陳彥融
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ACT Onco® + Report

PATIENT		
Identifier: 陳彥融		Patient ID: 49105284
Date of Birth: Mar 06, 1989		Gender: Male
Diagnosis: Salivary duct carcinoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S2219106	Collection site: Parotid gland	Type: FFPE tissue
Date received: Aug 10, 2023	Lab ID: AA-23-05250	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	
PIK3CA H1047R	-	-	Alpelisib, Everolimus
FGFR2(17)-TSC22D3(3) fusion	-	-	Futibatinib, Infigratinib, Pemigatinib

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
PIK3CA H1047R	Temsirolimus, Trametinib, Lapatinib†, Trastuzumab†	-
MCL1 Amplification	Regorafenib, Sorafenib	-
FGFR2(17)-TSC22D3(3) fusion	Erdafitinib	-

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

Note:

- The above summary tables present genomic variants and biomarkers based on the three-tiered approach proposed by US FDA for reporting tumor profiling NGS testing. "Variants/biomarkers with evidence of clinical significance" refers to mutations that are widely recognized as standard-of-care biomarkers (FDA level 2/AMP tier 1). "Variants/biomarkers with potential clinical significance" refers to mutations that are not included in the standard of care but are informational for clinicians, which are commonly biomarkers used as inclusion 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
PIK3CA	H1047R	45.8%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr11	*ATM*	Heterozygous deletion	1
Chr13	*BRCA2, RB1*	Heterozygous deletion	1
Chr17	*BRCA1, FLCN, NF1, RAD51C*	Heterozygous deletion	1
Chr1	*MCL1, NTRK1*	Amplification	6

- Fusions

Fusion Gene & Exon	Transcript ID
*FGFR2(17)-TSC22D3(3) fusion**	FGFR2(NM_000141.4), TSC22D3(NM_004089.3)

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	1.3 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 41% 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.
- *The result is a novel fusion. Confirmation by Sanger sequencing is necessary if residual specimen is available.
- 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 3A		
PIK3CA H1047R	Alpelisib, Everolimus	**sensitive**
FGFR2(17)-TSC22D3(3) fusion	Futibatinib, Infigratinib, Pemigatinib	**sensitive**
Level 3B		
PIK3CA H1047R	Temsirolimus	**sensitive**
FGFR2(17)-TSC22D3(3) fusion	Erdafitinib	**sensitive**
Level 4		
PIK3CA H1047R	Trametinib	**sensitive**
MCL1 Amplification	Regorafenib, Sorafenib	**sensitive**
PIK3CA H1047R	Lapatinib, Trastuzumab	**less sensitive**

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

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

HORMONAL THERAPIES

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

OTHERS

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AG	Irinotecan-based regimens	Level 1B
Clinical Interpretation: Patients with the AG genotype and cancer who are treated with irinotecan-based regimens may have an increased risk of diarrhea and neutropenia as compared to patients with the GG genotype, or a decreased risk of diarrhea and neutropenia compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk of diarrhea and neutropenia.				

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

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

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

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VARIANT INTERPRETATION

FGFR2(17)-TSC22D3(3) fusion

Biological Impact

The fibroblast growth factor receptor 2 (FGFR2) gene encodes a transmembrane receptor tyrosine kinase. Upon binding of the FGF ligand, the receptor activates downstream signaling pathways like RAS-MAPK and PI3K-AKT[1][2][3]. Aberrant activation of FGFR2 through genomic alterations like gain-of-function mutations, fusions, and amplification enhances tumorigenesis, angiogenesis, cell proliferation, and migration[1][2]. FGFR2 alterations are recurrently observed in prostate[4], breast, lung, uterine, and ovarian cancers[5]. While FGFR2 amplification and FGFR2 fusions are commonly detected in gastric cancer[6]and intrahepatic cholangiocarcinoma[3], respectively.

FGFR1/2/3 fusions with genes encoding other signaling proteins can result in FGFR kinases dimerized through protein-protein interactions through N-terminal regions derived from fusion partners in hematological malignancies (type I) and C-terminal regions derived from fusion partners in solid tumors (type II), leading to increased ligand-independent receptor activation[7].

Therapeutic and prognostic relevance

Futibatinib, pemigatinib, and infigratinib are FDA-approved for the treatment of patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma harboring a FGFR2 fusion or other rearrangement. Erdafitinib is FDA-approved for treating patients with locally advanced or metastatic urothelial carcinoma harboring FGFR2-BICC1 or FGFR2-CASP7 fusion.

FGFR2 fusion has been determined as an inclusion criterion for the trials evaluating futibatinib, ponatinib, infigratinib, erdafitinib, and pemigatinib efficacies in various types of solid tumors (NCT02265341, NCT02150967, NCT02699606, NCT03390504, NCT03914794, NCT02052778).

PIK3CA H1047R

Biological Impact

The PIK3CA gene encodes the catalytic subunit (p110α) of phosphatidylinositol 3-kinase (PI3K) that plays a key role in the PI3K/AKT signaling pathway and is involved in the regulation of cellular functions such as proliferation, metabolism and protein synthesis, angiogenesis and apoptosis. PIK3CA has long been described as an oncogene and the PIK3CA gene amplification, deletion, and mutations have been reported in a wide range of cancers, including colorectal, breast, brain, liver, ovarian, stomach and lung cancers[8][9][10][11]. Mutations located in the exon 9 that encodes the PI3K helical (like E542K, E545K) and the exon 20 that encodes the catalytic/kinase domain (like H1047R, H1047L, H1047Y) have been shown to result in the constitutively activated mutant, which could enhance downstream signaling and oncogenic transformation in vitro and in vivo[9][12][13][14].

Therapeutic and prognostic relevance

In a preclinical study, cells harbored different activating PIK3CA mutations (H1047R, E545K, G1049R, Q546K, N345K, H1047L, E542K) were significantly more sensitive to PIK3 pathway inhibitors (dactolisib, MK2206, alpelisib), and MEK1/2 inhibitor trametinib, compared to wild-type[15].

Alpelisib in combination with fulvestrant is FDA-approved for treating HR+, HER2-, PIK3CA-mutated, advanced breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

In NCCN guidelines for breast cancer, alpelisib plus fulvestrant has been recommended for HR-positive/HER2-negative breast cancer patients with PIK3CA activating mutation. Also, the NCCN guidelines for histiocytic neoplasms has recommended everolimus for patients with PIK3CA mutation.

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PIK3CA mutation has been determined as an inclusion criterion for the trials evaluating everolimus, temsirolimus, and alpelisib efficacies in various types of solid tumors (NCT03805399, NCT03203525, NCT04251533).

Everolimus has shown clinical benefit when added to trastuzumab for patients with HER2-overexpressing metastatic breast cancer, particularly in those with PIK3CA mutations, PTEN loss, or hyperactive PI3K pathway[16]. The addition of everolimus to trastuzumab plus vinorelbine has also prolonged PFS in patients with trastuzumab-resistant and taxane-pretreated, HER2-positive, advanced breast cancer. However, adverse events should be taken into consideration[17]. Patients with PIK3CA mutations have shown a favorable response to mTOR inhibitors-containing monotherapy or in combination with doxorubicin and bevacizumab. Combining PI3K-targeted agents with endocrine therapy is suggested[18][19][20][21].

Hyperactivation of the PI3K signaling pathway is associated with resistance to endocrine and HER2-targeting therapies in advanced breast cancer patients[22][23][24][25]. PIK3CA mutations also occur in 5% of EGFR-mutated lung cancers that developed resistance to EGFR TKI therapy[26][27].

In CRC patients, PIK3CA mutation and wild-type KRAS/BRAF showed fair responses to anti-EGFR therapies[28]. PIK3CA mutations are significantly correlated with better recurrence-free survival in unsorted breast cancer patients, according to two meta-analyses involving five studies[29][30][31]. However, in patients with advanced EGFR- or KRAS-mutant lung adenocarcinoma, a concurrent PIK3CA mutation is a poor prognostic factor[32].

ATM Heterozygous deletion

Biological Impact

The ataxia-telangiectasia mutated protein kinase (ATM) gene encodes a PI3K-related serine/threonine protein kinase involved in genomic integrity maintenance and plays central roles in DNA double-strand break (DSB) repair, which can be induced by ionizing radiation, chemotherapy drugs, or oxidative stress[33]. ATM is a well-characterized tumor suppressor gene, hereditary mutations and haploinsufficiency of ATM result in markedly increased susceptibility to a variety of cancer types[34][35][36][37][38]. Results from a case-cohort study of colorectal cancer and cancer-free control individuals suggested that germline pathogenic mutations in ATM and PALB2 should be added to established CRC risk genes as part of standard tumor genetic testing panels[39]. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies[40][41][42][43]and a board range of tumors such as prostate cancer[44], head and neck squamous cell carcinoma (HNSCC)[45], pancreatic cancer[46], lung adenocarcinoma[47], breast cancer[48], and ovarian cancer[35].

Therapeutic and prognostic relevance

Olaparib and talazoparib are FDA-approved for treating mCRPC patients harboring mutations in homologous recombination repair (HRR) genes, including ATM.

ATM mutation has been determined as an inclusion criterion for the trials evaluating olaparib, rucaparib, niraparib, and talazoparib efficacies in various types of solid tumors (NCT03297606, NCT01968213, NCT02952534, NCT03553004, NCT03840967).

Clinical trials have shown that olaparib treatment resulted in response rates in metastatic prostate cancer patients with ATM mutations in TOPARP-A and TOPARP-B trials[49][50], but no response was observed in metastatic breast cancer patients with ATM mutations in the TBCRC 048 trial[51]. In a randomized phase II trial in Asian patients with metastatic gastric cancer, olaparib addition to paclitaxel improved overall survival in patients with low or undetectable ATM protein expression[52], but the subsequent phase III trial did not show significant improvement[51]. In a phase II trial, rucaparib treatment had limited response in mCRPC patients with ATM alteration[53].

In preclinical studies, transformed cells harboing ATM mutation were sensitive to olaparib, niraparib, and talazoparib treatment in vitro and in vivo[54][55][56][57].

Also, a prospective study in muscle-invasive bladder cancer patients suggested that genomic alternations in the DNA repair genes ATMs, RB1 and FANCC could be recognized as biomarkers predictive of response to cisplatin-based neoadjuvant chemotherapy[58]. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer[59].

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer[60].

BRCA1 Heterozygous deletion

Biological Impact

The breast cancer 1, early onset (BRCA1) gene encodes for a multifunctional ubiquitin E3 ligase, a tumor suppressor that has diverse cellular functions, including transcription, protein ubiquitination, cell cycle regulation and DNA damage response, with a particularly important role in homologous recombination, a DNA double-strand break repair pathway. BRCA1 germline mutations confer an increased lifetime risk of developing breast, ovarian and prostate cancer[61][62]. BRCA1 is also a Fanconi anemia susceptibility gene in FANCS, a rare Fanconi anemia subtype[63]. Prevalence of BRCA1 somatic mutation is in non-small cell lung cancer (NSCLC), pancreatic cancer, and colon cancer[64]. Deletion of BRCA1 gene has been correlated to significantly lower expression levels of the BRCA1 mRNA and reduced BRCA1 protein dosage, leading to a reduction in the efficiency of homologous recombination repair of DNA double-strand breaks[65][66][67]. Deleterious BRCA1 mutations have been detected in 8.5% of patients with triple-negative breast cancer (TNBC) (n=1824) unselected for family history and TNBC patients with mutations in BRCA1/2 and genes involved in homologous recombination (including PALB2, BARD1, RAD51D, RAD51C and BRIP1) were diagnosed at an earlier age and had higher-grade tumors than those without mutations[68].

Therapeutic and prognostic relevance

Multiple PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have been approved by the U.S. FDA for the treatment of cancer. Olaparib is approved for multiple settings in advanced ovarian cancer, metastatic breast cancer with BRCA mutations, metastatic pancreatic cancer, and mCRPC with BRCA mutations or HRR gene mutations, including BRCA mutations. Rucaparib is approved for maintenance treatment of recurrent ovarian cancer with BRCA mutations and mCRPC with BRCA mutations. Niraparib is approved for maintenance treatment of advanced ovarian cancer and recurrent ovarian cancer with BRCA mutations, and mCRPC with BRCA mutations in combination with abiraterone acetate. Talazoparib is approved for locally advanced or metastatic breast cancer with BRCA mutations and mCRPC with HRR gene mutations, including BRCA1.

According to the NCCN guidelines, rucaparib is recommended as recurrence therapy for patients with BRCA-mutated ovarian cancer who have been treated with multiple lines of chemotherapy. It is also recommended as maintenance therapy for patients with metastatic pancreatic cancer who have undergone prior platinum-based therapy and harbor germline or somatic BRCA mutations. Additionally, niraparib is recommended as maintenance therapy for ovarian cancer patients with BRCA mutations.

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BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[69]. BRCA2 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[70]. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia[62]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[64].

Therapeutic and prognostic relevance

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According to the NCCN guidelines, rucaparib is recommended as recurrence therapy for patients with BRCA-mutated ovarian cancer who have been treated with multiple lines of chemotherapy. It is also recommended as maintenance therapy for patients with metastatic pancreatic cancer who have undergone prior platinum-based therapy and harbor germline or somatic BRCA mutations. Additionally, niraparib is recommended as maintenance therapy for ovarian cancer patients with BRCA mutations.

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[71]. 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[72][73]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[74][75]. 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[76].

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[77]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[78].

MCL1 Amplification

Biological Impact

The myeloid cell leukemia 1 (MCL1) gene encodes a member of the BCL2 pro-survival family[79]. MCL1 is highly regulated by various oncogenic signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway[80], the mTOR pathway[81], and the phosphatidylinositol-3 kinase (PI3K) pathway[82]. Oncogenic roles for MCL1 have been previously suggested by the report of increased rates of lymphoma in transgenic mice[83]. Somatic amplification of MCL1 may be a common mechanism in cancer cells to increase cell survival[84]. MCL1 overexpression was observed from a retrospective analysis of parotid gland carcinomas, including adenoid cystic carcinoma[85].

Therapeutic and prognostic relevance

Therapies targeting MCL1 and other BCL2 family members with the pan-BCL2 family inhibitors are currently under investigation[86]. A case report has demonstrated clinical efficacy of sorafenib, when combined with vorinostat, in a metastatic triple-negative breast cancer (TNBC) patient with MCL1-amplified tumor[87]. Several in vitro studies also showed that sorafenib induces cell death via inhibition of MCL1 expression in multiple cancer types including, hepatocellular carcinoma (HCC), lung cancer, breast cancer, cholangiocarcinoma, endometrial cancer and chronic lymphocytic leukemia[88][89][90][91][92][93]. Preclinical studies have also demonstrated the efficacy of regorafenib in reducing MCL1 expression in human colorectal cancer (CRC) cell lines[94][95]. In vivo models of colon cancer showed that MCL-1 expression is inhibited by targeting of the mTOR pathway using everolimus, promoting increased tumor cell killing of cancers with KRAS or BRAF mutations[96].

NF1 Heterozygous deletion

Biological Impact

The neurofibromin 1 (NF1) gene encodes a GTPase activating protein (GAP) which is an important negative regulator of the Ras cellular proliferation pathways[97][98][99][100]. Besides, NF1 also physically interacts with the N-terminal domain of focal adhesion kinase (FAK) and involves in the regulation of cell adhesion, growth, and other pathways[101][102]. NF1 is considered a classical haploinsufficient tumor suppressor gene with loss of one allele through inherited or acquired mutation may lead to reduced protein expression and is insufficient to execute normal cellular functions contributing to tumor development[103][104][105][106][107]. NF1 syndrome is a germline condition resulting in a predisposition to several types of cancer such as neurofibromas, melanoma, lung cancer, ovarian cancer, breast cancer, colorectal cancer, hematological malignancies[108][109][110]. Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types[111], including myelodysplastic syndromes, melanomas, colon cancer[112], glioblastomas[113], lung cancer[114], ovarian cancer, and breast cancer[108].

Therapeutic and prognostic relevance

Selumetinib is FDA-approved for treating pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

In the NCCN guidelines for CNS cancers, selumetinib is recommended as a treatment option for recurrent or progressive NF-1 mutated glioma patient.

NF1 mutation/ loss has been determined as an inclusion criterion for the trials evaluating selumetinib efficacy in solid tumors (NCT02664935, NCT03155620)[115].

NF1 depletion is associated with drug resistance to various inhibitors, such as RAF, EGFR, tamoxifen, and retinoic acid[111][116]. Loss of NF1 in lung adenocarcinomas, colorectal cancer, and BRAF-mutated melanomas is associated with resistance to anti-EGFR and BRAF inhibitors[117][118][119][120][121][122]. NF1 loss contributes to trastuzumab resistance in HER2-positive metastatic gastric cancer, but a combination of HER2 and MEK/ERK inhibitors may overcome this resistance[123]. Trametinib is effective in treating neurofibromatosis type I-associated glioblastoma[124]. Patients with

mutations in the mTOR pathway, including NF1, have responded to everolimus[125]. However, a patient with metastatic lung cancer harboring CCDC6-ROS1 and NF1 truncating mutation treated with crizotinib had a short overall survival of one month[126].

NF1 depletion has been linked to drug resistance to several inhibitors in vitro, including RAF, EGFR, and trastuzumab. However, adding MEK inhibitors could restore sensitivity to erlotinib[117], and MEK and mTOR inhibitors showed promise in NF1-deficient tumors[127][128]. Knockdown of NF1 also led to resistance to crizotinib and cabozantinib treatment in ROS1 fusion-positive cells[126].

NTRK1 Amplification

Biological Impact

The NTRK1 gene encodes the TRKA (tropomyosin receptor kinase) receptor which plays an important role in the development and function of the nervous system. Gene fusions of NTRK1 lead to constitutive activation of MAP-kinase, PI3-kinase, and PLC-γ pathways, and represent the main molecular alterations with known oncogenic and transforming potential in various malignancies, including soft tissue sarcoma, non-small cell lung cancer (NSCLC), glioblastoma multiforme (GBM), thyroid carcinoma, and pilocytic astrocytomas[129][130]. A pan-cancer study (n=1250) demonstrated that 2.2% of the metastatic cancer patients harbored NTRK amplification and NTRK protein overexpression was observed in 14.8% of NTRK-amplified tumors (doi.org/10.23838/pfm.2017.00142).

Therapeutic and prognostic relevance

Patients with NTRK1 amplification had only limited benefit from larotrectinib treatment according to the few clinical studies. One of them had a partial response with larotrectinib of short duration (3.7 months)[131], and the other one with metastatic NTRK1-amplified (copy number=8) esophageal carcinoma showed clinical efficacy for six weeks, and then a progressive disease of new lesions were observed[132].

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)[133][134][135][136][137]. Amplification of RAD51C has been implicated in tumor progression[138][139]. RAD51C is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function[140].

Therapeutic and prognostic relevance

Olaparib and talazoparib are FDA-approved for treating mCRPC patients harboring mutations in homologous recombination repair (HRR) genes, including RAD51C.

RAD51C mutation has been determined as an inclusion criterion for the trials evaluating olaparib, rucaparib, niraparib, and talazoparib efficacies in various types of solid tumors (NCT03786796, NCT02401347, NCT03148795, NCT03553004).

A preclinical study using gastric cancer xenograft model showed that RAD51C deficiency caused sensitivity to PARP inhibitor olaparib[141].

RB1 Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[142]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[143]. RB1 has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[144][145][146]. Deletion or inactivating mutation of RB1 is found in a number of tumors, including lung, prostate, bladder, breast cancers and sarcomas. RB1 mutations are found in approximately half of all retinoblastoma cases[147].

Therapeutic and prognostic relevance

A deleterious mutation in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response and better overall survival to cisplatin-based chemotherapy for muscle-invasive bladder cancer patients[58]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytoxan (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy[148].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[149][150].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[151]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[152].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[153][154]. Analyses of repeat biopsy samples from patients with EGFR-mutant adenocarcinoma that had transformed to the SCLC subtype have revealed that 100% of these patients have loss of RB1 and may be the alteration that induces this non-small-cell to small-cell transformation[150][155].

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US FDA-APPROVED DRUG(S)

Alpelisib (PIQRAY)

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models. Alpelisib is developed and marketed by Novartis under the trade name PIQRAY.

- FDA Approval Summary of Alpelisib (PIQRAY)

SOLAR-1[156] NCT02437318	**Hr-positive, her2-negative breast cancer** (Approved on 2019/05/24)
	PIK3CA mutation
	Alpelisib plus fulvestrant vs. Placebo plus fulvestrant [PFS(M): 11 vs. 5.7]

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

Cobimetinib (COTELLIC)

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

- FDA Approval Summary of Cobimetinib (COTELLIC)

coBRIM[158] NCT01689519	**Melanoma** (Approved on 2015/11/10)
	BRAF V600E/K
	Cobimetinib + vemurafenib vs. Placebo + vemurafenib [PFS(M): 12.3 vs. 7.2]

Erdafitinib (BALVERSA)

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

- FDA Approval Summary of Erdafitinib (BALVERSA)

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

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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[159] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[160] 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[161] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[162] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[163] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

Futibatinib (LYTGOBI)

Futibatinib is an orally bioavailable inhibitor of the fibroblast growth factor receptor (FGFR) with potential antineoplastic activity, which may result in the inhibition of both the FGFR-mediated signal transduction pathway and tumor cell proliferation, and increased cell death in FGFR-overexpressing tumor cells.LYTGOBI was discovered by Taiho Oncology's parent company, Taiho Pharmaceutical.

- FDA Approval Summary of Futibatinib (LYTGOBI)

TAS-120-101 NCT02052778	**Cholangiocarcinoma** (Approved on 2022/09/30)
	FGFR2 fusion
	Futibatinib [ORR(%): 42.0, DoR(M): 9.7]

Infigratinib (TRUSELTIQ)

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

- FDA Approval Summary of Infigratinib (TRUSELTIQ)

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

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)

MAGNITUDE NCT03748641	**Prostate cancer** (Approved on 2023/08/11) **BRCA mutation** Niraparib and abiraterone acetate plus prednisone vs. placebo and abiraterone acetate plus prednisone [rPFS(M): 16.6 vs. 10.9]
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[164] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27) - Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

Olaparib (LYNPARZA)

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

- FDA Approval Summary of Olaparib (LYNPARZA)

PROpel NCT03732820	**Prostate cancer** (Approved on 2023/05/31) **BRCA mutation** Olaparib + abiraterone + prednisone vs. Placebo + abiraterone + prednisone [rPFS(M): not reached vs. 8]
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[165] 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[166] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08) **HRD+** Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[167] 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[168] 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[169] NCT02000622	**Breast cancer** (Approved on 2018/02/06) **HER2-/gBRCA mutation** Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]

SOLO-2/ENGOT-Ov21[170] 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[171] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

Pemigatinib (PEMAZYRE)

Pemigatinib is a small molecule kinase inhibitor that targets FGFR1, 2, and 3 with IC50 values less than 2 nM. Pemigatinib is developed and marketed by Incyte under the tradename PEMAZYRE.

- FDA Approval Summary of Pemigatinib (PEMAZYRE)

FIGHT-202[172] NCT02924376	**Cholangiocarcinoma** (Approved on 2020/04/17)
	FGFR2 fusion
	Pemigatinib [ORR(%): 36.0]

Regorafenib (STIVARGA)

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

- FDA Approval Summary of Regorafenib (STIVARGA)

RESORCE[173] NCT01774344	**Hepatocellular carcinoma, Hepatocellular carcinoma** (Approved on 2017/04/27)
	-
	Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]
GRID[174] NCT01271712	**Gastrointestinal stromal tumor** (Approved on 2013/02/25)
	-
	Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]
CORRECT[175] NCT01103323	**Colorectal cancer** (Approved on 2012/09/27)
	-
	Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

Rucaparib (RUBRACA)

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

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]

ARIEL3[176] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	-
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]

Selumetinib (KOSELUGO)

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

- FDA Approval Summary of Selumetinib (KOSELUGO)

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

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[177] NCT00984282	**Differentiated thyroid carcinoma** (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
SHARP[178] NCT00105443	**Hepatocellular carcinoma** (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]
TARGET[179] 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)

TALAPRO-2 NCT03395197	**Prostate cancer** (Approved on 2023/06/20)
	HRR genes mutation
	Talazoparib + enzalutamide vs. Placebo + enzalutamide [rPFS(M): Not reached vs. 13.8]
EMBRACA[180] 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)

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

Trametinib (MEKINIST)

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

- FDA Approval Summary of Trametinib (MEKINIST)

CDRB436G2201 NCT02684058	**Low-grade glioma** (Approved on 2023/03/09)
	BRAF V600E
	Dabrafenib + trametinib vs. Carboplatin + vincristine [ORR(%): 46.6 vs. 10.8]
BRF117019, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060, NCT02124772	**Cancer** (Approved on 2022/06/22)
	BRAF V600E
	Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0]
BRF117019[182] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[183] NCT01336634	**Non-small cell lung cancer** (Approved on 2017/06/22)
	BRAF V600E
	Trametinib + dabrafenib vs. Dabrafenib [ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9]
COMBI-d[184] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[185] NCT01245062	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

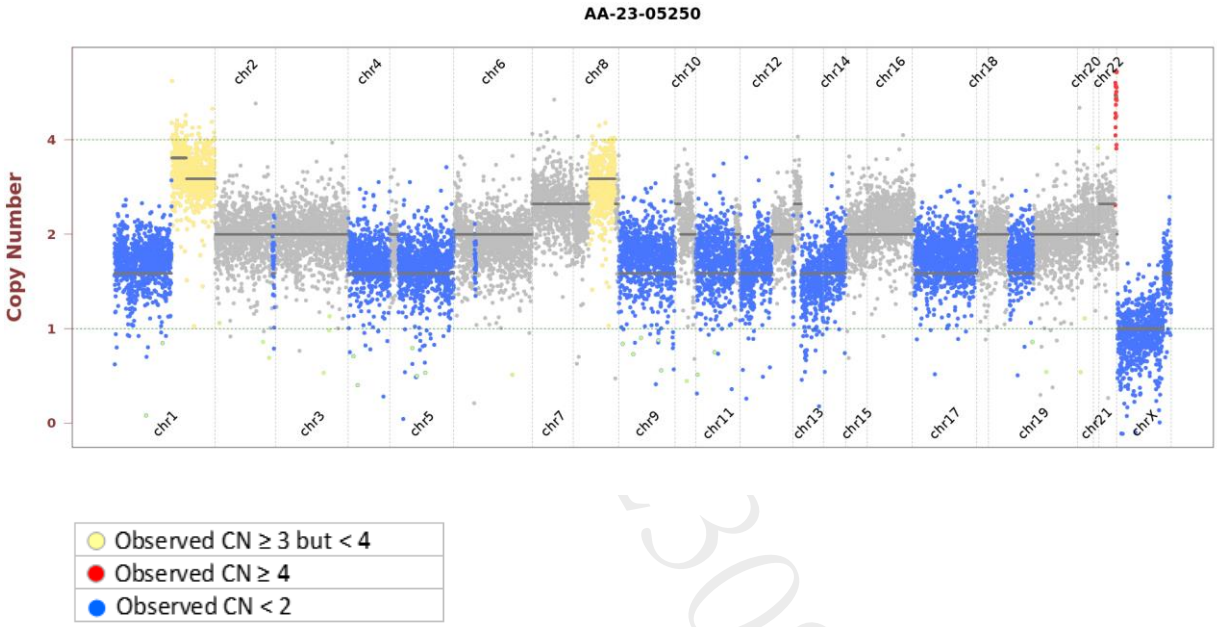
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
PIK3CA	H1047R	21	c.3140A>G	NM_006218	COSM775	45.8%	1384

- 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
ADAMTS1	A642V	7	c.1925C>T	NM_006988	COSM6593777	13.3%	1471
ARID1B	A1702T	19	c.5104G>A	NM_017519	COSM7335214	53.9%	1686
BCL9	M450V	8	c.1348A>G	NM_004326	-	66.2%	139
CARD11	A687V	16	c.2060C>T	NM_032415	-	58.0%	1250
CCNB3	R397H	5	c.1190G>A	NM_033031	COSM1122623	99.7%	624
FANCA	D999G	31	c.2996A>G	NM_000135	-	56.9%	1132
FLCN	R570C	14	c.1708C>T	NM_144997	COSM6956342	15.5%	1028
IL7R	R140W	4	c.418C>T	NM_002185	COSM1695578	38.5%	864
LRP1B	R3069S	58	c.9205C>A	NM_018557	-	31.2%	260
MUC16	G10108E	3	c.30323G>A	NM_024690	COSM2731565	48.1%	995
NOTCH2	M2099V	34	c.6295A>G	NM_024408	COSM6938259	56.4%	966
PIK3C2B	R1008Q	20	c.3023G>A	NM_002646	COSM1338083	59.5%	1512
PIK3CA	K733R	15	c.2198A>G	NM_006218	COSM6148	34.1%	946
PTCH1	D898N	16	c.2692G>A	NM_000264	COSM1111473	57.5%	929

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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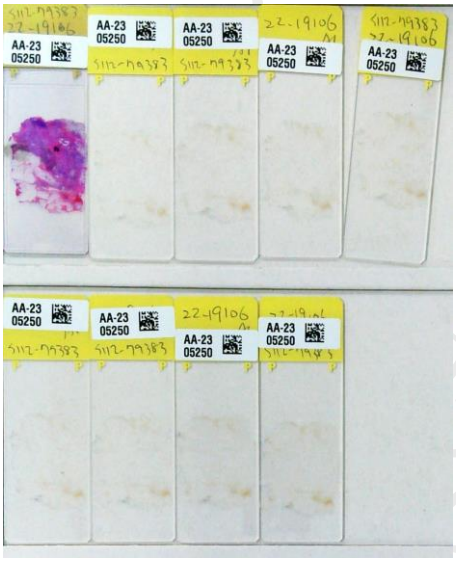
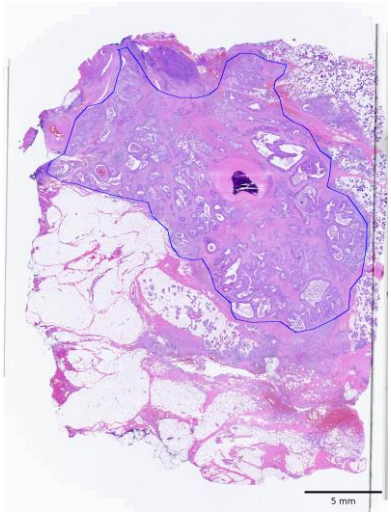
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: May 19, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S2219106
- Collection site: Parotid gland
- Examined by: Dr. Chien-Ta Chiang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 15%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 40%
    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: 1096x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 123

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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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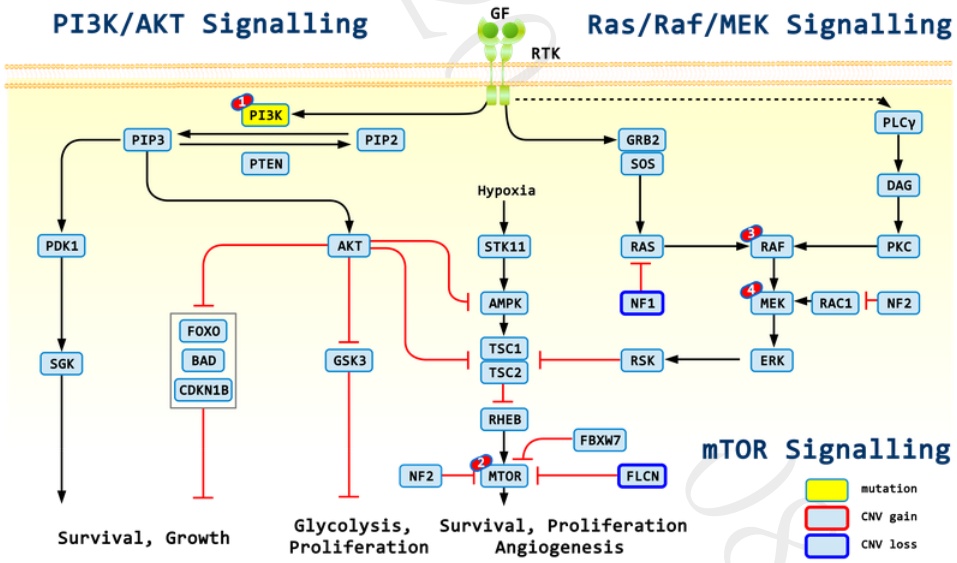
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

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

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Alpelisib; 2: Temsirolimus, Everolimus; 3: Sorafenib; 4: Trametinib, Selumetinib, Binimetinib, Cobimetinib

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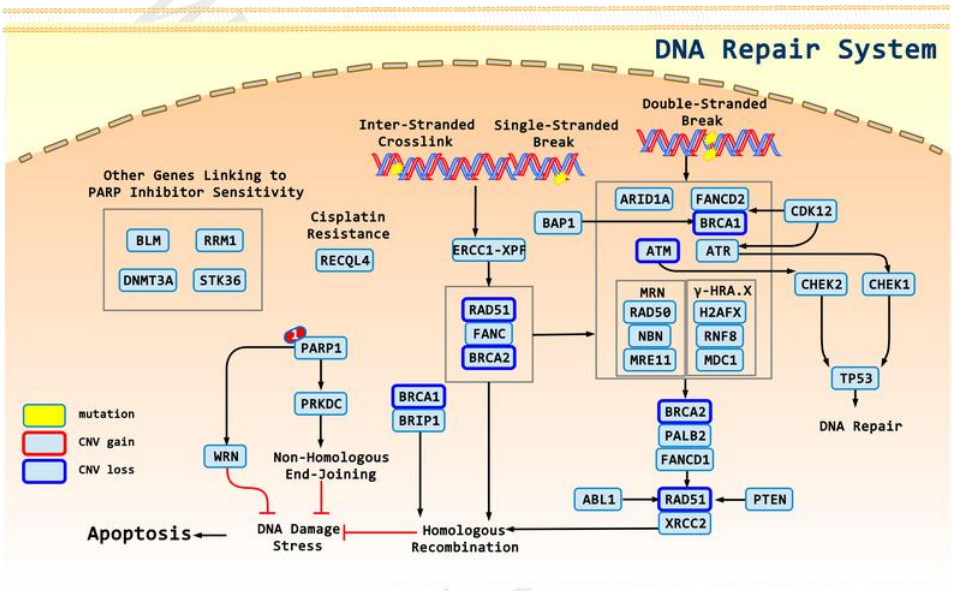
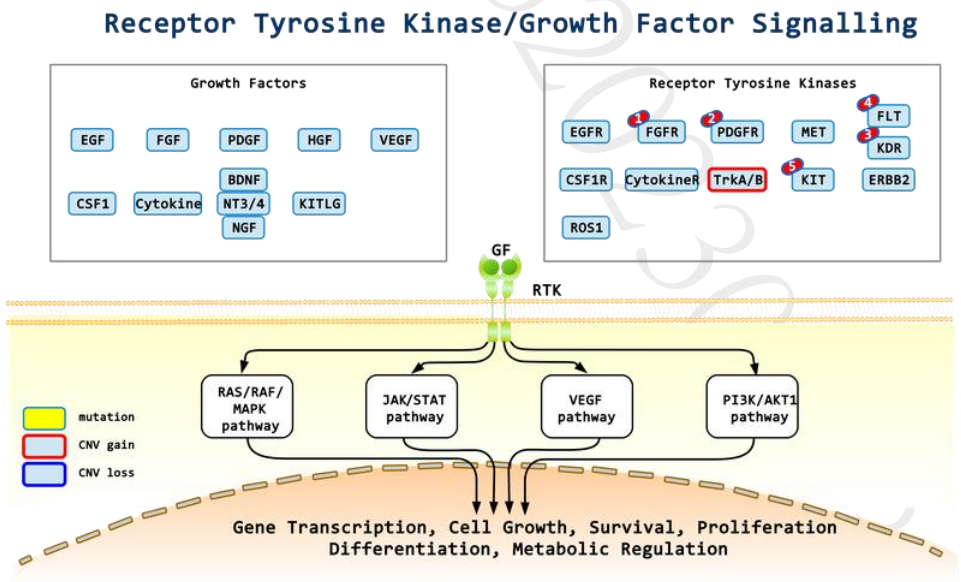


1: Olaparib, Niraparib, Rucaparib, Talazoparib



1: Erdafitinib, Infigratinib, Pemigatinib, Futibatinib; 2: Regorafenib, Erdafitinib; 3: Erdafitinib; 4: Erdafitinib; 5: Sorafenib, Regorafenib, Erdafitinib

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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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