楊雅綺
Project ID: C22-M001-03128
Report No.: AA-22-06190_ONC
Date Reported: Oct 26, 2022

ACT Onco® + Report

PATIENT		
Identifier: 楊雅綺		Patient ID: 20922796
Date of Birth: Feb 27, 1956		Gender: Female
Diagnosis: Poorly differentiated adenocarcinoma		
ORDERING PHYSICIAN		
Name: 黃子豪醫師		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: S11140383A	Collection site: Omentum	Type: FFPE tissue
Date received: Oct 13, 2022	Lab ID: AA-22-06190	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
FGFR1 Amplification	Erdafitinib, Infigratinib, Lenvatinib, Pazopanib, Ponatinib, Regorafenib, Sunitinib	Palbociclib, Ribociclib
LYN Amplification	Dasatinib	-

Note:

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

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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
TP53	R248W	69.1%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr20	*ZNF217*	Amplification	6
Chr8	*LYN, NBN*	Amplification	6
Chr18	*TYMS*	Amplification	7
Chr8	*KAT6A*	Amplification	7
Chr8	*FGFR1*	Amplification	15

- Fusions

Fusion Gene & Exon	Transcript ID
No fusion gene detected in this sample	

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	4.4 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 54% tumor purity.
- 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		
FGFR1 Amplification	Erdafitinib, Infigratinib, Ponatinib, Regorafenib, Sunitinib	**sensitive**
Level 4		
FGFR1 Amplification	Lenvatinib, Pazopanib	**sensitive**
LYN Amplification	Dasatinib	**sensitive**
FGFR1 Amplification	Palbociclib, Ribociclib	**resistant**

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

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

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
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
TYMS Amplification	Fluorouracil	**Less sensitive**	Clinical	Colorectal cancer
	Pemetrexed	**Less sensitive**	Clinical	Lung cancer
ZNF217 Amplification	Doxorubicin	**Less sensitive**	Clinical	Breast cancer
	Fluorouracil Mitomycin	**Less sensitive**	Clinical	Breast cancer
TP53 R248W	Platinum- and taxane-based regimens	**Less sensitive**	Clinical	Ovarian cancer

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
FGFR1 Amplification	Letrozole	**Resistant**	Clinical	Estrogen-receptor positive breast cancer
	Tamoxifen	**Resistant**	Preclinical	Breast cancer
ZNF217 Amplification	Tamoxifen	**Resistant**	Clinical	Estrogen-receptor positive breast cancer

OTHERS

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

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

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VARIANT INTERPRETATION

TP53 R248W

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[1]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[2].

R248W is a missense mutation located in the DNA-binding domain (DBD) of the p53 protein[3]. This mutation results in abrogation of the p53 tumor suppressor activity and a gain-of-function in ATM inactivation, resulting in increased genetic instability and increased tumorigenesis in mouse models[4].

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)[5].

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[6]. 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[7].

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[8][9][10]. 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)[11]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[12][13]. 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[14].

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[15].

FGFR1 Amplification

Biological Impact

The fibroblast growth factor receptor 1 (FGFR1) gene encodes a receptor tyrosine kinase that plays crucial roles in cellular proliferation, survival, migration and angiogenesis[16][17]. Several studies have demonstrated that FGFR1 amplification correlates with FGFR1 overexpression[18][19][20][21][22][23]. Overexpression of FGFR1 has also been shown to enhance both ligand-dependent, and independent activation of downstream signaling pathways such as the phosphoinositide-3 kinase (PI3K) and the extracellular signal-regulated kinase 1/2 (ERK1/2) cascades[24][25][26]. Amplification of FGFR1 has been associated with early relapse, and poor survival, specifically in ER+ breast cancer[24][27], and may be associated with progression of breast cancer from in situ-to-invasive transition[28].

FGFR1 amplifications have been reported in various types of cancer, including lung cancer[29], breast cancer[24], oral squamous cell carcinoma (OSCC)[30], prostate cancer[31], and esophageal cell carcinoma[32]. Besides, activating mutations (C381R and N330I) have been identified in giant cell lesions of the jaw[33].

Therapeutic and prognostic relevance

Non-selective TKI-targeting inhibitors such as pazopanib, regorafenib, and ponatinib are multi-kinase inhibitors with inhibitory activities towards FGFR1[34][35].FGFR1 mutations, amplifications, and fusions, have been determined as an inclusion criteria for a trial examining pemigatinib efficacies in advanced malignancies including solid tumor, endometrial carcinoma, gastric carcinoma, multiple myeloma, myeloproliferative neoplasm, squamous cell lung carcinoma, and urothelial carcinoma (FIGHT-101; NCT02393248).

To date, Erdafitinib (BALVERSATM), is the first and only pan-FGFR kinase inhibitor approved by U.S. FDA, for the treatment of patients with locally advanced or metastatic bladder cancer with FGFR3 mutations or FGFR2/FGFR3 fusions. Addition of the erdafitinib to palbociclib/fulvestrant induced complete responses of FGFR1-amplified/ER+ patient-derived-xenografts[36].

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

A case report of a patient with HR+, HER2- breast cancer harboring FGFR1 amplification responded well to pazopanib[37]. Another clinical study demonstrated that three patients with metastatic colorectal cancer achieved partial responses to regorafenib treatment, and all of them harbored FGFR1 amplification[38].

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

Several small molecule FGFR inhibitors such as AZD-4547 and NVP-BGJ398 (Infigratinib) are under clinical evaluation, although mainly in the early stages of trials[39]. Infigratinib has shown antitumor activity and manageable safety profile in patients with a variety of solid tumors, including FGFR1-amplified squamous cell lung cancer (sqNSCLC) and FGFR3-mutant bladder/urothelial cancers[40]. Meanwhile, Dovitinib, a potent FGFR inhibitor, in combination with fulvestrant showed promising clinical activity in the FGF pathway-amplified postmenopausal patients with HR+, HER2- advanced breast cancer[41].

In ER-positive breast cancer, FGFR1 amplification has been implicated as an acquired mechanism of resistance to endocrine therapies[42], such as letrozole, 4-hydroxytamoxifen, and anastrozole-containing regimen[43][24][44]. Besides, FGFR1/2 amplification or activating mutations were detected in ctDNA from post-progression ER-positive breast cancer patients after the fulvestrant plus palbociclib treatment. According to the subgroup analysis from MONALEESA-2 clinical trial, ER-positive breast cancer patients with FGFR1 amplification exhibited a shorter progression-free survival when treated with letrozole plus ribociclib[36].

Meanwhile, in non-small cell lung carcinoma (NSCLC), FGFR1 is considered as an alternative acquired mechanism of resistance to EGFR tyrosine kinase inhibitors[45]. For example, upregulated FGFR1-FGF2 autocrine loop was identified in a gefitinib-resistant cell model[46], and focal FGFR1 amplification was observed in an NSCLC patient who developed resistance to osimertinib treatment[47].

The BOLERO-2 clinical trial (everolimus plus exemestane) suggested that FGFR1 amplification and CCND1 amplification may be correlated with lessened progression-free survival (PFS) with the mTOR inhibitor everolimus[48][49].

In preclinical study, thyroid cancer cell with FGFR1 amplification is sensitive to lenvatinib treatment[50][51]. Ponatinib, a multi-targeted tyrosine kinase inhibitor, demonstrated anti-proliferative activity in lung cancer, breast cancer, and Ewing's sarcoma cells overexpressing FGFR1[52][34][53].

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KAT6A Amplification

Biological Impact

The KAT6A (Lysine Acetyltransferase 6A) gene encodes for a member of the MOZ, YBFR2, SAS2, TIP60 family of histone acetyltransferases. KAT6A is a HAT enzyme that controls fundamental cellular processes, including gene transcription and maintenance of normal hematopoietic stem cell[54]. Analysis of the genomic dataset from The Cancer Genome Atlas (TCGA) showed that KAT6A is amplified in at least 11% of breast tumors, at a higher frequency (22%) in the Luminal B subtype (HER2-)[55].

Therapeutic and prognostic relevance

A study of the TCGA data demonstrated a strong correlation between KAT6A copy number and mRNA expression levels. Besides, high level of KAT6A expression was associated with significant reduction in overall survival[56].

Preclinical study of gliomas showed that overexpression of KAT6A promotes PI3K/AKT signaling pathway activation by upregulating PIK3CA expression. Besides, the pan-PI3K inhibitor LY294002 is capable of abrogating the growth-promoting effect of KAT6A[57].

LYN Amplification

Biological Impact

The LYN Proto-Oncogene, Src Family Tyrosine Kinase (LYN) gene encodes a non-receptor tyrosine protein kinase of the Src family (SFK)[58]. LYN plays an important role in the regulation of immune responses, hematopoiesis, signal transduction of growth factors and cytokines and is activated in the cellular response to DNA damage and genotoxic agents[59][60][61][62]. LYN has been described to promote tumor growth, invasion, epithelial to mesenchymal transition (EMT) and ERK signaling in different cancer types[63][64][65]. Amplification of LYN has been identified in prostate cancer, breast cancer and ovarian cancer (cBioPortal).

Therapeutic and prognostic relevance

LYN could be pharmacologically targeted with Src-kinase inhibitors. Results of preclinical studies showed that dasatinib, a dual-specificity tyrosine kinase inhibitor of ABL and the Src-family tyrosine kinases, exerted antitumor activity in LYN-expressing breast cancer cells[63].

NBN Amplification

Biological Impact

The NBN gene encodes a component of the MRE11-RAD50-NBN (MRN) complex, which involves in DNA double-strand break sensing and repair[66]. NBN mutation is related to Nijmegen breakage syndrome, increased cancer incidence and ionizing radiation sensitivity[66][67]. NBN mutations have been found in various cancers, including cholangiocarcinoma, hepatocellular carcinoma[68], prostate cancer[69], leukemia, lymphoma[70], and triple-negative breast cancer[71].

Therapeutic and prognostic relevance

In a phase II trial (ARIEL2), an ovarian cancer patient harboring a NBN germline mutation showed responses to rucaparib treatment[72]. NBN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer[73]; the trials evaluating rucaparib efficacy in ovarian cancer[74]or prostate cancer[75]; the trials evaluating talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556), and the trials evaluating niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate) cancer (NCT03207347).

Germline and somatic mutations in homologous recombination genes, including NBN, have been suggested to be prognostic biomarkers for platinum-based treatment response and superior survival in patients with ovarian, fallopian tube, peritoneal carcinomas and pancreatic cancer[76][77].

In a retrospective study of localized prostate cancer, NBN gene amplification has been demonstrated to associate with overall tumor genomic instability and lower biochemical relapse-free rate following image-guided radiotherapy (IGRT)[78].

Another retrospective study showed that amplification of the NBN gene is associated with protein overexpression and mostly correlated with poor prognosis in several cancer types, including ovarian cancer, breast invasive carcinoma, uterine corpus endometrial carcinoma, and sarcoma. Besides, in vivo and in vitro assays demonstrated that amplification of the NBN gene could induce cisplatin and PARP inhibitor resistance in breast and ovarian cancer cells[79].

TYMS Amplification

Biological Impact

TYMS (Thymidylate Synthetase) gene encodes the thymidylate synthase that catalyzes the methylation of deoxyuridylate to deoxythymidylate. The enzyme is critical for DNA replication and repair[80][81][82]. TYMS polymorphisms may be associated with etiology of neoplasia, including acute lymphoblastic leukemia[83], breast cancer, and response to chemotherapy[84].

Therapeutic and prognostic relevance

Thymidylate synthase gene amplification was associated with pemetrexed resistance in patients with advanced non-small cell lung cancer[85][86][87][88], and 5-FU resistance in CRC patients[89]

ZNF217 Amplification

Biological Impact

The zinc-finger protein 217 (ZNF217) is a member of Kruppel-like family (KLF) of transcription factors[90][91]. ZNF217 is an oncogenic protein that plays deleterious functions in various human cancers[92]by inducing epithelial-mesenchymal transition (EMT)[93], activating the ERBB2/ERBB4/FAK[93]and AKT[94]pathways. The increased copy number of ZNF217 has been reported in breast cancer[95]. In colorectal cancer and ovarian cancer, amplification of the ZNF217 gene is associated with increased protein or mRNA expression[96][97]. Overexpression of ZNF217 has been found in solid tumors[98][99][100][101].

Therapeutic and prognostic relevance

A high expression level of ZNF217 has been shown to confer tamoxifen resistance in ER+ breast cancer cells and is a predictor of relapse under endocrine therapy in patients with ER+ breast cancer[102]. Overexpression of ZNF217 is also linked to poor outcome in ovarian and colon cancer[100][101].

ZNF217-overexpressing breast cancer cells were correlated with paclitaxel resistance in vitro[94][103]. In a retrospective study, tumors that responded to doxorubicin or a combination of 5-fluorouracil and mitomycin (FUMI) expressed less ZNF217 than did nonresponsive tumors[104]. Triciribine, a nucleoside analogue and DNA synthesis inhibitor, inhibits tumor growth of ZNF217-overexpressing tumor in vivo. However, results from a Phase II study showed that antitumor activity of triciribine was not evident in all patients, possibly due to a lack of biomarkers for patient selections[104]. Expression of ZNF217 may serve as a potential biomarker for the treatment of triciribine[104].

High level of ZNF217 expression represents a biomarker for poor prognosis associated with shorter relapse-free survival in breast cancer and ovarian cancer[93][97].

US FDA-APPROVED DRUG(S)

Dasatinib (SPRYCEL)

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

- FDA Approval Summary of Dasatinib (SPRYCEL)

DASISION[105] NCT00481247	**Chronic myeloid leukemia** (Approved on 2010/10/28)
	-
	Dasatinib vs. Imatinib [ORR(%): 76.8 vs. 66.2]
[106] NCT00123474	**Chronic myeloid leukemia** (Approved on 2007/11/08)
	-
	Dasatinib [ORR(%): 63.0]
[107] NCT00123487	**Acute lymphocytic leukemia** (Approved on 2006/06/28)
	-
	Dasatinib [ORR(%): 38.0]

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]

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]

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Lenvatinib (LENVIMA)

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

- FDA Approval Summary of Lenvatinib (LENVIMA)

KEYNOTE-775 (Study 309) NCT03517449	**Endometrial carcinoma** (Approved on 2021/07/22)
	MSS/pMMR
	Pembrolizumab + lenvatinib vs. Investigator's choice of doxorubicin or paclitaxel [PFS(M): 6.6 vs. 3.8, OS(M): 17.4 vs. 12]
KEYNOTE-146 NCT02501096	**Endometrial carcinoma** (Approved on 2019/09/17)
	MSS/pMMR
	Pembrolizumab + lenvatinib [ORR(%): 38.3, DOR(M): NR]
REFLECT[108] NCT01761266	**Hepatocellular carcinoma** (Approved on 2018/08/16)
	-
	Lenvatinib vs. Sorafenib [OS(M): 13.6 vs. 12.3]
SELECT[109] NCT01136733	**Renal cell carcinoma** (Approved on 2016/05/13)
	-
	Lenvatinib+ everolimus vs. Everolimus [PFS(M): 14.6 vs. 5.5]
SELECT[110] NCT01321554	**Thyroid cancer** (Approved on 2015/02/13)
	-
	Lenvatinib vs. Placebo [PFS(M): 18.3 vs. 3.6]

Pazopanib (VOTRIENT)

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

- FDA Approval Summary of Pazopanib (VOTRIENT)

PALETTE[111] NCT00753688	**Sarcoma** (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]
VEG105192[112] NCT00334282	**Renal cell carcinoma** (Approved on 2009/10/19)
	-
	Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]

Ponatinib (ICLUSIG)

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

- FDA Approval Summary of Ponatinib (ICLUSIG)

PACE[113] NCT01207440	**Chronic phase chronic myeloid leukemia** (Approved on 2014/03/12) - Ponatinib [MCyR(%): 55]
PACE[113] NCT01207440	**Accelerated phase chronic myeloid leukemia** (Approved on 2014/03/12) - Ponatinib [MaHR(%): 57]
PACE[113] NCT01207440	**Blast phase chronic myeloid leukemia** (Approved on 2014/03/12) - Ponatinib [MaHR(%): 31]
PACE[113] NCT01207440	**Philadelphia-positive acute lymphoblastic leukemia** (Approved on 2014/03/12) - Ponatinib [MaHR(%): 41]

Regorafenib (STIVARGA)

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

- FDA Approval Summary of Regorafenib (STIVARGA)

RESORCE[114] NCT01774344	**Hepatocellular carcinoma, Hepatocellular carcinoma** (Approved on 2017/04/27) - Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]
GRID[115] NCT01271712	**Gastrointestinal stromal tumor** (Approved on 2013/02/25) - Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]
CORRECT[116] NCT01103323	**Colorectal cancer** (Approved on 2012/09/27) - Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

Sunitinib (SUTENT)

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

- FDA Approval Summary of Sunitinib (SUTENT)

[117][118][119] NCT00428597	**Pancreatic cancer** (Approved on 2011/05/20) - Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]

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[120][121] NCT00083889	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib vs. Ifn-α [PFS(W): 47.3 vs. 22]
[122][123][121] NCT00077974	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 34.0]
[123][121] NCT00054886	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 36.5]
[124] NCT00075218	**Gastrointestinal stromal tumor** (Approved on 2006/01/26)
	-
	Sunitinib vs. Placebo [TTP(W): 27.3 vs. 6.4]

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

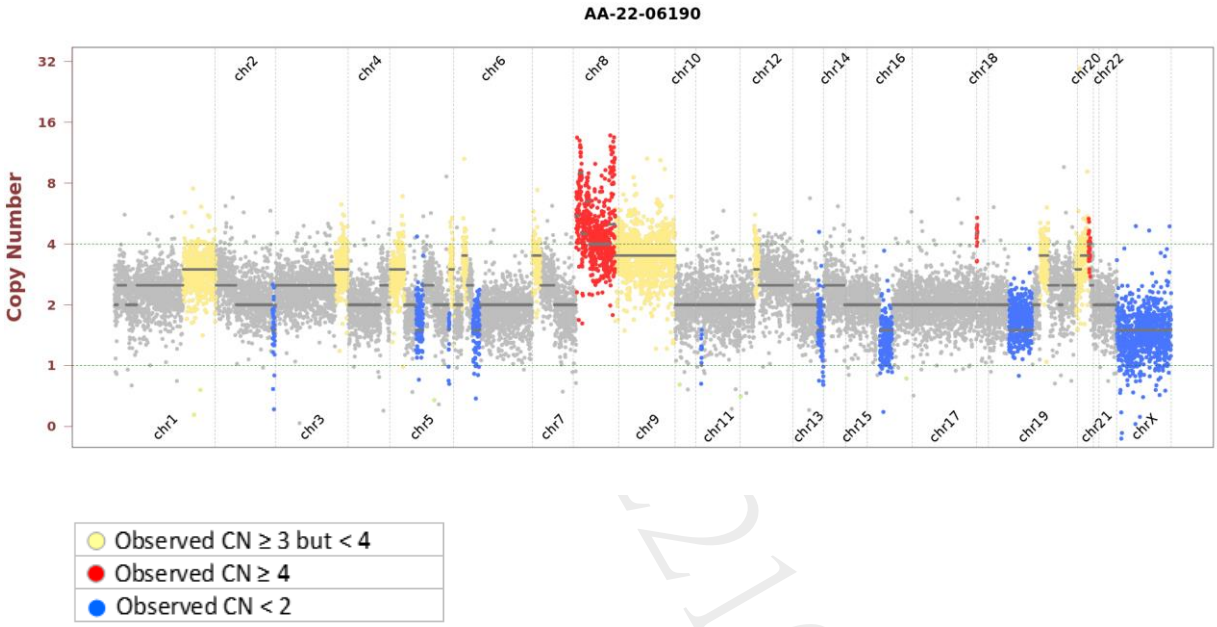
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
TP53	R248W	7	c.742C>T	NM_000546	COSM10656	69.1%	1242

- 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
ALK	P1215L	23	c.3644C>T	NM_004304	-	86.4%	1961
BRCA2	A2786T	19	c.8356G>A	NM_000059	-	80.9%	282
BUB1B	W722R	17	c.2164T>C	NM_001211	-	78.5%	507
CARD11	S694L	16	c.2081C>T	NM_032415	COSM5505215	30.0%	533
CCNE2	E45del	4	c.134_136del	NM_057749	-	13.9%	1119
CDK7	Q130R	6	c.389A>G	NM_001799	-	33.6%	110
DAXX	F87V	3	c.259T>G	NM_001141969	-	35.0%	246
ERBB4	D1257H	28	c.3769G>C	NM_005235	-	80.1%	613
ERBB4	T731M	18	c.2192C>T	NM_005235	COSM1172842	58.2%	486
ESR1	R300C	4	c.898C>T	NM_000125	COSM9113095	81.5%	879
FGFR1	D282G	7	c.845A>G	NM_023110	-	7.8%	1779
KDM6A	Splice region	-	c.226-8A>G	NM_021140	-	72.4%	210
LRP1B	A3191D	60	c.9572C>A	NM_018557	-	30.3%	1104
MUC16	N5131K	3	c.15393C>A	NM_024690	-	49.8%	1304
MUC16	W7646L	3	c.22937G>T	NM_024690	-	30.5%	508
PARP1	G974R	22	c.2920G>A	NM_001618	COSM378915	30.6%	899
POLE	M2201V	47	c.6601A>G	NM_006231	-	35.6%	1187
RB1	Splice region	-	c.608-8T>G	NM_000321	-	37.7%	334
SYNE1	R2368H	48	c.7103G>A	NM_182961	-	65.8%	240
TAP2	S408C	7	c.1222A>T	NM_018833	-	23.1%	1739
USH2A	E2613D	41	c.7839G>T	NM_206933	-	63.4%	1201

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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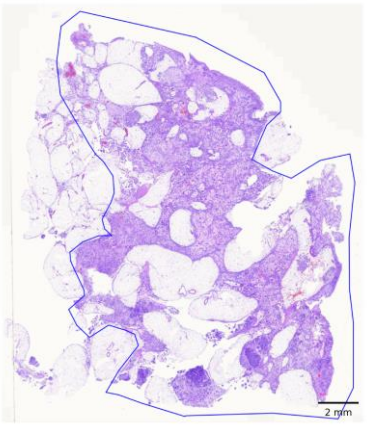
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Oct 06, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11140383A
- Collection site: Omentum
- Examined by: Dr. Chien-Ta Chiang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 10%
    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: 753x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 165

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).

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.

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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:
醫藥資訊研究員
楊杭哲 博士
Hang-Che Yang Ph.D.

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

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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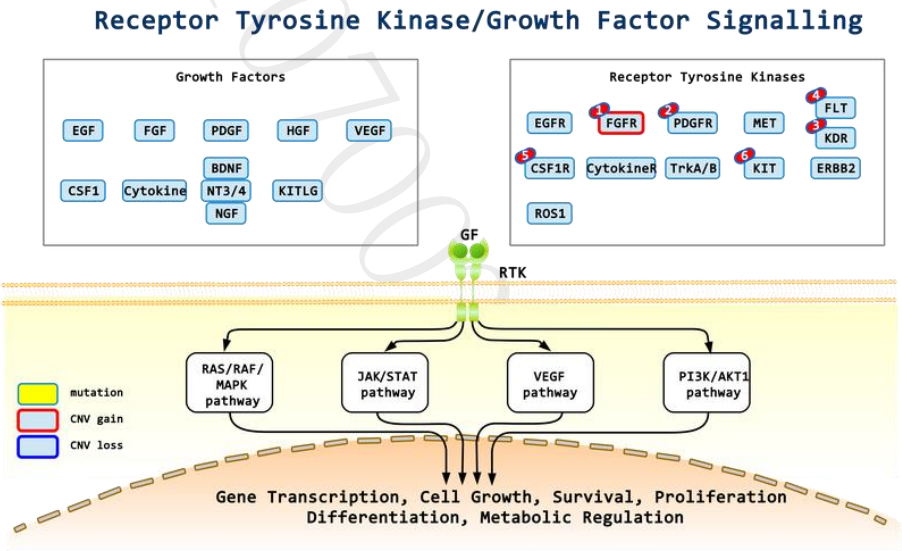
APPENDIX

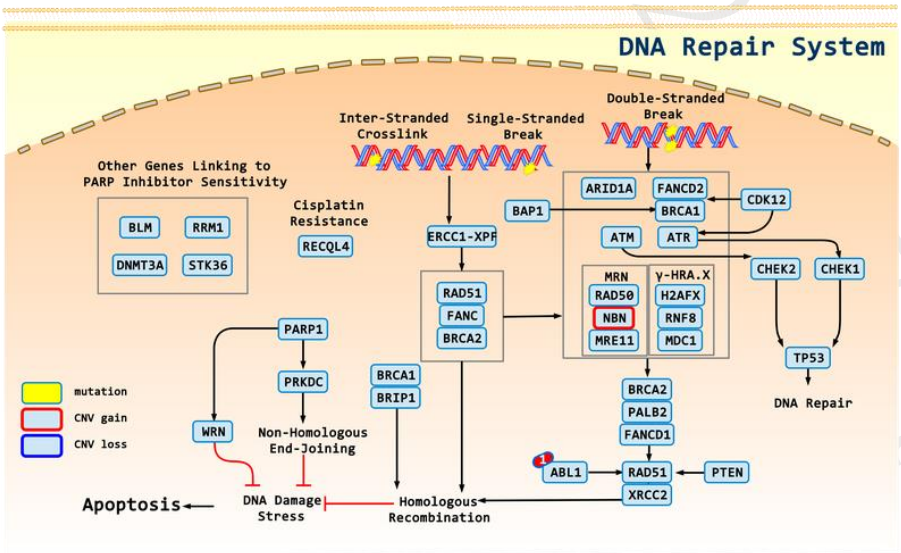
POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Not Applicable.

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Ponatinib, Lenvatinib, Erdafitinib, Infigratinib, Pazopanib; 2: Ponatinib, Pazopanib, Erdafitinib, Sunitinib, Dasatinib, Regorafenib; 3: Ponatinib, Lenvatinib, Pazopanib, Erdafitinib, Sunitinib; 4: Lenvatinib, Pazopanib, Sunitinib, Ponatinib, Erdafitinib; 5: Sunitinib; 6: Ponatinib, Regorafenib, Lenvatinib, Pazopanib, Erdafitinib, Sunitinib, Dasatinib



1: Ponatinib

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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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