王世功
Project ID: C23-M001-02070
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ACT Onco® + Report

PATIENT		
Identifier: 王世功		Patient ID: 3009765
Date of Birth: May 05, 1925		Gender: Male
Diagnosis: Melanoma		
ORDERING PHYSICIAN		
Name: 陳三奇醫師		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: S11209066A	Collection site: Skin	Type: FFPE tissue
Date received: Jul 05, 2023	Lab ID: AA-23-04402	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	
KIT L576P (Exon 11 mutations)	Dasatinib, Imatinib, Nilotinib, Ripretinib, Sunitinib	-	Ponatinib
KIT Amplification	-	Imatinib, Nilotinib, Sunitinib	-

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
KIT L576P (Exon 11 mutations)	Bevacizumab, Regorafenib, Sorafenib	-
KDR Amplification	Pazopanib, Sunitinib	-
PDGFRA Amplification	Imatinib, Pazopanib, Sorafenib, Sunitinib	-

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
KIT	L576P (Exon 11 mutations)	76.0%
TET2	L567fs	5.7%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr6	*E2F3*	Amplification	6
Chr4	*KDR*	Amplification	8
Chr4	*KIT, PDGFRA*	Amplification	9

- 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:
- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 50% 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 2		
KIT L576P (Exon 11 mutations)	Dasatinib, Imatinib, Nilotinib, Ripretinib, Sunitinib	**sensitive**
KIT Amplification	Imatinib, Nilotinib, Sunitinib	**resistant**
Level 3A		
KIT L576P (Exon 11 mutations)	Ponatinib	**sensitive**
Level 3B		
KIT L576P (Exon 11 mutations)	Regorafenib	**sensitive**
Level 4		
KIT L576P (Exon 11 mutations)	Bevacizumab, Sorafenib	**sensitive**
KDR Amplification	Pazopanib, Sunitinib	**sensitive**
PDGFRA Amplification	Imatinib, Pazopanib, Sorafenib, Sunitinib	**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

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

KIT L576P (Exon 11 mutations), Amplification

Biological Impact

KIT is a proto-oncogene that encodes a type 3 transmembrane receptor tyrosine kinase. Activation of KIT through dimerization and autophosphorylation upon binding by its ligand results in increased intracellular PI3K/AKT/mTOR, MAPK/ERK and JAK/STAT signaling pathways to promote cell proliferation and survival[1]. KIT activating mutations are frequently found in 80 - 90% of gastrointestinal stromal tumors (GISTs) which distributed over multiple exons with different frequencies (exons 11 (66.1%), exon 9 (13%), exon 13 (1.2%), and exon 17 (0.6%))[2][3].

KIT exon 11 L576P mutation lies within the juxtamembrane domain of the KIT protein[4]. L576P is a gain-of-function mutation which leads to constitutive phosphorylation of the KIT protein, which displays increased kinase activity and transforming activity in vitro[4].

Therapeutic and prognostic relevance

NCCN guidelines recommend using KIT inhibitors (imatinib, sunitinib, nilotinib) for cutaneous melanoma patients with specific KIT hotspot mutations in exon 11 and exon 13, but not for those with KIT exon 17 mutations or amplification. Dasatinib and ripretinib are recommended for metastatic or unresectable cutaneous melanoma patients with KIT activating mutations. Also, imatinib is a preferred regimen for neoadjuvant therapy of resectable GIST with significant morbidity patient harboring KIT mutation, and ponatinib is recommended for advanced GIST patients with KIT exon 11 mutations.

KIT mutation has been determined as an inclusion criterion for the trials evaluating dasatinib, avapritinib, sunitinib, ponatinib, regorafenib, ripretinib, imatinib, and cabozantinib efficacies in various types of solid tumors (NCT03297606, NCT03353753, NCT03465722, NCT02272998, NCT02501551, NCT03353753, NCT02461849, NCT02712112, NCT04631744, NCT04116541).

The efficacy of U.S. FDA-approved KIT TKIs such as imatinib, sunitinib, regorafenib, and ripretinib for GIST strongly depends on the location of the activating KIT mutations[5][6][7][8][9][10]. Patients with GIST harboring KIT exon 9 mutations have intermediate sensitivity to imatinib and better survival than those with KIT exon 11 mutations[6]. Newly developing agents, including avapritinib, show potential to be better inhibitors for clinically relevant KIT/PDGFRA mutations in GIST[11]. Ponatinib and dasatinib show promise in GIST patients with KIT exon 11 mutations, with a disease control rate of 67% and partial control rate of 32%(DOI:10.1200/jco.2011.29.15_suppl.10006)[12]. Meanwhile, a Phase II trial involving melanoma showed a 38.5% response rate to nilotinib in patients with KIT exon 11 mutations[13].

Both KIT and PDGFRA overexpression were associated with high tumor grade, high proliferation index, and poor outcome in patients with the serous type of ovarian carcinoma[14].

In a phase II trial, 7 melanoma patients harboring KIT L576P received imatinib treatment. Four patients showed clinical benefit from imatinib (CR: n=2, PR: n=2) and one patient had a stable disease[15]. In addition, in a case report, a melanoma patient harboring KIT L576P mutation had a stable disease by imatinib treatment[16]. However, in another case report, a melanoma patient with KIT L576P mutation developed progressive disease after imatinib treatment[17]. In a phase II trial, 3 out of 9 melanoma patients harboring KIT L576P mutation had partial responses with PFS of 24.9, 5.4, and 4.1 months and OS of 25.8, 9.4, and 21 months by nilotinib treatment, respectively[13].

In a phase I trial, a melanoma patient harboring KIT L576P was treated with sorafenib and bevacizumab, had a partial response for 8 months[18]. In a case report, two melanoma patient harboring KIT L576P mutation had partial response for 3 and 4 months by dasatinib treatment, respectively[19].

In preclinical studies, transformed cells expressing KIT L576P were sensitive to dasatinib, imatinib, nilotinib, nintedanib, regorafenib, ripretinib, and sunitinib treatment in vitro[4][19][20][21].

A phase II trial of imatinib in melanoma showed that patients with KIT amplification had lower disease control rate compared with patients carrying KIT mutations (18% amplified vs. 77% mutated)[22].

TET2 L567fs

Biological Impact

TET2 (ten-eleven translocation 2) gene encodes a DNA demethylase which plays an important role in cellular reprogramming and gene regulation[23]. TET2 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 function[24]. The presence of somatic mutations in TET2 was associated with an increased risk of developing hematologic cancer during aging[25]. Genetic aberrations of the TET2 gene are frequently observed in myeloid malignancies, such as acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML) and myelodysplastic syndrome (MDS)[26].

L567fs mutation results in a change in the amino acid sequence beginning at 567, likely to cause premature truncation of the functional TET2 protein (UniProtKB). This mutation is predicted to lead to a loss of TET2 protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

Low expression of TET2 has been associated with inferior patient survival in glioblastoma and head and neck squamous cell carcinoma[27][28].

E2F3 Amplification

Biological Impact

The E2F3 gene encodes a transcription factor that interacts directly with the retinoblastoma protein (pRB) to regulate the expression of genes involved in the cell cycle and DNA replication[29][30][31].

Amplification or overexpression of E2F3 has been reported in various types of cancers, including bladder cancer, hepatocellular carcinoma, retinoblastomas, and melanoma[32][33][34][35][36].

Therapeutic and prognostic relevance

A tissue microarray analysis indicated that amplification of the E2F3 gene is associated with increased E2F3 protein overexpression, accelerated cell proliferation, and poor prognosis in bladder cancer[33]. Besides, elevated E2F genes and E2F transcriptional targets in tumors have been linked with poor prognosis in the liver and pancreatic cancers[31].

KDR Amplification

Biological Impact

KDR (kinase domain receptor), also known as VEGFR2 or Flk-1, is a tyrosine kinase receptor for the vascular endothelial growth factor (VEGF) and involves in angiogenesis pathway[37]. Binding of VEGF to KDR results in activation of phospholipase C (PLC-gamma) and downstream signaling via protein kinase C (PKC) and RAF/MEK/ERK[38]. Mutations of KDR are rare in tumors, and alterations of KDR activity typically occur via KDR amplification and subsequent overexpression[39][40].

Therapeutic and prognostic relevance

To date, there are four VEGF inhibitors (sorafenib, sunitinib, pazopanib, bevacizumab) and one VEGFR2 inhibitor cabozantinib that are FDA-approved for the treatment of cancers[41][42][43]. Notably, a case report showed that an

angiosarcoma patient with concurrent KDR and FLT4 amplification developed a progressive disease when treated with sorafenib, but experienced a potent antitumor response and achieved clinically stable disease for 6 months after receiving pazopanib therapy[44]. Besides, an angiosarcoma patient with upregulated VEGFR2 responded to sunitinib treatment[45]. VEGFR2 inhibitors like apatinib and vandetanib are in early clinical phase trial [46][47][48].

KDR amplification and/or mutation has been selected as an inclusion criteria for the trial examining cabozantinib in metastatic castrate resistant prostate cancer (mCRPC) (NCT04631744) and sunitinib in malignant solid tumors (NCT03297606). The increased copy number of KIT or KDR significantly correlated with a worse 5-year breast cancer-specific survival (BCSS) in triple-negative breast cancer (TNBC) patients [49].

PDGFRA Amplification

Biological Impact

The PDGFRA gene encodes for the protein platelet-derived growth factor alpha (PDGFRA). The Ligand binding to the extracellular domain of PDGFRA induces receptor dimerization, enabling autophosphorylation of specific tyrosine residues and subsequently results in the activation of downstream pathways such as RAS-MAPK, PI3K and PLC-γ that are involved in developmental and cellular responses[50][51]. Mutations, insertions, deletions, fusions and genomic amplification of PDGFRA lead to its activation in several tumor types: ~7% of gastrointestinal stromal tumors (GISTs) have PDGFRA activating mutations and these mutations are mutually exclusive from KIT mutations [52]; activating mutations in PDGFRA have been observed in ~5% of Chinese melanoma patients [53]; amplification of PDGFRA is the second most frequent receptor tyrosine kinase amplification in glioblastoma (GBM)[54][55][56][57][58], intimal sarcomas[59], malignant peripheral nerve sheath tumors [60], non-small cell lung adenocarcinomas and non-small cell lung squamous cell carcinomas[61].

Therapeutic and prognostic relevance

A retrospective study showed that either KIT, PDGFRA, or EGFR amplification in glioma at the time of the first diagnosis was associated with an unfavorable overall survival[62].

In a preclinical study, a PDGFRA-amplified cell line was sensitive to imatinib, sunitinib and sorafenib treatment, demonstrated by disruption of downstream signaling and reduced cell viability in vitro [63]. Another study also showed that pazopanib could inhibit tumor growth in the PDGFRA-amplified pleomorphic liposarcoma xenograft mouse model[64].

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US FDA-APPROVED DRUG(S)

Bevacizumab (AVASTIN)

Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting VEGF-A. Bevacizumab is developed and marketed by Genentech/Roche under the trade name AVASTIN.

- FDA Approval Summary of Bevacizumab (AVASTIN)

IMbrave150 NCT03434379	**Hepatocellular carcinoma** (Approved on 2020/05/29)
	-
	Atezolizumab plus bevacizumab vs. Sorafenib [PFS(M): 6.8 vs. 4.3, OS(M): NR vs. 13.2]
OCEANS[65] NCT00434642	**Peritoneal carcinoma, Ovary epithelial cancer, Fallopian tube cancer** (Approved on 2016/12/06)
	-
	Bevacizumab + carboplatin + gemcitabine vs. Carboplatin + gemcitabine [PFS(M): 12.4 vs. 8.4]
GOG-0213[66] NCT00565851	**Peritoneal carcinoma, Ovary epithelial cancer, Fallopian tube cancer** (Approved on 2016/12/06)
	-
	Bevacizumab + carboplatin + paclitaxel vs. Carboplatin + paclitaxel [OS(M): 42.6 vs. 37.3]
AURELIA [67] NCT00976911	**Peritoneal carcinoma, Ovary epithelial cancer, Fallopian tube cancer** (Approved on 2014/11/14)
	-
	Bevacizumab + chemotherapy vs. Chemotherapy [PFS(M): 6.8 vs. 3.4]
GOG-0240[68] NCT00803062	**Cervical cancer** (Approved on 2014/08/14)
	-
	Bevacizumab + chemotherapy vs. Chemotherapy [OS(M): 16.8 vs. 12.9]
ML18147[69] NCT00700102	**Colorectal cancer** (Approved on 2013/01/23)
	-
	Bevacizumab + chemotherapy vs. Chemotherapy [OS(M): 11.2 vs. 9.8]
BO17705[70] NCT00738530	**Renal cell carcinoma** (Approved on 2009/07/31)
	-
	Bevacizumab + ifn-α2a vs. Ifn-α2a [PFS(M): 10.2 vs. 5.4]
AVF3708g[71] NCT00345163	**Glioblastoma multiforme** (Approved on 2009/05/06)
	-
	Bevacizumab + irinotecan vs. Bevacizumab [ORR(%): 25.9]
E4599[72] NCT00021060	**Non-small cell lung carcinoma** (Approved on 2006/10/11)
	-
	Bevacizumab + paclitaxel + carboplatin vs. Paclitaxel + carboplatin [OS(M): 12.3 vs. 10.3]
E3200[73] NCT00025337	**Colorectal cancer** (Approved on 2006/06/20)
	-
	Bevacizumab + oxaliplatin + fluorouracil + leucovorin vs. Oxaliplatin + fluorouracil + leucovorin [OS(M): 13 vs. 10.8]
AVF2107g[74] NCT00109070	**Colorectal cancer** (Approved on 2004/02/26)
	-
	Bevacizumab + irinotecan+5-fu + leucovorin vs. Irinotecan + 5-fu + leucovorin [OS(M): 20.3 vs. 15.6]

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

Imatinib (GLEEVEC)

Imatinib is an oral, small molecule inhibitor of tyrosine kinase enzymes, namely, the Abelson proto-oncogene (ABL), c-KIT, and platelet-derived growth factor receptor (PDGFR). Imatinib is developed and marketed by Novartis under the trade name GLEEVEC.

- FDA Approval Summary of Imatinib (GLEEVEC)

[78] NCT00022737	**Acute lymphocytic leukemia** (Approved on 2013/01/25)
	-
	Imatinib [EFS(%): 70]
	Gastrointestinal stromal tumor (Approved on 2012/01/31)
	KIT positive
	Imatinib [RFS(%): 42 (imatinib for 12)| 25 (imatinib for 36)]
	Gastrointestinal stromal tumor (Approved on 2009/02/10)
	KIT+
	Imatinib vs. Placebo [RFS(%): 21 vs. 28]
	Myelodysplastic myeloproliferative cancer (Approved on 2006/10/19)
	-
	Imatinib [MCyR(%): 39, CHR(%): 45]
[79]	**Acute lymphocytic leukemia** (Approved on 2006/10/19)
	Ph+
	Imatinib [MCyR(%): 35, CHR(%): 19]
	Dermatofibrosarcoma protuberans (Approved on 2006/10/19)
	-
	Imatinib [ORR(%): 83.0]
	Systemic mastocytosis (Approved on 2006/10/19)
	-
	Imatinib [CHR(%): 29]

	Chronic eosinophilic leukemia (Approved on 2006/10/19)
	-
	Imatinib [CHR(%): 61]
[80] NCT00471497	**Chronic myeloid leukemia** (Approved on 2003/05/20)
	Ph+
	Imatinib vs. Nilotinib [MMR(%): 22 vs. 44]
[81] NCT00333840	**Chronic myeloid leukemia** (Approved on 2003/04/18)
	-
	Imatinib vs. Interferon-α+ cytarabine [PFS(%): 81.2 vs. 60.6]
[82] NCT00009906	**Gastrointestinal stromal tumor** (Approved on 2002/02/01)
	-
	Imatinib [PFS(M): 18.9 (imatinib 400 mg)| 23.2 (imatinib 800 mg)]

Nilotinib (TASIGNA)

Nilotinib is an inhibitor of the BCR-ABL kinase. Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of ABL protein. Nilotinib is developed and marketed by Novartis under the trade name TASIGNA.

- FDA Approval Summary of Nilotinib (TASIGNA)

ENESTnd[80] NCT00471497	**Chronic myeloid leukemia** (Approved on 2010/06/17)
	-
	Nilotinib vs. Imatinib [ORR(%): 26.0 vs. 1.00]

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[83] NCT00753688	**Sarcoma** (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]
VEG105192[84] NCT00334282	**Renal cell carcinoma** (Approved on 2009/10/19)
	-
	Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]

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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[85] NCT01207440	**Chronic phase chronic myeloid leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MCyR(%): 55]
PACE[85] NCT01207440	**Accelerated phase chronic myeloid leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MaHR(%): 57]
PACE[85] NCT01207440	**Blast phase chronic myeloid leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MaHR(%): 31]
PACE[85] 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[86] NCT01774344	**Hepatocellular carcinoma, Hepatocellular carcinoma** (Approved on 2017/04/27)
	-
	Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]
GRID[7] NCT01271712	**Gastrointestinal stromal tumor** (Approved on 2013/02/25)
	-
	Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]
CORRECT[87] NCT01103323	**Colorectal cancer** (Approved on 2012/09/27)
	-
	Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

Ripretinib (QINLOCK)

Ripretinib is a tyrosine kinase inhibitor that inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase, including wild type, primary, and secondary mutations. Ripretinib is developed and marketed by Decipera Pharmaceuticals under the trade name QINLOCK.

- FDA Approval Summary of Ripretinib (QINLOCK)

INVICTUS NCT03353753	**Gastrointestinal stromal tumor** (Approved on 2020/05/15)
	-
	Ripretinib vs. Placebo [PFS(M): 6.3 vs. 1]

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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[88] NCT00984282	**Differentiated thyroid carcinoma** (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
SHARP[89] NCT00105443	**Hepatocellular carcinoma** (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]
TARGET[90] NCT00073307	**Renal cell carcinoma** (Approved on 2005/12/20)
	-
	Sorafenib vs. Placebo [PFS(D): 167 vs. 84]

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)

[91][92][93] NCT00428597	**Pancreatic cancer** (Approved on 2011/05/20)
	-
	Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]
[94][95] NCT00083889	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib vs. Ifn-α [PFS(W): 47.3 vs. 22]
[96][97][95] NCT00077974	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 34.0]
[97][95] NCT00054886	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 36.5]
[98] NCT00075218	**Gastrointestinal stromal tumor** (Approved on 2006/01/26)
	-
	Sunitinib vs. Placebo [TTP(W): 27.3 vs. 6.4]

D=day; W=w eek; 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

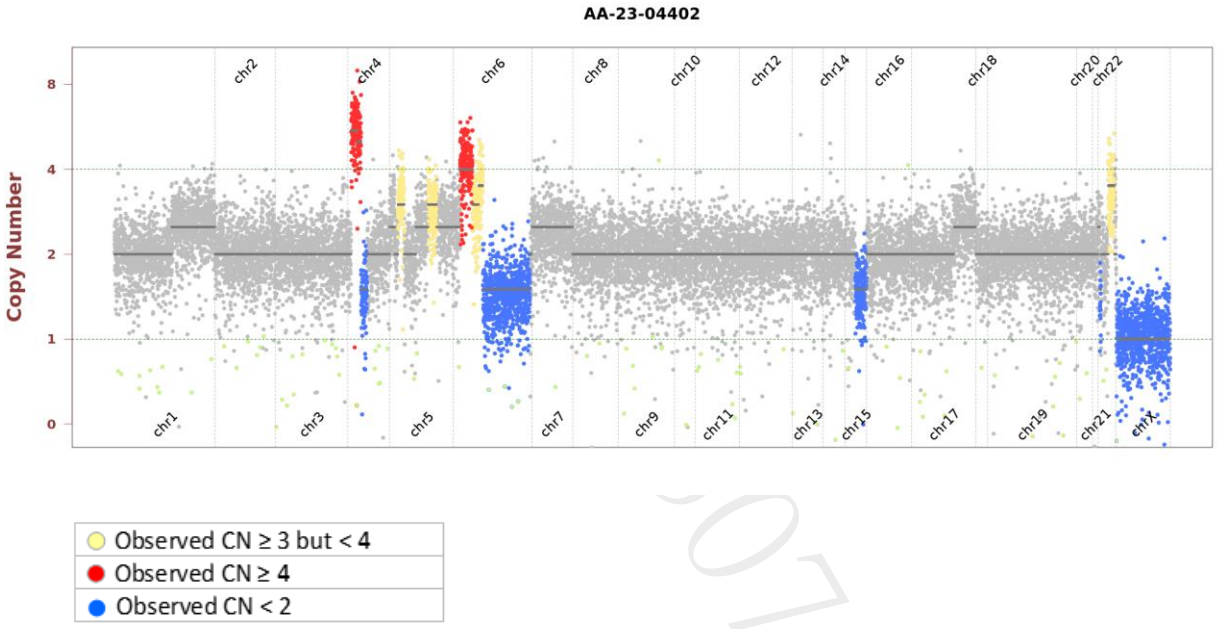
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
KIT	L576P (Exon 11 mutations)	11	c.1727T>C	NM_000222	COSM1290	76.0%	2212
TET2	L567fs	3	c.1699_1703del	NM_001127208	COSM6498556	5.7%	1521

- 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 show n in color. Regions w ithout 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
ABL2	C82F	3	c.245G>T	NM_007314	-	60.7%	1807
ARID1A	L1768V	20	c.5302C>G	NM_006015	-	56.0%	1177
BRD4	Splice region	-	c.2581+7C>T	NM_058243	-	49.9%	521
CCND1	E280*	5	c.838G>T	NM_053056	COSM8510176	30.7%	1428
DOT1L	Q653R	20	c.1958A>G	NM_032482	-	50.2%	1170
EGFR	C510R	13	c.1528T>C	NM_005228	-	25.7%	1174
ERCC5	T971M	14	c.2912C>T	NM_000123	-	52.8%	1158
FANCL	I290L	11	c.868A>C	NM_018062	-	42.3%	504
IRS1	Q882dup	1	c.2645_2647dup	NM_005544	COSM3046888	51.4%	1262
KMT2D	L4006R	39	c.12017T>G	NM_003482	-	49.3%	2021
NF1	L1196V	27	c.3586C>G	NM_001042492	-	25.4%	1205
NTRK1	Q626K	15	c.1876C>A	NM_002529	COSM424159	24.7%	503
PIK3C2B	R1008Q	20	c.3023G>A	NM_002646	COSM1338083	37.4%	1002
PIK3C2B	H847L	17	c.2540A>T	NM_002646	-	38.4%	1493
PIK3CD	C416R	10	c.1246T>C	NM_005026	COSM6997584	28.9%	1027
SYNE1	C4575F	78	c.13724G>T	NM_182961	-	27.8%	396

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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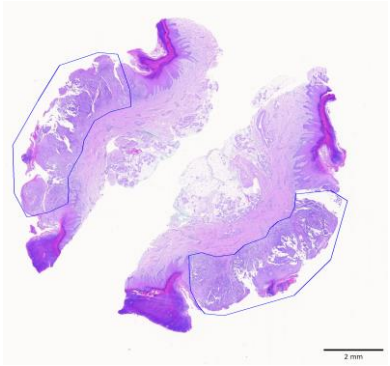
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Mar 06, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11209066A
- Collection site: Skin
- Examined by: Dr. Yun-An Chen
    1. The percentage of viable tumor cells in total cells in the w hole slide (%): 20%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the w hole slide (%): 50%
    3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the w hole slide (%): 2%
    4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the w hole slide (%): 5%
    5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 1016x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 131

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 w as reverse-transcribed and subjected to library construction. Sequencing w as 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 ow ned and maintained by ArcherDX. In general, samples w ith detectable fusions need to meet the follow ing criteria: (1) Number of unique start sites (SS) for the GSP2 ≥ 3; (2) Number of supporting reads spanning the fusion junction ≥ 5; (3) Percentage of supporting reads spanning the fusion junction ≥ 10%; (4) Fusions annotated in Quiver Gene Fusion Database.

DATABASE USED

- Reference genome: Human genome sequence hg19
- COSMIC v.92
- Genome Aggregation database r2.1.1
- ClinVar (version 20210404)
- ACT Genomics in-house database
- Quiver Gene Fusion Database version 5.1.18

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

Sign Off
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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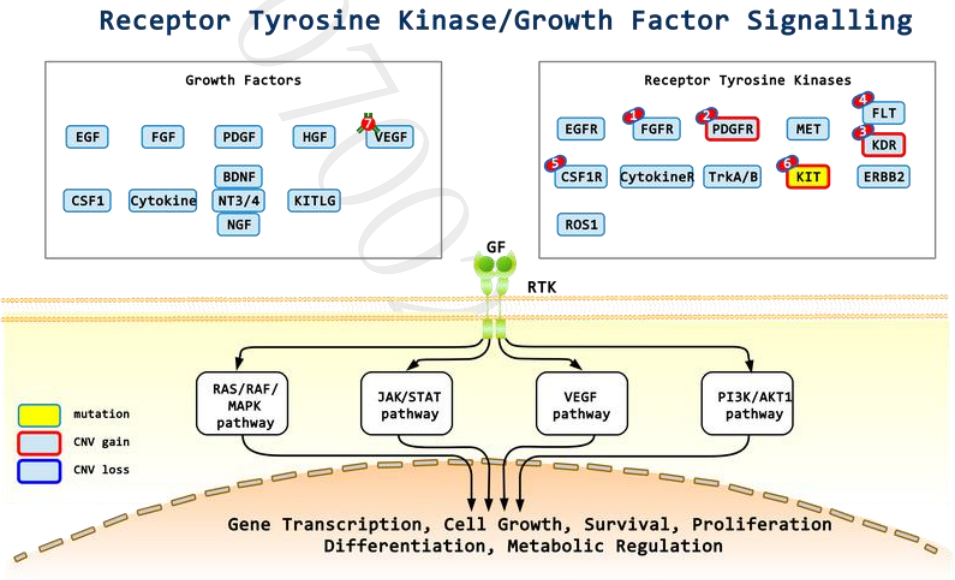
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Not Applicable.

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Ponatinib, Pazopanib; 2: Imatinib, Sunitinib, Ripretinib, Dasatinib, Ponatinib, Pazopanib, Regorafenib; 3: Sunitinib, Ponatinib, Pazopanib; 4: Sunitinib, Pazopanib, Ponatinib; 5: Sunitinib, Nilotinib; 6: Imatinib, Sunitinib, Nilotinib, Sorafenib, Regorafenib, Ripretinib, Dasatinib, Ponatinib, Pazopanib; 7: Bevacizumab

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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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