楊坤仁
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ACT Onco® + Report

PATIENT		
Identifier: 楊坤仁		Patient ID: 45525266
Date of Birth: Sep 08, 1964		Gender: Male
Diagnosis: Colon cancer		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11171573	Collection site: Liver	Type: FFPE tissue
Date received: Nov 22, 2022	Lab ID: AA-22-07099	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, Ipilimumab, Nivolumab, Pembrolizumab	-	Atezolizumab, Avelumab, Cemiplimab-rwlc, Durvalumab, Tremelimumab
KRAS, NRAS, BRAF Wild type	Cetuximab, Panitumumab	-	-

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
EGFR S492R	Afatinib, Osimertinib, Panitumumab	Cetuximab
LYN Amplification	Dasatinib	-

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
APC	R232*	63.5%
APC	L2452*	5.6%
EGFR	S492R (c.1474A>C)	27.8%
EGFR	S492R (c.1476C>G)	3.0%
JAK2	R443*	30.6%
TP53	G266R	73.5%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr17	*FLCN*	Heterozygous deletion	1
Chr18	*SMAD4*	Heterozygous deletion	1
Chr5	*RAD50*	Heterozygous deletion	1
Chr20	*AURKA, GNAS, SRC, TOP1, ZNF217*	Amplification	6
Chr8	*KAT6A, LYN, MYC, NBN, RECQL4*	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)	9.4 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 68% 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		
KRAS, NRAS, BRAF Wild type	Cetuximab, Panitumumab	**sensitive**
Level 4		
EGFR S492R	Afatinib, Osimertinib, Panitumumab	**sensitive**
LYN Amplification	Dasatinib	**sensitive**
EGFR S492R	Cetuximab	**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 (9.4 muts/Mb)	Dostarlimab-gxly, Ipilimumab, Nivolumab, Pembrolizumab	Atezolizumab, Avelumab, Cemiplimab-rwlc, Durvalumab, Tremelimumab

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

- 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
MYC Amplification	FAC CMF and P-FEC regimens	**Sensitive**	Clinical	Breast cancer
	Platinum-based regimens	**Sensitive**	Clinical	Ovarian cancer
ZNF217 Amplification	Doxorubicin	**Less sensitive**	Clinical	Breast cancer
	Fluorouracil Mitomycin	**Less sensitive**	Clinical	Breast cancer
AURKA Amplification	Taxane-based regimens	**Less sensitive**	Clinical	Breast cancer
	Platinum-based regimens	**Resistant**	Clinical	Ovarian carcinoma

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
AURKA Amplification	Tamoxifen	**Resistant**	Clinical	Estrogen-receptor positive breast cancer
ZNF217 Amplification	Tamoxifen	**Resistant**	Clinical	Estrogen-receptor positive breast cancer

OTHERS

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

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

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VARIANT INTERPRETATION

Tumor mutational burden (TMB): High (9.4 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].

APC L2452*, R232*

Biological Impact

APC (adenomatous polyposis coli) gene encodes a negative regulator of the WNT/β-catenin signaling pathway. It binds to β-catenin, leading to its degradation and subsequently inhibits transcriptional activation[11]. APC is also associated with cell migration and adhesion, apoptosis, and DNA repair[12][13]. APC mutations are commonly observed in colorectal cancer and are also reported in lung, breast, prostate, uterine, skin, bladder, stomach and head and neck cancers (cBioPortal, MSKCC, April 2015). L2452* mutation results in a premature truncation of the APC protein at amino acid 2452 (UniProtKB). This mutation is predicted to lead to a loss of APC function, despite not having characterized in the literature. R232* mutation results in a premature truncation of the APC protein at amino acid 232 (UniProtKB). This mutation is predicted to lead to a loss of APC function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

A study of colorectal cancer patients (n= 468) indicated that MSS tumors without any APC mutation carry a worse prognosis than single APC mutation tumors. However, tumors with two APC, KRAS, and TP53 mutations confer the poorest survival among all the subgroups examined[14].

EGFR S492R

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[15]. 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[16]. 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[17]. On the other hand, in the brain and colorectal cancers, the most prevalent EGFR alteration is copy number amplification that results in receptor overexpression[18].

EGFR S492R lies within the extracellular domain of the EGFR protein (UniProt.org). S492R was annotated as activating mutation[19]. However, overexpression of EGFR S492 mutant in colorectal cancer cells (CRCs) resulted in similar cell growth when compared with wild-type[20]. Therefore, its effect on EGFR protein function remains inconclusive. EGFR S492R was initially found in patients with wild-type KRAS exon two metastatic colorectal cancer (mCRC) who were treated with cetuximab or panitumumab (less frequent)[21](DOI: 10.1200/jco.2015.33.3_suppl.740)[22].

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

EGFR S492R mutant has been suggested as an acquired mutation during cetuximab treatment and conferring resistance to cetuximab but not to panitumumab. In vitro and in vivo data showed that cells or patients harboring the EGFR S492R mutant displayed resistance to cetuximab but still responded to treatment with panitumumab[24][22]. In a preclinical study, transformed cells expressing EGFR S492R were sensitive to panitumumab, afatinib, and osimertinib treatment, but resistant to cetuximab treatment in vitro[25][26].

JAK2 R443*

Biological Impact

The JAK2 (Janus kinase 2) gene encodes one of four members of the JAK family of non-receptor tyrosine kinases and is involved in the interferon-alpha/beta/gamma pathway and is a member of the JAK/STAT signaling pathway[27][28]. JAK2 signaling is required for the normal production of blood cells such as erythrocytes and thrombocytes[29].

R443* mutation results in a premature truncation of the JAK2 protein at amino acid 443 (UniProtKB). This mutation is predicted to lead to a loss of JAK2 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

Biallelic inactivation of JAK1/2 was associated with primary and acquired resistance to PD-1 blockade due to defects in the pathways involved in interferon-receptor signaling[30][31].

TP53 G266R

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[32]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[33].

TP53 G266R mutation is located in the DNA-binding domain of the p53 protein (UniProtKB) and has been shown to have decreased transactivation activity in vitro[34][35].

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)[36].

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[37]. 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[38].

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[39][40][41]. 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)[42]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[43][44]. 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[45].

AURKA Amplification

Biological Impact

The Aurora kinase A (AURKA) gene encodes a serine/threonine kinase involved in the regulation of cell cycle and maintenance of genomic integrity[46]. AURKA gene amplification is commonly observed in a wide range of human cancers, including breast cancer[47], ovarian cancer[48], gastric cancer[49], colorectal[50], esophageal cancer[51], bladder cancer[52]and leukemia[53].

Therapeutic and prognostic relevance

Small-molecule inhibitors targeting AURKA (and the related Aurora B and C kinases) are currently studied in clinical trials. A Phase II study of the investigational aurora kinase A inhibitor, alisertib, demonstrated activity and safety in patients with breast and small-cell lung cancer (SCLC)[54].

Elevated AURKA activity was associated with poor response to taxane-based regimens in breast cancer patients[55], and platinum resistance in high-grade serous ovarian carcinoma patients[56].

Estrogen receptor positive breast cancer patients with increased AURKA expression were resistant to tamoxifen treatment and had a poorer prognosis[57][58].

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[59]. 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[60][61]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[62][63]. 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[64].

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[65]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[66].

GNAS Amplification

Biological Impact

GNAS encodes the alpha subunit of the stimulator G protein (Gs-alpha), a guanine-nucleotide binding protein (G protein) involved in the hormonal regulation of adenylate cyclase[67]. The common mutations of GNAS have been identified in tumors, including R201C, R201H, and Q227R, resulting in constitutive activation of Gs-alpha and its effector adenylate cyclase, leading to increased cAMP accumulation, and constitutive cAMP signaling, associated with excessive proliferation and tumor development[68][69][67]. GNAS activation may affect downstream MAPK and Wnt signaling pathway, suggesting activating mutation of GNAS can modify cell growth and may be oncogenic[69].

Amplification of GNAS is commonly observed in ER-positive breast cancers[70], which is associated with increased MAPK/ERK signaling and tumor pathogenesis[70].

Therapeutic and prognostic relevance

Low expression of GNAS has been reported to associate with both poor overall survival and PSA progression-free survival in prostate cancer[71].

GNAS amplification was significantly associated with poor progression-free survival (PFS) in advanced epithelial ovarian cancer patients receiving standard therapy and poor survival in intrahepatic cholangiocarcinoma[72][73].

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[74]. 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-)[75].

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[76].

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[77].

LYN Amplification

Biological Impact

The LYN Proto-Oncogene, Src Family Tyrosine Kinase (LYN) gene encodes a non-receptor tyrosine protein kinase of the Src family (SFK)[78]. LYN plays an important role in the regulation of immune responses, hematopoiesis, signal transduction of growth factors and cytokines and is activated in the cellular response to DNA damage and genotoxic agents[79][80][81][82]. LYN has been described to promote tumor growth, invasion, epithelial to mesenchymal transition (EMT) and ERK signaling in different cancer types[83][84][85]. Amplification of LYN has been identified in prostate cancer, breast cancer and ovarian cancer (cBioPortal).

Therapeutic and prognostic relevance

LYN could be pharmacologically targeted with Src-kinase inhibitors. Results of preclinical studies showed that dasatinib, a dual-specificity tyrosine kinase inhibitor of ABL and the Src-family tyrosine kinases, exerted antitumor activity in LYN-expressing breast cancer cells[83].

MYC Amplification

Biological Impact

The v-myc avian myelocytomatosis viral oncogene homolog, also known as c-myc (MYC) gene encodes a transcription factor involved in cellular proliferation, inhibiting exit from the cell cycle, stimulating vascularization and enhancing genomic instability[86][87][88]. Dysregulated MYC expression is implicated in a wide range of human cancers[89].

Therapeutic and prognostic relevance

MYC amplification was associated with better clinical outcome in breast cancer patients treated with FAC (5-fluorouracil, doxorubicin, and cyclophosphamide), CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and P-FEC (paclitaxel followed by 5-fluorouracil, epirubicin and cyclophosphamide) and higher expression of MYC was also associated with

a better response rate in platinum-treated ovarian cancer patients[90][91][92].

CDK inhibition using the dinaciclib, a CDK1, 2, 5 and 9 inhibitors, exerted antitumor activity in triple-negative breast cancer (TNBC) tumor xenograft and cell lines with increased activity of the MYC pathway[93][94].

Overexpression of MYC has been reported as a favorable prognostic biomarker in colorectal carcinoma (CRC)[95][96]. However, the favorable prognostic value of MYC in CRC is abrogated by the TP53 mutation[96].

MYC amplification with the loss of tumor suppressor pathways such as p53 and RB has been shown to be associated with poor outcomes and was correlated with shortened disease-free survival in breast cancer with BRCA1 deficiency in TNBC[93][97].

NBN Amplification

Biological Impact

The NBN gene encodes a component of the MRE11-RAD50-NBN (MRN) complex, which involves in DNA double-strand break sensing and repair[98]. NBN mutation is related to Nijmegen breakage syndrome, increased cancer incidence and ionizing radiation sensitivity[98][99]. NBN mutations have been found in various cancers, including cholangiocarcinoma, hepatocellular carcinoma[100], prostate cancer[101], leukemia, lymphoma[102], and triple-negative breast cancer[103].

Therapeutic and prognostic relevance

In a phase II trial (ARIEL2), an ovarian cancer patient harboring a NBN germline mutation showed responses to rucaparib treatment[104]. NBN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer[105]; the trials evaluating rucaparib efficacy in ovarian cancer[106]or prostate cancer[107]; the trials evaluating talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556), and the trials evaluating niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate) cancer (NCT03207347).

Germline and somatic mutations in homologous recombination genes, including NBN, have been suggested to be prognostic biomarkers for platinum-based treatment response and superior survival in patients with ovarian, fallopian tube, peritoneal carcinomas and pancreatic cancer[108][109].

In a retrospective study of localized prostate cancer, NBN gene amplification has been demonstrated to associate with overall tumor genomic instability and lower biochemical relapse-free rate following image-guided radiotherapy (IGRT)[110].

Another retrospective study showed that amplification of the NBN gene is associated with protein overexpression and mostly correlated with poor prognosis in several cancer types, including ovarian cancer, breast invasive carcinoma, uterine corpus endometrial carcinoma, and sarcoma. Besides, in vivo and in vitro assays demonstrated that amplification of the NBN gene could induce cisplatin and PARP inhibitor resistance in breast and ovarian cancer cells[111].

RAD50 Heterozygous deletion

Biological Impact

The RAD50 gene encodes a highly-conserved DNA double-strand break (DSB) repair factor. It forms MRN complex with NBS1 and MRE11 protein and is involved in sensing and early processing of DSB, cell cycle checkpoints, DNA recombination and maintenance of telomeres[112][113]. Mutations in the components of the MRN complex could increase susceptibility to familial breast cancer[114][115], gastric cancer[116], colorectal cancer[117], and urothelial cancer[118]. RAD50 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is

insufficient to execute its original physiological functions[119]. Besides, RAD50 deletion was also suggested as a marker of BRCAness, a phenotype shared between non-BRCA1/2-mutated ovarian cancers and BRCA1/2-mutated ovarian cancers[120].

Therapeutic and prognostic relevance

Preclinical data showed that knockdown of the RAD50 gene in ovarian cancer cell lines was significantly associated with better responses to two PARP inhibitors, olaparib and rucaparib[120]. RAD50 has been selected as an inclusion criterion for the trials examining talazoparib efficacy in HER2-negative breast cancer, olaparib efficacy in breast cancer, rucaparib efficacy in metastatic prostate cancer and niraparib efficacy in any malignancy (except prostate) (NCT02401347, NCT03207347, NCT03344965, NCT03413995).

RECQL4 Amplification

Biological Impact

The RECQL4 gene encodes a member of the RECQ helicase family that plays an important role in DNA replication and various types of DNA repair, including double-strand break repair, nucleotide excision repair, base excision repair, and single-strand repair[121][122][123][124].

Therapeutic and prognostic relevance

There are currently no therapies targeting RECQL4 mutations. Expression of RECQL4 has been shown to drive cisplatin resistance in gastric cancer cell lines[125]. In contrast, RECQL4-deficient breast cancer cell lines were sensitive to cisplatin and PARP inhibitions (AG14361 and olaparib). but demonstrated resistance to taxane[126]. In a precilinical study, RECQL4-deficient colon cancer cell lines were also sensitive to cisplatin and olaparib treatment[127]. RECQL4 mutations have been selected as an inclusion criteria for the trials examining olaparib efficacy in metastatic urothelial cancer (NCT03448718) and relapsed small cell lung cancer (NCT03009682).

In breast cancers, the amplification of RECQL4 was significantly associated with aggressive tumor behavior, including lymph node positivity, larger tumor size, HER2 overexpression and poor survival[128]

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[129]. 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[130]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)[131][132][133][134]. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer[135], colorectal cancer (CRC)[133][136][137], and less frequently seen in other cancers such as lung adenocarcinoma[138], head and neck cancer[139][140], and cutaneous squamous cell carcinoma[141].

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[142]. 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[143].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)[144][145]. 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[146].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis[147][148][149][150][151][152][153][154]. 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[155].

SRC Amplification

Biological Impact

The SRC gene encodes for the proto-oncogene tyrosine protein kinase SRC, a member of multiple signaling pathways implicated in cell cycle control, cytokinesis, cell survival/ proliferation and migration/motility. Activation and/or overexpression has been observed in a wide range of cancers, including prostate, colorectal, lung and breast cancer[156][157][158][159][160][161][162].

Therapeutic and prognostic relevance

In a Phase I trial, ARQ 087, an ATP-competitive inhibitor of FGFR 1-3, demonstrated anti-tumor activity in a squamous non-small cell lung carcinoma patient (NSCLC) harboring SRC amplification (J Clin Oncol 33, 2015 (suppl; abstr 2545)). Preclinical data suggest that elevated SRC activity may also predict sensitivity to inhibitors of SRC family, such as TPX-0005 (AACR, Cancer Res: April 2016; Volume 57, Abstract #2132), Sprycel (dasatinib)[163][164]and bosutinib[165].

Increased Src family kinase activity has been observed in cetuximab-resistant cells, and treatment of dasatinib re-sensitized the cells to cetuximab[166]. Given that Src activation has been implicated as a mechanism of acquired resistance to chemotherapy and anti-EGFR treatment[167][168][166], and addition of Src inhibitor to stand-of-care treatment was considered as a potential therapeutic strategy. A phase IB study of patients with mCRC who failed prior treatments indicated that 6 out of 30 patients had a reduction in the size of their tumor, and 7 showed stable disease when treated with dasatinib, the oral tyrosine kinase Src inhibitor, in combination with cetuximab and FOLFOX[169].

TOP1 Amplification

Biological Impact

TOP1 encodes for topoisomerase 1 protein that involves in various vital cellular processes, including DNA replication, transcription, translation, recombination, and repair[170]. TOP1 is the target of irinotecan (CPT-11), a camptothecin derivative, which is metabolized to the active metabolite SN-38. Irinotecan induces cytotoxic effect by interacting with TOP1 and results in DNA double-strand breaks during DNA replication[171][172]. TOP1 gene copy number increase has been observed in stage III colorectal (CRC) patient cohort[173]and is correlated with mRNA and protein level in CRC cell lines[174].

Therapeutic and prognostic relevance

TOP1 expression is a potential predictive biomarker for irinotecan sensitivity in CRC patients, based on data from several prospective clinical trials[175][176][177].

TOP1 amplification is associated with advanced tumors and poor prognosis in melanoma[178].

ZNF217 Amplification

Biological Impact

The zinc-finger protein 217 (ZNF217) is a member of Kruppel-like family (KLF) of transcription factors[179][180]. ZNF217 is an oncogenic protein that plays deleterious functions in various human cancers[181]by inducing epithelial-mesenchymal transition (EMT)[182], activating the ERBB2/ERBB4/FAK[182]and AKT[183]pathways. The increased copy number of ZNF217 has been reported in breast cancer[184]. In colorectal cancer and ovarian cancer, amplification of the ZNF217 gene is associated with increased protein or mRNA expression[185][186]. Overexpression of ZNF217 has been

found in solid tumors[187][188][189][190].

Therapeutic and prognostic relevance

A high expression level of ZNF217 has been shown to confer tamoxifen resistance in ER+ breast cancer cells and is a predictor of relapse under endocrine therapy in patients with ER+ breast cancer[191]. Overexpression of ZNF217 is also linked to poor outcome in ovarian and colon cancer[189][190].

ZNF217-overexpressing breast cancer cells were correlated with paclitaxel resistance in vitro[183][192]. In a retrospective study, tumors that responded to doxorubicin or a combination of 5-fluorouracil and mitomycin (FUMI) expressed less ZNF217 than did nonresponsive tumors[193]. Triciribine, a nucleoside analogue and DNA synthesis inhibitor, inhibits tumor growth of ZNF217-overexpressing tumor in vivo. However, results from a Phase II study showed that antitumor activity of triciribine was not evident in all patients, possibly due to a lack of biomarkers for patient selections[193]. Expression of ZNF217 may serve as a potential biomarker for the treatment of triciribine[193].

High level of ZNF217 expression represents a biomarker for poor prognosis associated with shorter relapse-free survival in breast cancer and ovarian cancer[182][186].

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US FDA-APPROVED DRUG(S)

Afatinib (GILOTRIF)

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

- FDA Approval Summary of Afatinib (GILOTRIF)

LUX-Lung 8[194] 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[195] 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[196] 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[197] NCT02008227	**Non-small cell lung carcinoma** (Approved on 2016/10/18)
	PD-L1
	Atezolizumab vs. Docetaxel [OS(M): 13.8 vs. 9.6]
POPLAR[198] NCT01903993	**Non-small cell lung carcinoma** (Approved on 2016/10/18)
	PD-L1
	Atezolizumab vs. Docetaxel [OS(M): 12.6 vs. 9.7]
IMvigor210[199] 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[200] 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[201] NCT02155647	**Merkel cell carcinoma** (Approved on 2017/03/23)
	-
	Avelumab [ORR(%): 33.0, DOR(M): 2.8 to 23.3+]

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 16113 NCT03409614	**Lung non-small cell carcinoma** (Approved on 2022/11/08)
	-
	Platinum-based chemotherapy [OS(M): 21.9 vs. 13.0]
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[202] 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[203] 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[204] 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]
[205] NCT00004227	**Head and neck cancer** (Approved on 2006/03/01)
	-
	Cetuximab + radiation vs. Radiation [OS(M): 49 vs. 29.3]
[206] NCT00063141	**Colorectal cancer** (Approved on 2004/02/12)
	KRAS Wild-type/EGFR-expressing
	Cetuximab + irinotecan vs. Irinotecan [DOR(M): 5.7 vs. 4.2]

Dasatinib (SPRYCEL)

Dasatinib is an oral Bcr-Abl tyrosine kinase inhibitor (inhibits the "Philadelphia chromosome") and Src family tyrosine kinase inhibitor. Dasatinib is produced by Bristol-Myers Squibb and sold under the trade name SPRYCEL.

- FDA Approval Summary of Dasatinib (SPRYCEL)

DASISION[207] NCT00481247	**Chronic myeloid leukemia** (Approved on 2010/10/28)
	-
	Dasatinib vs. Imatinib [ORR(%): 76.8 vs. 66.2]
[208] NCT00123474	**Chronic myeloid leukemia** (Approved on 2007/11/08)
	-
	Dasatinib [ORR(%): 63.0]
[209] NCT00123487	**Acute lymphocytic leukemia** (Approved on 2006/06/28)
	-
	Dasatinib [ORR(%): 38.0]

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]
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[210] 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[211] NCT02125461	**Non-small cell lung carcinoma** (Approved on 2018/02/16)
	-
	Durvalumab vs. Placebo [PFS(M): 16.8 vs. 5.6]

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[212] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[213] 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[214] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05) - Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[215] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29) - Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[216] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30) - Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

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[217] 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[218] NCT02231749	**Renal cell carcinoma** (Approved on 2018/04/16) - Nivolumab plus ipilimumab vs. Sunitinib [OS(M): 67.1 vs. 55.5]
EORTC 18071[219] NCT00636168	**Melanoma** (Approved on 2015/10/28) - Ipilimumab vs. Placebo [RFS(M): 26 vs. 17]

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MDX010-20[220] NCT00094653	**Melanoma** (Approved on 2011/03/25)
	-
	Ipilimumab vs. Peptide vaccine with incomplete freund's adjuvant (gp100) [OS(M): 10 vs. 6]

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[221] 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]

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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]
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[222] 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[223] NCT02181738	**Hodgkin's lymphoma** (Approved on 2016/05/17) - Nivolumab [ORR(%): 66.0]
CheckMate 039[224] NCT01592370	**Hodgkin's lymphoma** (Approved on 2016/05/17) - Nivolumab [ORR(%): 66.0]
CheckMate 067[225] NCT01844505	**Melanoma** (Approved on 2016/01/23) - Ipilimumab vs. Placebo [PFS(M): 11.5 vs. 2.9]
CheckMate 066[226] NCT01721772	**Melanoma** (Approved on 2015/11/24) **BRAF V600 wild-type** Nivolumab vs. Dacarbazine [OS(M): Not Reached vs. 10.8]
CheckMate 025[227] NCT01668784	**Renal cell carcinoma** (Approved on 2015/11/23) - Nivolumab vs. Everolimus [OS(M): 25 vs. 19.6]
CheckMate 057[228] NCT01673867	**Non-small cell lung carcinoma** (Approved on 2015/10/09) - Nivolumab vs. Docetaxel [OS(M): 12.2 vs. 9.4]
CheckMate 017[229] NCT01642004	**Non-small cell lung carcinoma** (Approved on 2015/03/04) - Nivolumab vs. Docetaxel [OS(M): 9.2 vs. 6]
CheckMate 037[230] NCT01721746	**Melanoma** (Approved on 2014/12/22) - Nivolumab vs. Dacarbazine or carboplatin + paclitaxel [ORR(%): 32.0]

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[231] 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[232] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[233] 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[234] 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[235] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[236] 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[237] 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[238] 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[239] NCT02151981	**Non-small cell lung carcinoma** (Approved on 2017/03/30)
	EGFR T790M
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA[240] 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[241] NCT01412957	**Colorectal cancer** (Approved on 2017/06/29)
	KRAS Wild-type
	Panitumumab + bsc vs. Bsc [OS(M): 10 vs. 6.9]
PRIME[242] NCT00364013	**Colorectal cancer** (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab + folfox vs. Folfox [PFS(M): 9.6 vs. 8]
ASPECCT[243] NCT01001377	**Colorectal cancer** (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab vs. Cetuximab [OS(M): 10.4 vs. 10]
Study 20080763[244] 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]

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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[245] 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[246] NCT02267603	**Merkel cell carcinoma** (Approved on 2018/12/19)
	-
	Pembrolizumab [ORR(%): 56.0]

KEYNOTE-224[247] NCT02702414	**Hepatocellular carcinoma** (Approved on 2018/11/09)
	-
	Pembrolizumab [ORR(%): 17.0]
KEYNOTE-407[248] 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[248] 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[249][250] NCT02054806	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-012[251][252][253][254] NCT01848834	**Cancer** (Approved on 2017/05/23)
	MSI-H or dMMR
	Pembrolizumab [ORR(%): 39.6]
KEYNOTE-045[255] 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[256] NCT02453594	**Hodgkin's lymphoma** (Approved on 2017/03/14)
	-
	Pembrolizumab [ORR(%): 69.0]

KEYNOTE-024[257] NCT02142738	**Non-small cell lung carcinoma** (Approved on 2016/10/24)
	PD-L1
	Pembrolizumab vs. Chemotherapy [PFS(M): 10.3 vs. 6]
KEYNOTE-012[252] NCT01848834	**Head and neck squamous cell carcinoma** (Approved on 2016/08/05)
	-
	Pembrolizumab [ORR(%): 16.0]
KEYNOTE-006[258] NCT01866319	**Melanoma** (Approved on 2015/12/18)
	-
	Pembrolizumab vs. Ipilimumab (3mg/kg every 3 weeks) [OS(M): NR vs. 16]
KEYNOTE-010[259] NCT01905657	**Non-small cell lung carcinoma** (Approved on 2015/10/02)
	PD-L1
	Pembrolizumab [OS(M): 10.4 vs. 8.5]
KEYNOTE-002[260] 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[106] 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]

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[261] 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)

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

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)

POSEIDON NCT03164616	**Lung non-small cell carcinoma** (Approved on 2022/11/10)
	-
	Durvalumab and platinum-based chemotherapy [PFS(M): 6.2 vs. 4.8, OS(M): 14 vs. 11.7]
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

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

- 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

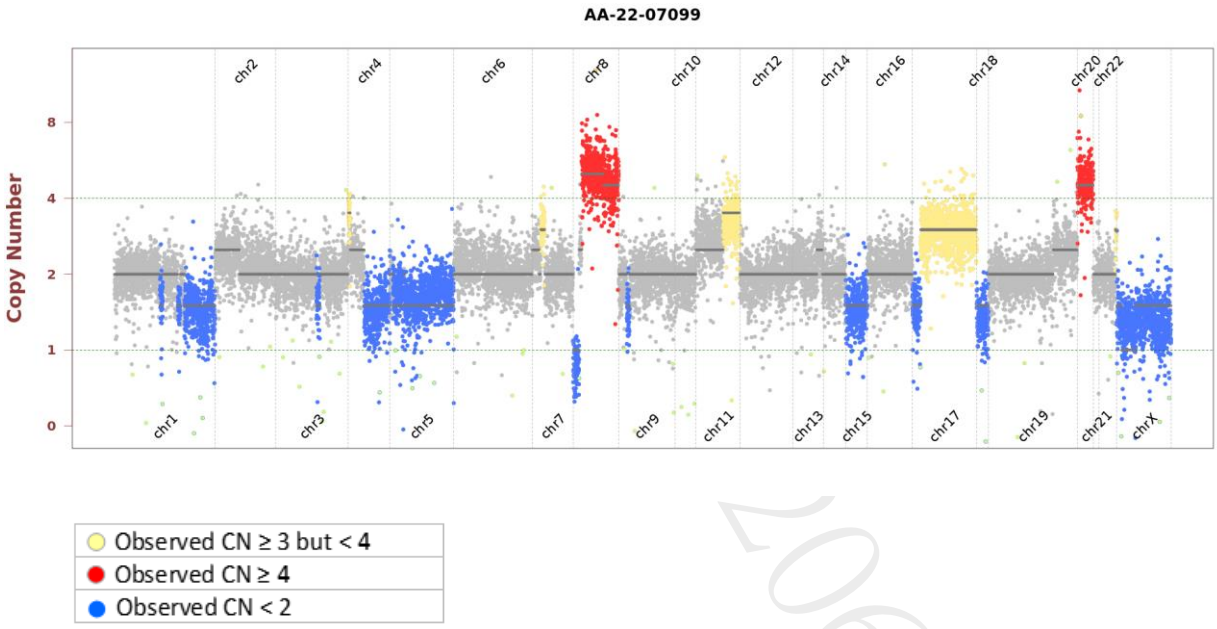
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
APC	R232*	7	c.694C>T	NM_000038	COSM13130	63.5%	919
APC	L2452*	16	c.7355T>A	NM_000038	-	5.6%	835
EGFR	S492R	12	c.1474A>C	NM_005228	COSM236671	27.8%	1404
EGFR	S492R	12	c.1476C>G	NM_005228	-	3.0%	1405
JAK2	R443*	11	c.1327C>T	NM_004972	COSM9238900	30.6%	291
TP53	G266R	8	c.796G>A	NM_000546	COSM10794	73.5%	483

- 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
ADAMTS18	A815T	16	c.2443G>A	NM_199355	COSM256247	23.3%	1186
APC	S2296N	16	c.6887G>A	NM_000038	COSM1580517	24.9%	1071
BRCA2	E1213V	11	c.3638A>T	NM_000059	-	5.6%	1061
CCNB1	V379G	8	c.1136T>G	NM_031966	-	32.6%	666
EPHA2	T898M	16	c.2693C>T	NM_004431	COSM6005522	36.3%	3163
FGF1	K115M	4	c.344A>T	NM_001144892	-	10.2%	1095
FRG1	R135K	5	c.404G>A	NM_004477	-	5.1%	467
IGF1R	Splice region	-	c.3723-4G>A	NM_000875	-	85.3%	617
JAK2	Splice region	-	c.2762-7T>C	NM_004972	-	78.9%	114
KDR	A1073T	24	c.3217G>A	NM_002253	-	5.5%	1505
KMT2C	A1685S	34	c.5053G>T	NM_170606	COSM249560	5.6%	408
MUC16	R3634H	3	c.10901G>A	NM_024690	-	27.0%	1415
NOTCH4	R585C	11	c.1753C>T	NM_004557	-	55.9%	1629
NSD1	Q2474P	23	c.7421A>C	NM_022455	-	24.2%	1219
PIK3C3	S128L	3	c.383C>T	NM_002647	COSM1388665	88.4%	1230
PTPRD	G1819V	41	c.5456G>T	NM_002839	-	42.6%	392
STK11	L386F	9	c.1156C>T	NM_000455	-	58.6%	1062
SYK	E420D	10	c.1260A>C	NM_001174167	-	25.1%	2111
USH2A	P3741S	57	c.11221C>T	NM_206933	-	36.4%	771
XPO1	A947V	23	c.2840C>T	NM_003400	COSM6413252	11.9%	268
ZNF217	M34I	1	c.102G>A	NM_006526	-	69.5%	3999

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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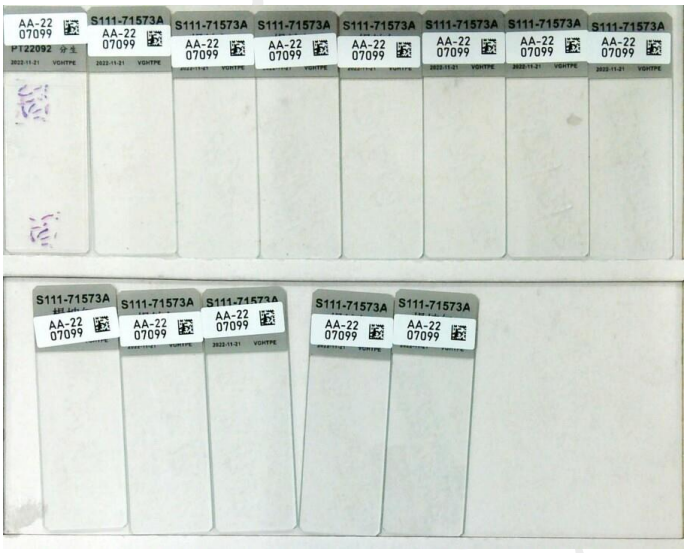
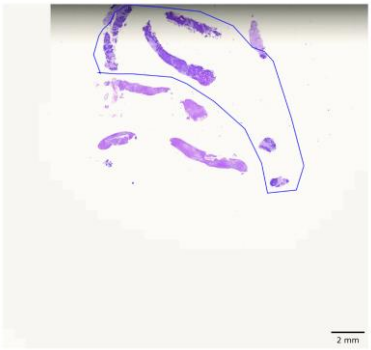
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: Nov 10, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11171573
- Collection site: Liver
- Examined by: Dr. Chien-Ta Chiang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 25%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 60%
    3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 5%
    4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 5%
    5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 1214x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 124

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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

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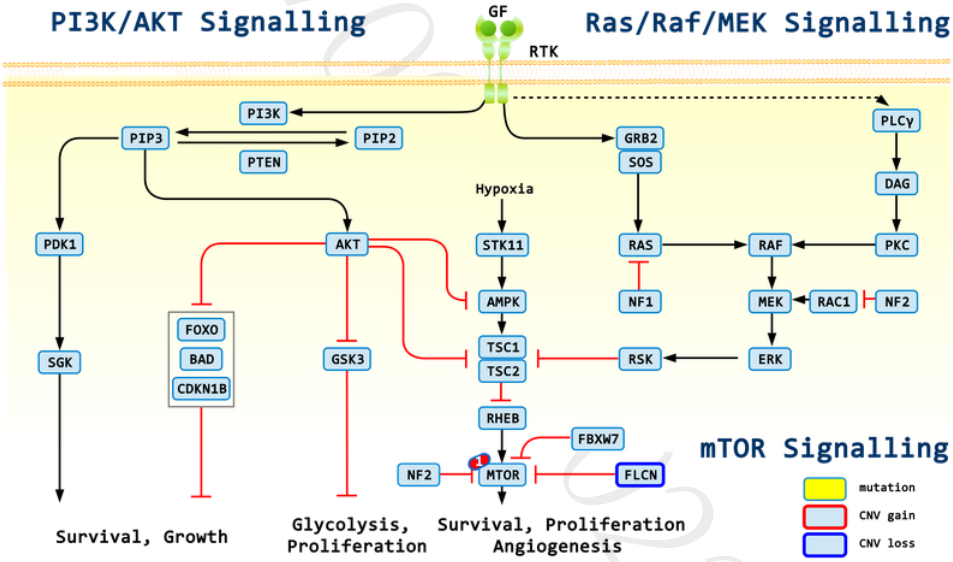
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
FLCN	Everolimus, Temsirolimus	**sensitive**
RAD50	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
SMAD4	Cetuximab	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Everolimus, Temsirolimus

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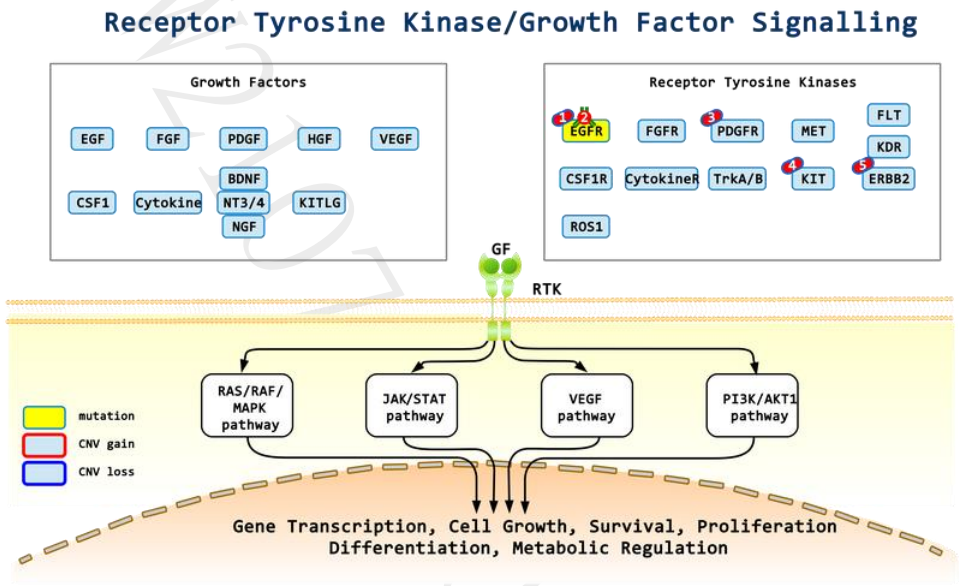
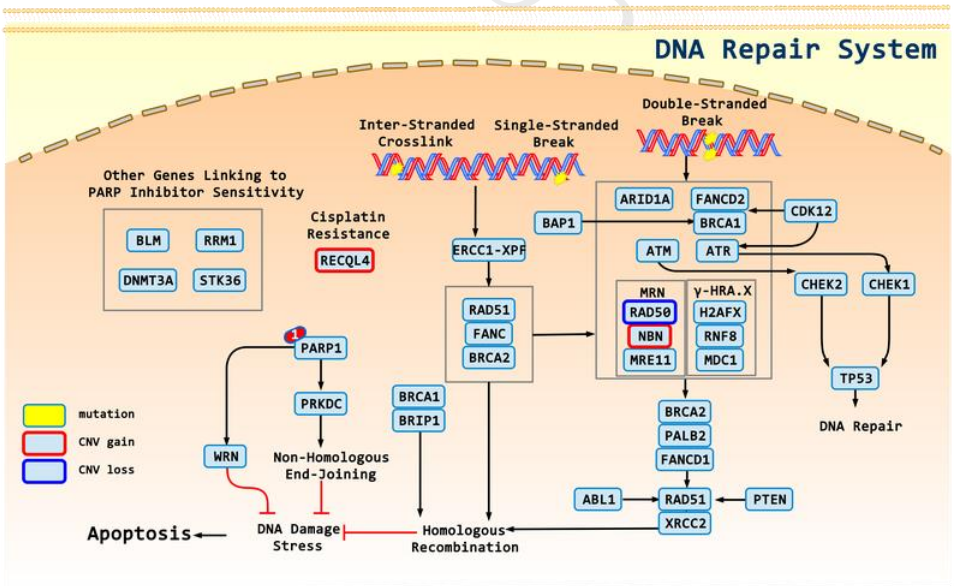


1: Afatinib, Osimertinib; 2: Panitumumab; 3: Dasatinib; 4: Dasatinib; 5: Afatinib



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。

責任

本檢驗報告僅提供專業醫療參考，本公司及其員工不對任何由使用本報告之內容引起的直接、間接、特殊、連帶或衍生的損失或損害承擔責任。

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