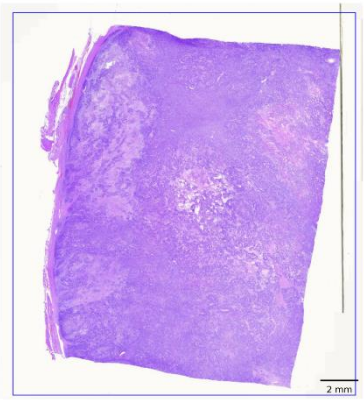
Note:

- 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.

ACTOnco®+ Report

TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Sep 23, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11168422S
- Collection site: Uterus
- Examined by: Dr. Chien-Ta Chiang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 75%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 75%
    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: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 625x
- Target Base Coverage at 100x: 92%

RNA test

- Average unique RNA Start Sites per control GSP2: 157

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

ACT Onco® + Report

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).

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

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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:
醫檢師黃靖婷 博士
Ching-Ting Huang Ph.D.
檢字第 016511 號

CT Huang

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

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GENE LIST

SNV & CNV

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

*Analysis of copy number alterations NOT available.

FUSION

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

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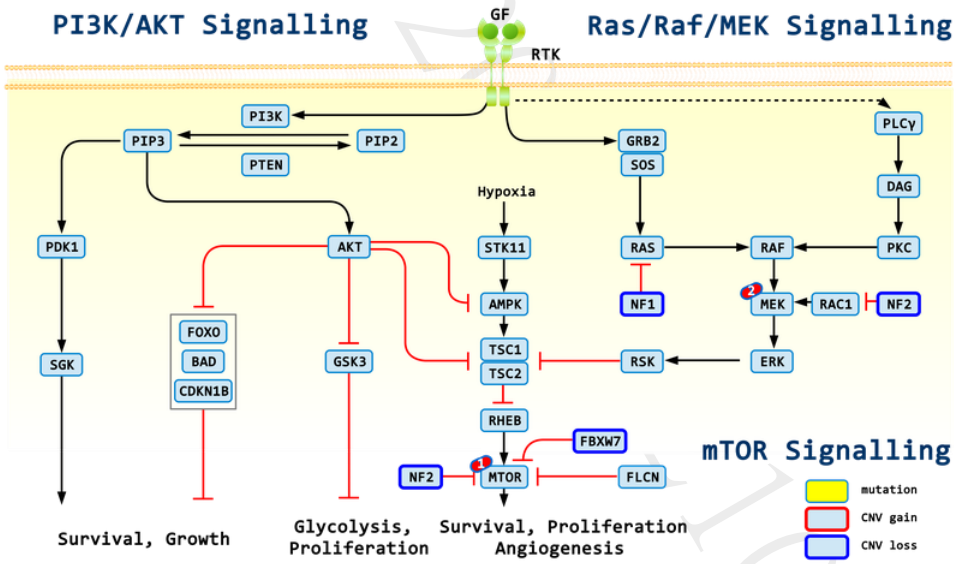
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
NF1	Binimetinib, Cobimetinib, Everolimus, Selumetinib, Temsirolimus, Trametinib	**sensitive**
FBXW7	Everolimus, Temsirolimus	**sensitive**
NF2	Everolimus, Temsirolimus	**sensitive**
BRCA1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RAD51C	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
NF1	Afatinib, Cetuximab, Erlotinib, Gefitinib, Lapatinib, Trastuzumab, Vemurafenib	**resistant**
FBXW7	Gefitinib, Regorafenib	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



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

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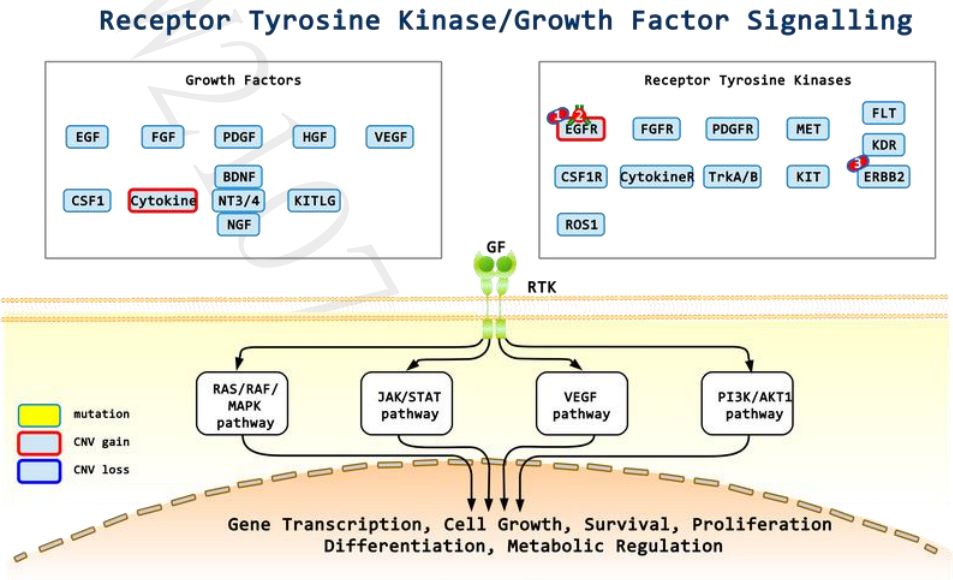
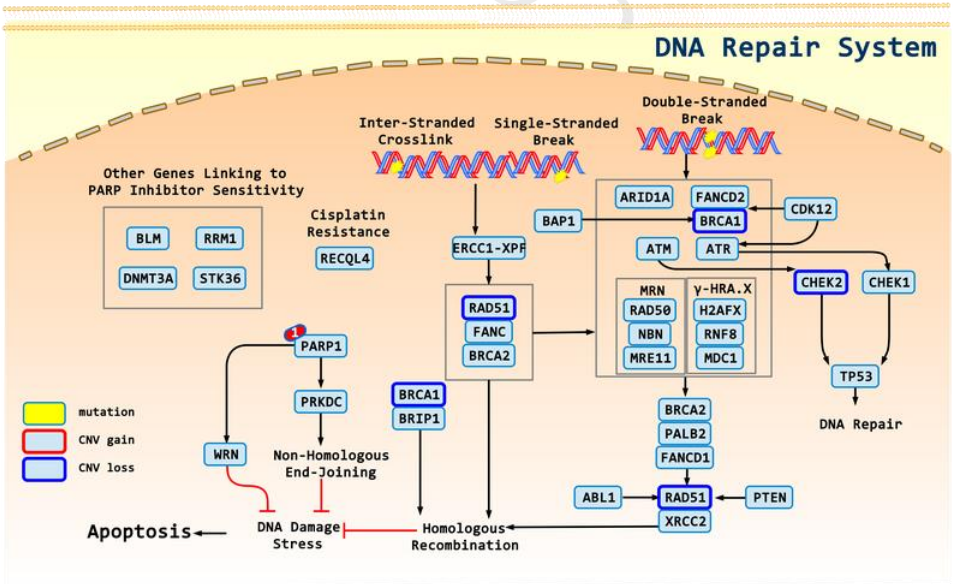


1: Gefitinib, Erlotinib, Afatinib, Osimertinib; 2: Cetuximab, Panitumumab, Necitumumab; 3: Afatinib



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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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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