ACT Onco® + Report

PATIENT		
Name: 史玉琴		Patient ID: 48538267
Date of Birth: Mar 24, 1968		Gender: Female
Diagnosis: Thymic carcinoma		
ORDERING PHYSICIAN		
Name: 顏厥全醫師		Tel: 886-228712121
Facility: 臺北榮總		
Address: 臺北市北投區石牌路二段 201 號		
SPECIMEN		
Specimen ID: S11120097A	Collection site: Soft tissue	Type: FFPE tissue
Date received: Jul 22, 2022	Lab ID: AA-22-04243	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	
Not detected			

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
BRAF D594G	Binimetinib, Encorafenib, Sorafenib, Vemurafenib	-
CAPZA2(1)-MET(2) fusion	-	Cabozantinib, Crizotinib

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.

TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
BRAF	D594G	32.5%
MUC4	P4858fs	48.1%
TP53	R248Q	51.8%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr10	*PTEN*	Heterozygous deletion	1
Chr11	*CHEK1*	Heterozygous deletion	1
Chr16	*PALB2, TSC2*	Heterozygous deletion	1
Chr17	*RAD51C*	Heterozygous deletion	1
Chr18	*SMAD4*	Heterozygous deletion	1
Chr22	*CHEK2, NF2*	Heterozygous deletion	1
Chr4	*FBXW7*	Heterozygous deletion	1
Chr9	*CDKN2A*	Heterozygous deletion	1
Chr17	*ERBB2*	Amplification	6[¥]

[¥] Increased gene copy number was observed.

- Fusions

Fusion Gene & Exon	Transcript ID
CAPZA2(1)-MET(2) fusion	CAPZA2(NM_006136.2), MET(NM_000245.3)

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	6.3 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:

- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 61% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- The fusion gene reported above is confirmed to be in-frame and includes the kinase/functional domain. Such alteration may indicate potential benefits from kinase inhibitors. However, for a novel fusion, its functional significance and response to kinase inhibitors are undetermined.
- 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		
BRAF D594G	Binimetinib, Encorafenib	**sensitive**
Level 4		
BRAF D594G	Sorafenib, Vemurafenib	**sensitive**
CAPZA2(1)-MET(2) fusion	Cabozantinib, Crizotinib	**resistant**

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

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

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
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

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
TP53 R248Q	Platinum- and taxane-based regimens	**Less sensitive**	Clinical	Ovarian cancer

HORMONAL THERAPIES

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

OTHERS

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

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

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VARIANT INTERPRETATION

CAPZA2(1)-MET(2) fusion

Biological Impact

The Mesenchymal-Epithelial Transition (MET) is an oncogene that encodes the MET receptor tyrosine kinase (c-MET, also called HGFR, hepatocyte growth factor receptor). Binding of HGF leads to autophosphorylation and activation of MET and downstream effectors through the PI3K/AKT and RAS/RAF/MEK pathways, which regulates cell growth, proliferation, migration, and angiogenesis[1][2]. Gene amplification or overexpression of the MET occur in a wide range of cancers, including breast cancer[3], non-small cell lung cancer (NSCLC)[4], prostate cancer[5], renal papillary carcinoma[6][7], glioblastoma[8], hepatocellular carcinoma[9], and gastric cancer[10].

CAPZA2-MET fusion has been identified in glioblastoma[11] (DOI: 10.1200/JCO.2017.35.15_suppl.2019), non-small cell lung cancer (https://doi.org/10.1016/j.jtho.2018.08.451) and endometrial cancer[12].

MET gene rearrangement, which resulting in constitutively active MET fusion kinase, has been identified in various tumor types (DOI: 10.1200/JCO.2019.37.15_suppl.3078)[13][14].

Therapeutic and prognostic relevance

Preclinical data showed that 5-8F cell line which harbors CAPZA2-MET fusion gene is sensitive to tivantinib but resistance to crizotinib and cabozantinib (Int J Clin Exp Pathol 2016;9(8):8308-8317). Results from a MET-amplified glioblastoma patient-derived xenograft (PDX) model study revealed that capmatinib, a selective c-MET inhibitor, can improve overall survival of PDX models carrying MET amplification and in-frame fusion of exon 1 of CAPZA2 to exon 2 of MET, which resulted in full-length MET coding region, with altered 5’ cis-regulatory sequences. However, no improvement of survival was observed in PDXs harboring MET amplification and in-frame fusion of exon 1 of CAPZA2 to exon 6 of MET (Abstract 2519, 2018 AACR).

BRAF D594G

Biological Impact

BRAF is a serine/threonine kinase that belongs to the RAF family. The protein plays an essential role in the regulation of mitogen-activated protein kinase (MAPK) cascade, which affects a range of cellular response including cell division, differentiation, and secretion[15][16]. Mutations in the BRAF gene, most commonly the V600 residue, are the most frequently identified oncogenic mutations in melanomas, and have been identified in several types of cancers including non-Hodgkin lymphoma, thyroid cancers, non-small cell lung carcinoma, hairy cell leukemia, glioma, gastrointestinal stromal tumor, and colorectal cancers (CRCs)[17][18]. Of note, in the vast majority of cases, BRAF mutations are non-overlapping with other oncogenic mutations (e.g., NRAS mutations, KIT mutations, etc.) found in melanoma. V600E has been determined to be an activating mutation, which results in enhanced BRAF kinase activity and constitutive activation of downstream MEK/ERK signaling cascade[19][20].

BRAF D594G mutation is located within the protein kinase domain of the BRAF protein, resulting in impaired BRAF kinase activity. Meanwhile, expression of this mutant in melanoma cells models induces constitutive levels of pERK through CRAF[21][22].

Therapeutic and prognostic relevance

In the phase II NCI-MATCH trial (NCT02465060), trametinib treatment resulted in stable disease in two patients with prostate cancer and lung adenocarcinoma respectively, both harboring BRAF D594G. However, four gastrointestinal system cancer patients harboring BRAF D594G resulted in progression disease under trametinib treatment[23]. In the phase II BEAVER trial (NCT03839342), an ampullary cancer patient harboring BRAF D594G achieved a confirmed partial response to combination treatment with binimetinib and encorafenib, and continued to be on treatment for 5.4 months (Annals of Oncology 32 (2021): S596).

Data from cell-based and xenograft studies demonstrated that the CRAF inhibitor, sorafenib, induced apoptosis and reduces tumor growth in melanoma cell lines harboring BRAF D594G mutation[21]. Besides, a preclinical study revealed that cells harboring BRAF D594N/G/A mutant are sensitive to trametinib but are insensitive to vemurafenib[22]. However, there is a case report showed that responses to vemurafenib were observed in a patient with advanced melanoma harboring D594G[24].

The NCCN guidelines for central nervous system cancers recommended selumetinib for pilocytic astrocytoma patients with BRAF fusion or BRAF V600E activating mutation. BRAF activating mutations have been determined as an inclusion criterion for the trials evaluating selumetinib efficacies in cancers (NCT01089101, NCT00888134, NCT00866177, and NCT00936221).

MUC4 P4858fs

Biological Impact

Mucin 4 (MUC4) gene encodes a membrane protein of the mucin family which is expressed in normal stomach, ovary, salivary gland, colon, and lung[25]. Because of its large size and extended conformation, MUC4 can protect the epithelium from invasion by microbes[26]. Similarly, MUC4 also can protect tumor cells from killing mechanisms by immune cells and anti-HER2 therapy[27][28]. In cancer, MUC4 has been proposed to promote cell differentiation and proliferation via interaction with ERBB2 and activating downstream signaling pathway[29]. Of note, it is able to disrupt tumor cell-cell interaction and promote invasion and metastasis[30]. Overexpression of MUC4 has been reported in many cancers such as pancreatic cancer[31][32], ovarian cancer[33], breast cancer[34], and colorectal cancer[35].

P4858fs mutation results in a change in the amino acid sequence beginning at 4858, likely to cause premature truncation of the functional MUC4 protein (UniProtKB). This mutation is predicted to lead to a loss of MUC4 protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

Relatively low expression of MUC4 was associated with better survival in patients with resectable pancreatic cancer receiving adjuvant gemcitabine[36]. However, low MUC4 expression was correlated with shorter overall survival in clear-cell renal cell carcinoma[25].

TP53 R248Q

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[37]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[38].

R248Q is a missense mutation located in the DNA-binding domain (DBD) of the p53 protein (UniProtKB). This mutation causes oncogenic gain-of-function phenotypes in a breast cancer cell line[39]and has been reported to target the proteasome activator REG gamma to promote endometrial cancer progression[40].

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)[41].

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[42]. 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[43].

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[44][45][46]. 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)[47]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[48][49]. 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[50].

TP53 oncomorphic mutations, including P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L and R282W have been shown to predict resistance to platinum- and taxane-based chemotherapy in advanced serous ovarian carcinoma patients[51].

CDKN2A Heterozygous deletion

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53[52][53][54]. CDKN2A has been reported as a haploinsufficient tumor suppressor with one copy loss that may lead to weak protein expression and is insufficient to execute its original physiological functions[55]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[56][57].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[58][59]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[60][61][62]. However, there are clinical studies that demonstrated CDKN2A nuclear expression, CDKN2A/CDKN2B co-deletion, or CDKN2A inactivating mutation was not associated with clinical benefit from CDK4/6 inhibitors, such as palbociclib and ribociclib, in RB-positive patients[63][64][65]. However, CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for the treatment of ER+ and HER2- breast cancer[59][66][67].

In a Phase I trial, a KRAS wild-type squamous non-small cell lung cancer (NSCLC) patient with CDKN2A loss had a partial response when treated with CDK4/6 inhibitor abemaciclib[61]. Administration of combined palbociclib and MEK inhibitor PD-0325901 yield promising progression-free survival among patients with KRAS mutant non-small cell lung cancer (NSCLC) (AACR 2017, Abstract CT046). Moreover, MEK inhibitor in combination with CDK4/6 inhibitor demonstrates significant anti-KRAS-mutant NSCLC activity and radiosensitizing effect in preclinical models[68].

A retrospective analysis demonstrated that concurrent deletion of CDKN2A with EGFR mutation in patients with non-small cell lung cancer (NSCLC), predicts worse overall survival after EGFR-TKI treatment[69].

CHEK1 Heterozygous deletion

Biological Impact

The checkpoint kinase 1 (CHEK1 or CHK1) gene encodes a protein kinase involved in transducing DNA damage signals and is required for both the intra-S phase and G2/M checkpoints[70]. CHEK1 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[71][72]. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors[73], and CHEK1 mutations are extremely rare[70]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer[74], breast cancer[75], colorectal cancer[76], non-small cell lung (NSCLC) cancer[77], and nasopharyngeal cancer[78].

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[79].

In addition, CHEK1 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[80], prostate cancer (NCT03533946), niraparib efficacy in pancreatic cancer (NCT03553004), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in lung cancer (NCT03377556), respectively.

Selective inhibitors for CHEK1 and CHEK2 alone or in combination with other agents are currently being investigated in clinical trials[81].

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[82]. 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[71][72]. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers[83][84][85][86][87].

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[79].

In addition, CHEK2 has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer(NCT03533946)[80][88], niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

In a phase 2 trial, two prostate cancer patients harboring CHEK2 homozygous deletion was enrolled. One of the two patients had a response to olaparib[89].

ERBB2 Amplification

Biological Impact

The epidermal growth factor receptor 2 (HER2, or ERBB2) gene encodes a transmembrane receptor tyrosine kinase that belongs to the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases[90]. Amplification or activating mutations of ERBB2 can lead to aberrant activation of downstream pathways, such as phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) cascades, which are involved in cell survival and proliferation, respectively[90][91]. ERBB2 mutations are mostly observed in HER2-negative (non-overexpressed or non-amplified) samples[92].

Therapeutic and prognostic relevance

Early Phase clinical trials and case reports have reported clinical benefits to afatinib and dacomitinib treatment in non-small cell lung cancer (NSCLC) patients harboring ERBB2 exon 20 in-frame insertion mutations[93][94][95][96][97][98]. A preclinical study in lung cancer cell lines demonstrated that ERBB2 exon 20 in-frame insertion mutations resulted in constitutive phosphorylation and activation of ERBB2 and resistance to EGFR tyrosine kinase inhibitors, erlotinib and gefitinib[99][96]. ERBB2 exon 20 in-frame insertion mutations in NSCLC cells were shown to be sensitive to neratinib and poziotinib[100][101].

There were case reports showing NSCLC patients with ERBB2 exon 20 in-frame insertion mutations derived benefit from trastuzumab-based therapies[94][102][103][104], or trastuzumab emtansine[104][105].

In NCCN guidelines for NSCLC, ERBB2 (HER2) mutations have been suggested as an emerging biomarker for ado-trastuzumab emtansine and fam-trastuzumab deruxtecan-nxki (T-DXd; DS-8201) in patients with NSCLC (DOI: 10.1200/JCO.2020.38.15_suppl.9504)[106]. ERBB2 mutations have been determined as an inclusion criterion for the trials evaluating neratinib, lapatinib, afatinib, dacomitinib, and trastuzumab efficacies in multiple types of solid tumors (NCT01670877, NCT01953926, NCT01306045, NCT02780687, NCT00818441, and NCT02693535).

FDA has approved several HER2 targeting drugs including trastuzumab (NCT00004067, NCT00005970)[107][108], pertuzumab (NCT01358877)[109], ado-trastuzumab emtansine (NCT01772472)[110], fam-trastuzumab deruxtecan-nxki (DS-8201) (NCT03248492)[111], lapatinib (NCT00078572)[112], neratinib (NCT01808573, NCT00878709) (DOI 10.1200/JCO.2019.37.15_suppl.1002)[113][114][115], and tucatinib (NCT02614794)[116]for HER2-positive breast cancer under different clinical settings.

Besides, fam-trastuzumab deruxtecan-nxki also has been approval by the US FDA for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Afatinib also demonstrates remarkable anti-tumor activity against HER2-amplified uterine serous endometrial cancer in vitro and in vivo[117].

Aberrant activation of ERBB2 by gene amplification or activating mutations may confer increased sensitivity to several ERBB-directed agents, such as trastuzumab[118], ado-trastuzumab emtansine (T-DM1)[119][120], lapatinib[121][122], and neratinib[123][124][125]in breast cancer and ovarian cancer[126](DOI 10.3816COC.2008.n.005).

Of note, combined neoadjuvant therapy consisting of pertuzumab and trastuzumab achieved a significantly higher response rate than with trastuzumab alone[120][127][128]. FDA has approved trastuzumab for metastatic gastric or gastroesophageal junction adenocarcinoma (NCT01041404)[107][129].

In NCCN guidelines for colon cancer, HER2 amplification has been suggested as an emerging biomarker for fam-trastuzumab deruxtecan-nxki or trastuzumab plus either pertuzumab or lapatinib in mCRC patients[130][131]. For salivary

gland tumors, the NCCN guidelines for head and neck cancer also suggested that HER2 amplification is an emerging biomarker for trastuzumab, T-DM1, pertuzumab, and fam-trastuzumab deruxtecan-nxki[132][126][133][134](DOI: 10.1200/JCO.2021.39.15_suppl.6079). For esophageal cancer, the NCCN guidelines suggested that HER2 amplification is an emerging biomarker for fam-trastuzumab deruxtecan-nxki, trastuzumab and FDA-approved biosimilar of trastuzumab[129][111]. For patients with stage III/IV or recurrent HER2-positive uterine serous carcinoma, the NCCN guidelines suggested that HER2 amplification is an emerging biomarker for carboplatin/paclitaxel plus trastuzumab[135].

Clinical studies have shown that neither trastuzumab nor lapatinib exhibited significant activity in HER2-overexpressing advanced salivary gland tumors[136][137]. However, although no response of lapatinib was observed, it was well tolerated, with prolonged tumor stabilization of more than 6 months in 36% (95% CI, 21% to 54%) of patients[137]. In addition, trastuzumab in combination with paclitaxel and carboplatin showed a durable clinical response in a patient with HER2-positive metastatic submandibular salivary ductal carcinoma[138].

In ovarian cancers, clinical evaluation of trastuzumab and pertuzumab in Phase 2 studies showed clinical benefit of in 7.3% and 14.5%, respectively in unselected patients[139][140].

Beyond EGFR T790M, several mechanisms of acquired resistance to first- and second-generation EGFR-TKIs have been identified in lung cancer patients, including rare EGFR resistance-associated point mutations and HER2 amplification[141]. The NCCN guidelines for NSCLC suggests that acquired resistance can also be mediated by the acquisition of ERBB2 amplification[142].

As reviewed in Nahta et al. and Rexer[143][144], accumulated evidence have suggested several intrinsic or acquired mechanisms that could contribute to trastuzumab and lapatinib resistance, such as alternations of the drug-binding domain of the HER2 gene that abrogate trastuzumab binding, overexpression of mucins that block the binding of trastuzumab, loss-of-function mutations of the phosphatase and tensin homolog (PTEN) gene or activating mutations of PIK3CA gene, and upregulation of IGF-1 or MET[145][146][147][148][149]. However, there is conflicting data suggested that gain-of-function PIK3CA mutations may not be associated with anti-HER2 resistance[150]. Several clinical trials of inhibitors targeting PI3K/AKT pathway combined with HER2-targeted treatments are underway[151][152].

ERBB2 gene amplification is associated with shorter overall survival and time to disease recurrence in breast cancers[153][154][155]. ERBB2 amplification has been implicated in colorectal cancer patients who exhibited either de novo or acquired resistance to cetuximab-based therapy[156]. Studies also suggested that overexpression of the ERBB2 gene is associated with resistance to tamoxifen therapy in patients with advanced breast cancer[157][158][159]. HER2 positivity was correlated with a worse survival outcome in endometrial cancer[160][161][162].

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[163][164], c-Jun[165], cyclin E[166], Notch family members[167][168], Aurora-A[169], mTOR[170], KLF5[171], and MCL-1[172]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation[173]. 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[171][172][174].

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)[175][176]. Moreover, in vitro

assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor[170].

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[177][178][179][180].

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[181][179].

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[182][183][184]. 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[185]. 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[182][186]. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas[187], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers[188].

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[189][190][191][192]. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer and urothelial carcinoma[193][194], 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[195].

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[196].

PALB2 Heterozygous deletion

Biological Impact

The partner and localizer of BRCA2 (PALB2) gene encodes a protein that plays a critical role in homologous recombination repair (HRR) through its ability to interact with BRCA2 in nuclear foci, promoting its localization and stability in key nuclear structures[197]. The Fanconi anemia complementation group (FANC) which includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (also called BRIP1), FANCL, FANCM and FANCN (also called PALB2) are involved in the repair of DNA double-strand breaks (DSBs) by homologous recombination (HR)[198][199][200]. PALB2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function[201]. Biallelic germline loss-of-function mutations in PALB2 cause Fanconi anemia, whereas monoallelic loss-of-function mutations are associated with an increased risk of breast cancer and pancreatic cancer[202]. Fanconi Anemia is an autosomal recessive disease characterized by hematological abnormalities, bone marrow failure, limb deformities, skin hyperpigmentation, and susceptibility to hematologic and solid malignancies, such as acute myeloid leukemia and head and neck carcinoma[203][204].

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[79].

PALB2 loss of function mutation has been determined as an inclusion criterion for the trial evaluating rucaparib efficacy in ovarian cancer[80]or prostate cancer[88]; talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556); niraparib efficacy in pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), or any malignancy (except prostate) cancer (NCT03207347).

A case report demonstrated an exceptional response to mitomycin C and cisplatin treatment in a gemcitabine-resistant pancreatic cancer patient with biallelic inactivation of PALB2[205].

PTEN Heterozygous deletion

Biological Impact

The phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene encodes a lipid/protein phosphatase that is important for the regulation of cell proliferation, survival, homologous recombination and maintenance of genomic integrity[206][207]. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway[208]. PTEN is a haploinsufficient tumor suppressor gene, in which having only one copy of the wild-type allele does not produce enough protein product to execute wild-type functions[38][209][210]. Germline loss-of-function PTEN mutations are found in approximately 80% of patients with Cowden syndrome, a disorder that is associated with high-penetrance breast and thyroid cancer[211][212][213]. Somatic mutations or monoallelic loss of PTEN is regularly observed in a significant fraction of human cancers, including sporadic breast cancer, colon cancer, endometrial cancer, prostate cancer, and glioblastoma[214][215][216][217][218].

Therapeutic and prognostic relevance

Somatic loss of PTEN results in aberrant activation of PI3K/AKT/mTOR signaling pathway and provides a mechanistic rationale for PI3K pathway inhibitors treatment[219][220]. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes[221][222][223][224][225][226]. Moreover, early clinical data also indicated that PTEN loss was associated with improved response and longer PFS in patients with advanced breast cancer[189], advanced pancreatic neuroendocrine tumors[227], and metastatic castration-resistant prostate cancer treated with mTORC1 inhibitor, everolimus[228].

Several groups found that PTEN loss was generally associated with poor response to trastuzumab therapy, whether this agent was administered in the neoadjuvant, adjuvant, or metastatic settings[145][147][229][148][149].

Loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab[230][231][232][233][234][235]. However, encouraging anti-tumor activity of the combination of an EGFR antibody and a mTORC1 inhibitor (everolimus or temsirolimus) have been reported in early-phase clinical studies (J Clin Oncol. 2011;29 (suppl): abstr 3587; J Clin Oncol. 2013;31 (suppl): abstr 608). Ongoing phase I/II studies testing combinations of EGFR antibodies and PI3K/AKT/mTOR pathway inhibitors (e.g., NCT01816984, NCT01252628, NCT01719380) will provide larger numbers of patients to assess the role of PTEN status in therapeutic response.

Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib[236][237]. Inhibition of the PI3K/AKT/mTOR signal pathway has been shown to be an effective strategy to radiosensitize NSCLC cells harboring the EGFR activating mutation that acquires resistance to both TKIs due to PTEN loss or inactivation mutations[238].

Loss or biallelic inactivation of PTEN is associated with resistance to anti-PD-1 checkpoint blockade therapies, including pembrolizumab and nivolumab in melanoma and leiomyosarcoma patients[239][240][241].

PTEN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy

in metastatic biliary tract cancer (NCT04042831); talazoparib efficacy in HER2-negative breast cancer (NCT02401347), and niraparib efficacy in breast cancer (NCT04508803) or any malignancy (except prostate) cancer (NCT03207347). Clinical data also suggested that PTEN deficient cancers may be sensitive to olaparib[242].

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)[243][244][245][246][247]. Amplification of RAD51C has been implicated in tumor progression[248][249]. RAD51C is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function[250].

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[79].

A preclinical study using gastric cancer xenograft model showed that RAD51C deficiency caused sensitivity to PARP inhibitor olaparib[251].

RAD51C loss of function mutation has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer[80][88]; talazoparib efficacy in HER2-negative breast cancer (NCT02401347) or prostate cancer (NCT03148795), and niraparib efficacies in pancreatic cancer (NCT03553004).

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[252]. 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[253]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)[254][255][256][257]. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer[258], colorectal cancer (CRC)[256][259][260], and less frequently seen in other cancers such as lung adenocarcinoma[261], head and neck cancer[262][263], and cutaneous squamous cell carcinoma[264].

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[265]. 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[266].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)[267][268]. 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[269].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis[270][271][272][273][274][275][276][277]. 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[278].

TSC2 Heterozygous deletion

Biological Impact

The tuberous sclerosis complex 2 (TSC2) gene encodes a protein called tuberin, which interact with a protein called hamartin (encoded by the TSC1 gene). This hamartin-tuberin tumor suppressor complex plays a critical role in growth control as a negative regulator of the mammalian target of rapamycin (mTOR) pathway[279][280]. Mutations in TSC1/TSC2 tumor suppressor genes that result in inactivation of the complex are commonly found in patients with tuberous sclerosis complex[281][282][283], while the loss of heterozygosity (LOH) in TSC1/TSC2 has been identified in head and neck squamous cell carcinoma (HNSCC)[284]and endometrial cancer[285]. TSC2 deletion, splicing-mutant, and inactivating mutations such as A1141T, G305V, S1514X, and R1032X, has been identified in TSC2-null hepatocellular carcinoma (HCC) cell lines, patient-derived xenograft, and primary tumors. Mutations in the TSC1 and TSC2 genes cause the autosomal dominant genetic disorder tuberous sclerosis complex (TSC)[286].

Therapeutic and prognostic relevance

Genomic alterations with activating effects of the mTOR signaling pathway (including deletion/inactivation of TSC1/TSC2) have been shown to confer sensitivity to everolimus across multiple cancer types, such as bladder cancer, gastric cancer, sarcoma, thyroid cancer, hepatocellular carcinoma (HCC) as well as head and neck squamous cell carcinoma (HNSCC)[193][192][287]. Results from one Phase II study of advanced endometrial cancer showed that mutations in AKT1, TSC1, and TSC2 might predict sensitivity to temsirolimus[288]. Recent studies indicated that there are mTORC1-independent signaling pathways downstream of hamartin-tuberin, which may represent new therapeutic targets[289].

Everolimus has been approval by the U.S. FDA for Tuberous Sclerosis Complex (TSC)-associated renal angiomyolipoma and Tuberous Sclerosis Complex (TSC)-associated subependymal giant cell astrocytoma (SEGA). This approval is based on the results from EXIST-1, EXIST-2, and Study 2485 trials (NCT00789828, NCT00790400, and NCT00411619).

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US FDA-APPROVED DRUG(S)

Abemaciclib (VERZENIO)

Abemaciclib is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. Abemaciclib is developed and marketed by Eli Lilly under the trade name VERZENIO.

- FDA Approval Summary of Abemaciclib (VERZENIO)

monarchE NCT03155997	**Breast cancer** (Approved on 2021/10/12)
	HR-positive, HER2-negative
	Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3[290] NCT02246621	**Breast cancer** (Approved on 2018/02/26)
	HR-positive, HER2-negative
	Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 2[67] NCT02107703	**Breast cancer** (Approved on 2017/09/28)
	HR-positive, HER2-negative
	Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1[291] NCT02102490	**Breast cancer** (Approved on 2017/09/28)
	HR-positive, HER2-negative
	Abemaciclib [ORR(%): 19.7 vs. 17.4]

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

Encorafenib (BRAFTOVI)

Encorafenib is an oral kinase inhibitor that targets BRAF. Encorafenib is developed and marketed by Array BioPharma under the trade name BRAFTOVI.

- FDA Approval Summary of Encorafenib (BRAFTOVI)

BEACON CRC[293] 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]
COLUMBUS[292] NCT01909453	**Melanoma** (Approved on 2018/06/27)
	BRAF V600E/K
	Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3]

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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[294] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[295] NCT00863655	**Breast cancer** (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
EXIST-2 NCT00790400	**Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma** (Approved on 2012/04/26)
	-
	Everolimus vs. Placebo [ORR(%): 41.8 vs. 0]
RADIANT-3[227] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[296] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[297] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

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]
QUADRA[298] NCT02354586	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2019/10/23)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Niraparib [ORR(%): 24.0, DOR(M): 8.3]
NOVA[299] 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]

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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)
	gBRCA
	Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound[79] NCT02987543	**Prostate cancer** (Approved on 2020/05/19)
	ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm, RAD54Lm
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1[300] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[301] NCT02184195	**Pancreatic adenocarcinoma** (Approved on 2019/12/27)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1[302] NCT01844986	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19)
	Germline or somatic BRCA-mutated (gBRCAm or sBRCAm)
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD[303] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[304] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA+
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19[305] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]
Study 42[306] NCT01078662	**Ovarian cancer** (Approved on 2014/12/19)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

Palbociclib (IBRANCE)

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

- FDA Approval Summary of Palbociclib (IBRANCE)

PALOMA-2[307] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+, HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]

PALOMA-3[308] NCT01942135	**Breast cancer** (Approved on 2016/02/19)
	ER+, HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

Ribociclib (KISQALI)

Ribociclib is a cyclin-dependent kinase (CDK) inhibitor specifically targeting cyclin D1/CDK4 and cyclin D3/CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Ribociclib is developed by Novartis and Astex Pharmaceuticals and marketed by Novartis under the trade name KISQALI.

- FDA Approval Summary of Ribociclib (KISQALI)

MONALEESA-2[66] NCT01958021	**Breast cancer** (Approved on 2017/03/13)
	HR+, HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

Rucaparib (RUBRACA)

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

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA+, sBRCA
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[80] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	All|HRD|tBRCA
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]
ARIEL2[309] NCT01482715, NCT01891344	**Ovarian cancer** (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation
	Rucaparib [ORR(%): 54.0]

Sorafenib (NEXAVAR)

Sorafenib is a small molecule multi-kinase inhibitor that targets multiple kinase families including VEGFR, PDGFRB, and the RAF family kinases. Sorafenib is co-developed and co-marketed by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals under the trade name NEXAVAR.

- FDA Approval Summary of Sorafenib (NEXAVAR)

DECISION[310] NCT00984282	**Differentiated thyroid carcinoma** (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
SHARP[311] NCT00105443	**Hepatocellular carcinoma** (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]

TARGET[312] NCT00073307	**Renal cell carcinoma** (Approved on 2005/12/20)
	-
	Sorafenib vs. Placebo [PFS(D): 167 vs. 84]

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[313] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

Temsirolimus (TORISEL)

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

- FDA Approval Summary of Temsirolimus (TORISEL)

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

Vemurafenib (ZELBORAF)

Vemurafenib is an anti-cancer inhibitor which targets B-Raf. Vemurafenib is developed and marketed by Genentech under the trade name ZELBORAF.

- FDA Approval Summary of Vemurafenib (ZELBORAF)

VE-BASKET [315] NCT01524978	**Erdheim-chester disease** (Approved on 2017/11/06)
	BRAF V600
	Vemurafenib [ORR(%): 54.5]
BRIM 3[316] NCT01006980	**Melanoma** (Approved on 2011/08/17)
	BRAF V600E
	Vemurafenib vs. Dacarbazine [PFS(M): 5.3 vs. 1.6, OS(M): 13.6 vs. 10.3]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

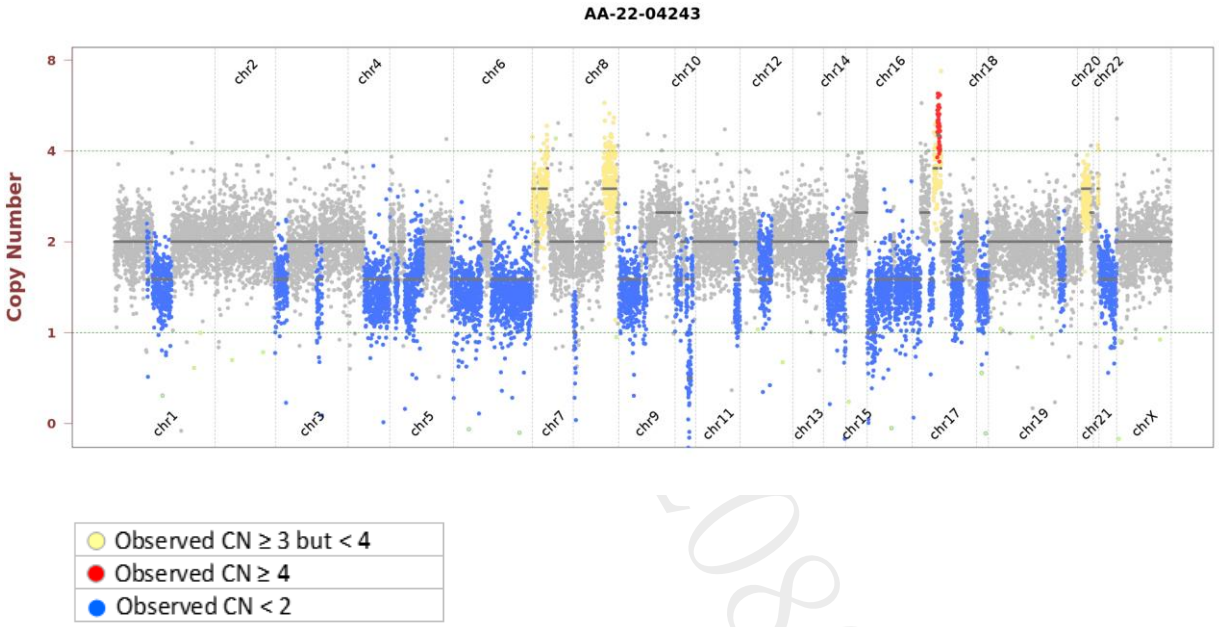
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
BRAF	D594G	15	c.1781A>G	NM_004333	COSM467	32.5%	1478
MUC4	P4858fs	15	c.14573del	NM_018406	-	48.1%	954
TP53	R248Q	7	c.743G>A	NM_000546	COSM10662	51.8%	2120

- 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
AMER1	R641*	2	c.1921C>T	NM_152424	COSM174910	37.7%	1150
AR	A597T	3	c.1789G>A	NM_000044	COSM1468978	28.3%	1697
ARID2	Q1462*	15	c.4384C>T	NM_152641	COSM2067865	31.8%	2444
ARID2	Q995*	15	c.2983C>T	NM_152641	COSM7318561	30.7%	2119
ATM	R2443Q	50	c.7328G>A	NM_000051	COSM20404	29.6%	778
BCOR	D1133Y	7	c.3397G>T	NM_001123385	-	37.8%	757
BRIP1	N196S	6	c.587A>G	NM_032043	COSM249456	71.6%	578
CREBBP	G447E	6	c.1340G>A	NM_004380	-	51.6%	1555
ERBB2	R143Q	3	c.428G>A	NM_004448	COSM1382867	20.4%	3164
FAT1	T1679I	10	c.5036C>T	NM_005245	-	72.1%	1095
FLT4	V528M	12	c.1582G>A	NM_182925	-	52.7%	431
INSR	K294R	3	c.881A>G	NM_000208	COSM2728577	47.6%	1146
LRP1B	E1327Q	25	c.3979G>C	NM_018557	-	35.0%	1303
NTRK1	R748W	17	c.2242C>T	NM_002529	-	54.5%	861
RAD51D	I311N	10	c.932T>A	NM_002878	-	73.4%	2154
RARA	P440R	9	c.1319C>G	NM_000964	-	21.6%	222
SMAD4	V128_Y131del	3	c.382_393del	NM_005359	-	46.8%	808

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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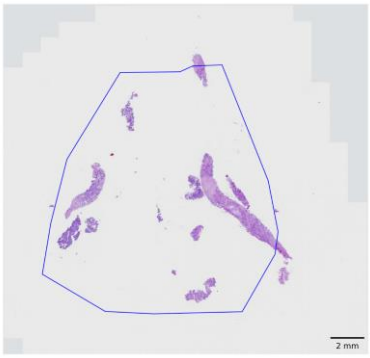
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: May 2022
- Facility retrieved: 臺北榮總桃園分院
- H&E-stained section No.: S11120097A
- Collection site: Soft tissue
- Examined by: Dr. Chien-Ta Chiang
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 25%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 30%
  3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
  4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
  5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 1298x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 49

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

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

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GENE LIST

SNV & CNV

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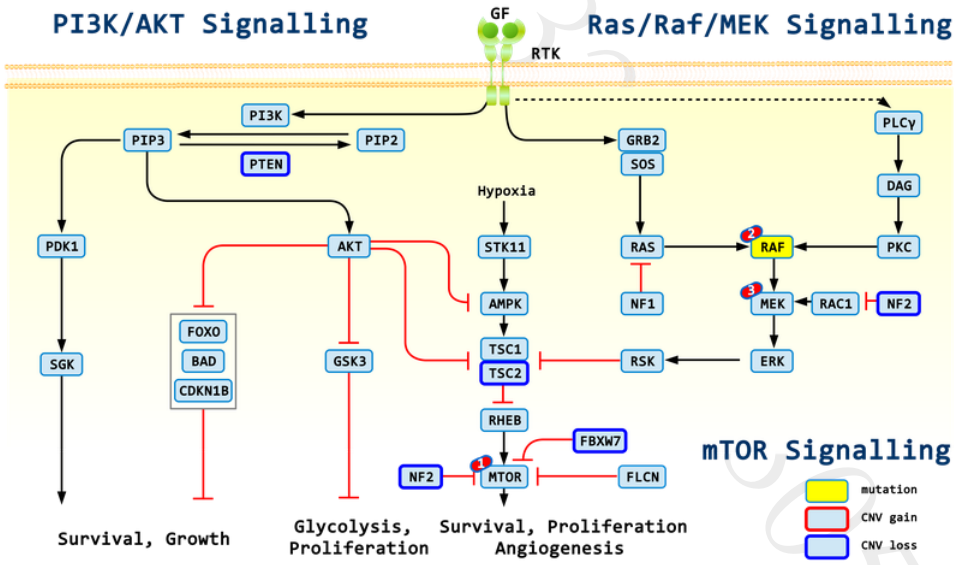
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
CDKN2A	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
PTEN	Everolimus, Temsirolimus, Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
FBXW7	Everolimus, Temsirolimus	**sensitive**
NF2	Everolimus, Temsirolimus	**sensitive**
TSC2	Everolimus, Temsirolimus	**sensitive**
CHEK1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
PALB2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RAD51C	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
SMAD4	Cetuximab	**resistant**
PTEN	Erlotinib, Gefitinib, Panitumumab, Cetuximab,Trastuzumab	**resistant**
FBXW7	Gefitinib, Regorafenib	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Everolimus, Temsirolimus; 2: Sorafenib, Encorafenib, Vemurafenib; 3: Binimetinib

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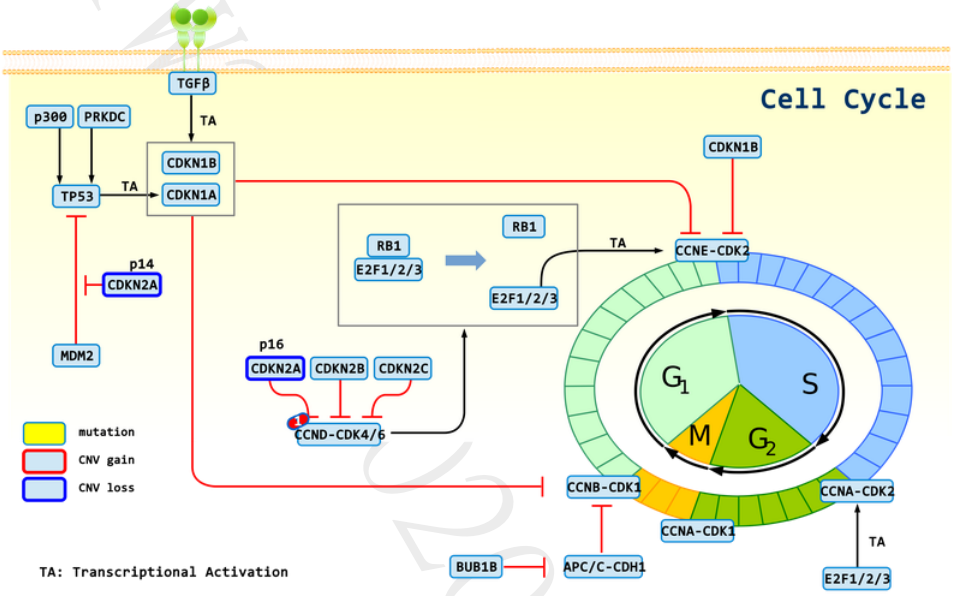
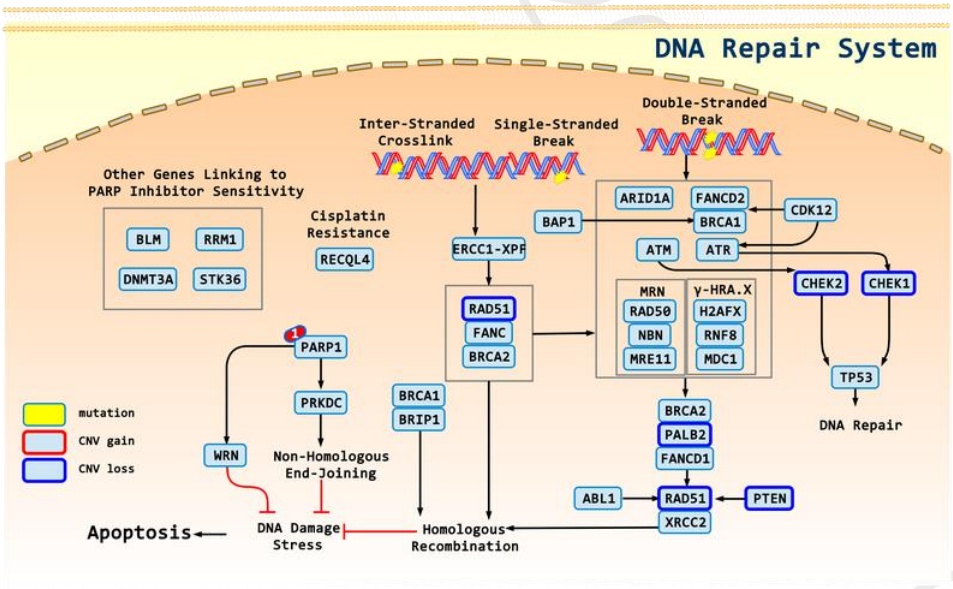


1: Abemaciclib, Palbociclib, Ribociclib



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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