ACTOnco®+ Report



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## PATIENT AND SAMPLE INFORMATION

| PATIENT | SPECIMEN | ORDERING PHYSICIAN |
|---|---|---|
| Name: 斯湯堡 | Type: FFPE tissue | Name: 周德盈醫師 |
| Gender: Male | Date received: Dec 21, 2021 | Facility: 臺北榮總 |
| Date of Birth: Dec 16, 1991 | Collection site: Sacrum | Tel: 886-228712121 |
| Patient ID: 47679549 | Specimen ID: S11035749D | Address: 臺北市北投區石牌路二段 201 號 |
| Diagnosis: Myxoid chondrosarcoma | Lab ID: AA-21-06351 | |
| | D/ID: NA | |

## VARIANT(S) WITH CLINICAL RELEVANCE

**Only variant(s) with clinical significance are listed. See the "DETAILED TEST RESULTS" section for full details.**

### SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

Not detected.

### COPY NUMBER VARIANTS (CNVS)

Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on **42%** tumor purity.

**Amplification (Copy number ≥ 8)**

| Chr | Gene | Copy Number |
|---|---|---|
| chr17 | *CD79B, RPTOR* | 6¥ |
| chr8 | *MYC* | 7¥ |
| chr12 | *KRAS* | 8 |
| chr8 | *FGFR1* | 12 |

**Homozygous deletion (Copy number=0)**

| Chr | Gene |
|---|---|
| ND | ND |

**Heterozygous deletion (Copy number=1)**

| Chr | Gene |
|---|---|
| ND | ND |

**¥ Increased gene copy number was observed.**

ND, Not Detected

### TUMOR MUTATIONAL BURDEN (TMB)

1.9 muts/Mb

Muts/Mb, mutations per megabase

### MICROSATELLITE INSTABILITY (MSI)

Microsatellite stable (MSS)

Note:
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%.

**Variant Analysis:**
醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

**Sign Off**
醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

## 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** |
| ***KRAS*** Amplification | Sorafenib | **sensitive** |
| ***FGFR1*** Amplification | Palbociclib, Ribociclib | **resistant** |
| ***KRAS*** Amplification | Cetuximab, Panitumumab, Crizotinib | **resistant** |

‡ Refer to "ONGOING CLINICAL TRIALS" section for detailed trial information.

**Note: Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence.**

| Level | | Description |
|---|---|---|
| 1 | | FDA-recognized biomarker predictive of response to an FDA approved drug in this indication |
| 2 | | Standard care biomarker (recommended as standard care by the NCCN or other expert panels) predictive of response to an FDA approved drug in this indication |
| 3 | A | Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor |
| | B | Biomarkers that serve as inclusion criteria for clinical trials |
| 4 | | Biomarkers that show plausible therapeutic significance based on small studies, few case reports or preclinical studies |

## IMMUNE CHECKPOINT INHIBITORS (ICI) THERAPIES

**Genomic markers and alterations that are associated with response to ICI therapies**

| Positive Biomarker | Negative Biomarker |
|---|---|
| TMB-H: ND | EGFR aberration: ND |
| MSI-H: ND | MDM2/MDM4 amplification: ND |
| MMR biallelic inactivation: ND | STK11 biallelic inactivation: ND |
| PBRM1 biallelic inactivation: ND | PTEN biallelic inactivation: ND |
| SERPINB3/SERPINB4 mutation: ND | B2M biallelic inactivation: ND |
| | JAK1/2 biallelic inactivation: ND |

MMR, mismatch repair; ND, 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

| Therapies | Genomic Alterations | Effect | Gene / Variant Level Evidence | Cancer Type |
|---|---|---|---|---|
| Tamoxifen | ***FGFR1*** Amplification | **resistant** | Preclinical | Breast cancer |

## OTHERS

**Pharmacogenomic implication**

| Gene | Detection Site | Genotype | Drug Impact | Clinical Interpretation | Level of Evidence* |
|---|---|---|---|---|---|
| UGT1A1 | rs4148323 | AG | Irinotecan-based regimens | 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 1B** |

* 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.

## VARIANT INTERPRETATION

### *CD79B* Amplification

**Biological Impact**

CD79B encodes a surface immunoglobulin that forms a heterodimer with CD79A and non-covalently assembles with membrane-bound IgM to form the B cell receptor (BCR) which plays essential roles in B cell development, activation and survival of mature B cells[1][2]. Activating mutations of CD79B has been demonstrated resulting in chronic BCR signaling and constitutive activation of the NF-kB pathway. Besides, recurrent mutations of CD79B and MYD88 genes have been suggested as a genetic hallmark in primary central nervous system lymphoma[3]and diffuse large B-cell lymphoma[4].

**Therapeutic and prognostic relevance**

A preclinical study has demonstrated that CD79B up-regulation associates with limited response to ibrutinib, a selective and reversible inhibitor of BCR, in diffuse large B cell lymphoma[5].Combined therapy consisting of polatuzumab vedotin, an antibody-drug conjugate targeting CD79B, with bendamustine and rituximab, have been shown with significant efficacy in relapsed/ refractory (R/R) diffuse large B cell lymphoma. (DOI:10.1200/ JCO.2018.36.15_suppl.7507)

### *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[6][7]. Several studies have demonstrated that FGFR1 amplification correlates with FGFR1 overexpression[8][9][10][11][12][13]. 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[14][15][16]. Amplification of FGFR1 has been associated with early relapse, and poor survival, specifically in ER+ breast cancer[14][17], and may be associated with progression of breast cancer from in situ-to-invasive transition[18].

FGFR1 amplifications have been reported in various types of cancer, including lung cancer[19], breast cancer[14], oral squamous cell carcinoma (OSCC)[20], prostate cancer[21], and esophageal cell carcinoma[22]. Besides, activating mutations (C381R and N330I) have been identified in giant cell lesions of the jaw[23].

**Therapeutic and prognostic relevance**

Non-selective TKI-targeting inhibitors such as pazopanib, regorafenib, and ponatinib are multi-kinase inhibitors with inhibitory activities towards FGFR1[24][25].

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[26].

A case report of a patient with HR+, HER2- breast cancer harboring FGFR1 amplification responded well to pazopanib[27].

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[28]. 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[29]. 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[30].

In ER-positive breast cancer, FGFR1 amplification has been implicated as an acquired mechanism of resistance to endocrine therapies[31], such as letrozole, 4-hydroxytamoxifen, and anastrozole-containing regimen[32][14][33]. 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[26].

Meanwhile, in non-small cell lung carcinoma (NSCLC), FGFR1 is considered as an alternative acquired mechanism of resistance to EGFR tyrosine kinase inhibitors[34]. For example, upregulated FGFR1-FGF2 autocrine loop was identified in a gefitinib-resistant cell model[35], and focal FGFR1 amplification was observed in an NSCLC patient who developed resistance to osimertinib treatment[36].

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[37][38].

In preclinical study, thyroid cancer cell with FGFR1 amplification is sensitive to lenvatinib treatment[39][40]. Ponatinib, a multi-targeted tyrosine kinase inhibitor, demonstrated anti-proliferative activity in lung cancer, breast cancer, and Ewing's sarcoma cells overexpressing FGFR1[41][24][42].

## *KRAS* Amplification

### Biological Impact

The V-Ki-Ras2 Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (KRAS) gene encodes a small GTPase protein, a member of the RAS family of small GTPases, which catalyze the hydrolysis of GTP to GDP. RAS proteins cycle between an active (GTP-bound) and an inactive (GDP-bound) state, to activate the downstream oncogenic pathways, including the PI3K/AKT/mTOR and MAPK pathways[43]. KRAS mutations occur primarily in three hotspots G12, G13 and Q61, and less frequently in codon A146[43][44]. These are activating mutations that lead to constitutive activation and persistent stimulation of the downstream signaling pathways[45][46]. Mutations in KRAS have been reported in a diverse spectrum of human malignancies, including pancreatic carcinomas (>80%)[43][47], colon carcinomas (40-50%)[48][49], and lung carcinomas (30-50%)[50][51], but are also present in biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer, liver cancer, myeloid leukemia and breast cancer[44].

### Therapeutic and prognostic relevance

Except for KRAS G12C, other KRAS mutants are not currently targetable, but the downstream MEK serves as a potential target[52]. MEK inhibitors trametinib, cobimetinib, and binimetinib were approved by the U.S. FDA for patients with advanced metastatic melanoma whose tumors harbor BRAF V600 mutations[53][54][55][56].

There are case reports indicated that patients harboring a KRAS mutation may benefit from MEK inhibitor treatment. A patient with small cell neuroendocrine carcinoma (SCNEC) of the cervix harboring a KRAS G12D mutation showed significant response with trametinib[57]. Another low-grade serous carcinoma case with KRAS G12D also has sustained response to trametinib (Am J Clin Exp Obstet Gynecol 2015;2(3):140-143). In addition, a low-grade serous ovarian cancer patient harboring KRAS G12V mutation showed stable disease after 8 weeks of binimetinib treatment, and demonstrated a partial response after another 26 weeks of treatment[58]. However, trametinib did not demonstrate superiority to docetaxel in KRAS-mutant non-small cell lung cancer (NSCLC) patients, based on results from a randomized Phase II study[59].

Both clinical and preclinical studies demonstrated a limited response to monotherapy using MEK inhibitors[60]. Moreover, several clinical trials are in progress to evaluate the combination of MEK and mTOR inhibition as a new potential therapeutic strategy in CRC[61], and in patient-derived xenografts of RAS-mutant CRC, inhibition of MEK and mTOR suppressed tumor growth, but not tumor regression[62]. A study using the CRC patient-derived xenograft (PDX) model showed that the combination of trametinib, a MEK inhibitor, and palbociclib, a CDK4/6 inhibitor, was well tolerated and resulted in objective responses in all KRAS mutant models[63].

KRAS mutation has been determined as an inclusion criterion for the trials evaluating MEK inhibitors efficacies in various types of solid tumors (NCT03704688, NCT02399943, NCT02285439, NCT03637491, NCT04214418).

Cetuximab and panitumumab are two EGFR-specific antibodies approved by the U.S. FDA for patients with KRAS wild-type metastatic colorectal cancer (NCT00154102, NCT00079066, NCT01412957, NCT00364013). Results from

the PRIME and FIRE-3 trials indicated that panitumumab and cetuximab did not benefit patients with KRAS or NRAS mutations and may even have a detrimental effect in these patients[64]. Taken together, the National Comprehensive Cancer Network (NCCN) recommended that, cetuximab and panitumumab should only be used if both KRAS and NRAS genes are normal (NCCN guidelines)[65][66]. Numerous studies have demonstrated the presence of KRAS or NRAS mutations at exon 2, 3 or 4 as a predictor of resistance to anti-EGFR therapies[67][68][69][70][71][72][73].

Sorafenib, a multi-kinase inhibitor, has been shown to be beneficial in KRAS-mutant CRC[74], KRAS-mutant NSCLC[75], and KRAS-amplified melanoma[76].

There has been conflicting data on the effect of KRAS mutation on the efficacy of bevacizumab in metastatic CRC patients(J Clin Oncol 34, 2016 (suppl; abstr 3525))[77][78].

In NCCN guidelines for NSCLC (version 5. 2021), KRAS mutations have been suggested as an emerging biomarker for EGFR TKIs in NSCLC patients. KRAS mutations are associated with a lack of efficacy of EGFR TKIs, including erlotinib, gefitinib, afatinib, and osimertinib, in NSCLC patients[79][80][81].

Studies have shown that KRAS mutation, especially those occurs in exon 2 (codon 12 or 13) and codon 61 indicated a poor prognosis for patients with CRC[82].

In low-grade serous carcinoma of the ovary or peritoneum, patients with KRAS or BRAF mutations (n=21) had a significantly better OS than those with wild-type KRAS or BRAF (n=58) (106.7 months vs 66.8 months), respectively[83]. In ovarian serous borderline tumor with recurrent low-grade serous carcinoma, patient harboring KRAS G12V mutation appeared to have shorter survival time[84].

Metastatic colorectal cancer patients harboring KRAS amplification were resistant to anti-EGFR therapy such as cetuximab and panitumumab[85][86].

Some in vitro studies showed that activation of the RAS, due to either KRAS/NRAS mutations or to KRAS amplification, rendered lung cancer cells resistant to ROS1 inhibition by crizotinib[87][88][89].

## ***MYC* Amplification**

### Biological Impact

The v-myc avian myelocytomatosis viral oncogene homolog, also known as c-myc (MYC) gene encodes a transcription factor involved in cellular proliferation, inhibiting exit from the cell cycle, stimulating vascularization and enhancing genomic instability[90][91][92]. Dysregulated MYC expression is implicated in a wide range of human cancers[93].

**Therapeutic and prognostic relevance**

MYC amplification was associated with better clinical outcome in breast cancer patients treated with FAC (5-fluorouracil, doxorubicin, and cyclophosphamide), CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and P-FEC (paclitaxel followed by 5-fluorouracil, epirubicin and cyclophosphamide) and higher expression of MYC was also associated with a better response rate in platinum-treated ovarian cancer patients[94][95][96].

CDK inhibition using the dinaciclib, a CDK1, 2, 5 and 9 inhibitors, exerted antitumor activity in triple-negative breast cancer (TNBC) tumor xenograft and cell lines with increased activity of the MYC pathway[97][98].

Overexpression of MYC has been reported as a favorable prognostic biomarker in colorectal carcinoma (CRC)[99][100]. However, the favorable prognostic value of MYC in CRC is abrogated by the TP53 mutation[100].

MYC amplification with the loss of tumor suppressor pathways such as p53 and RB has been shown to be associated with poor outcomes and was correlated with shortened disease-free survival in breast cancer with BRCA1 deficiency in TNBC[97][101].

## ***RPTOR* Amplification**

**Biological Impact**

RPTOR (regulatory-associated protein of mTOR, also known as RAPTOR) gene encodes a scaffold protein which is involved in assembly, localization and substrate binding of the mTORC1 complex and plays essential roles in mTOR signaling[102][103][104][105]. Conditional disruption of RAPTOR has been reported to result in a development block of B cell[106].

**Therapeutic and prognostic relevance**

RAPTOR overexpression has been reported to associate with acquired resistance to mTOR inhibition in vitro[107].

A study of breast cancer patients (n=150) indicated that higher expression of RAPTOR was associated with higher tumor grade[108].

A study of hepatocellular carcinoma patients (n=62) indicated that high Rictor/Raptor ratio was associated with shorter disease-free survival[109].

## US FDA-APPROVED DRUG(S)

### 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**<br>NCT02365597 | **Bladder urothelial carcinoma** (Approved on 2019/04/12) |
| | - |
| | Erdafitinib<br>[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**<br>NCT02150967 | **Cholangiocarcinoma** (Approved on 2021/05/28) |
| | **FGFR2 fusion** |
| | Infigratinib<br>[ORR(%): 23.0, DOR(M): 5] |

### 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)**<br>NCT03517449 | **Endometrial carcinoma** (Approved on 2021/07/22) |
| | **Not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)** |
| | Pembrolizumab + lenvatinib vs. Investigator's choice of doxorubicin or paclitaxel<br>[PFS(M): 6.6 vs. 3.8, OS(M): 17.4 vs. 12] |
| **KEYNOTE-146**<br>NCT02501096 | **Endometrial carcinoma** (Approved on 2019/09/17) |
| | **Not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR)** |
| | Pembrolizumab + lenvatinib<br>[ORR(%): 38.3, DOR(M): NR] |

| | |
|---|---|
| **REFLECT**[110]<br>NCT01761266 | **Hepatocellular carcinoma** (Approved on 2018/08/16) |
| | - |
| | Lenvatinib vs. Sorafenib<br>[OS(M): 13.6 vs. 12.3] |
| **SELECT**[111]<br>NCT01136733 | **Renal cell carcinoma** (Approved on 2016/05/13) |
| | - |
| | Lenvatinib+ everolimus vs. Everolimus<br>[PFS(M): 14.6 vs. 5.5] |
| **SELECT**[112]<br>NCT01321554 | **Thyroid cancer** (Approved on 2015/02/13) |
| | - |
| | Lenvatinib vs. Placebo<br>[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**[113]<br>NCT00753688 | **Sarcoma** (Approved on 2016/04/26) |
| | - |
| | Pazopanib vs. Placebo<br>[PFS(M): 4.6 vs. 1.6] |
| **VEG105192**[114]<br>NCT00334282 | **Renal cell carcinoma** (Approved on 2009/10/19) |
| | - |
| | Pazopanib vs. Placebo<br>[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**[115]<br>NCT01207440 | **Chronic phase chronic myeloid leukemia** (Approved on 2014/03/12) |
| | - |
| | Ponatinib<br>[MCyR(%): 55] |
| **PACE**[115]<br>NCT01207440 | **Blast phase chronic myeloid leukemia** (Approved on 2014/03/12) |
| | - |
| | Ponatinib<br>[MaHR(%): 31] |
| **PACE**[115]<br>NCT01207440 | **Philadelphia-positive acute lymphoblastic leukemia** (Approved on 2014/03/12) |
| | - |
| | Ponatinib<br>[MaHR(%): 41] |
| **PACE**[115]<br>NCT01207440 | **Accelerated phase chronic myeloid leukemia** (Approved on 2014/03/12) |
| | - |
| | Ponatinib<br>[MaHR(%): 57] |

## 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**[116]<br>NCT01774344 | **Hepatocellular carcinoma, Hepatocellular carcinoma** (Approved on 2017/04/27) |
| | - |
| | Bsc vs. Placebo<br>[OS(M): 10.6 vs. 7.8] |
| **GRID**[117]<br>NCT01271712 | **Gastrointestinal stromal tumor** (Approved on 2013/02/25) |
| | - |
| | Regorafenib vs. Placebo<br>[PFS(M): 4.8 vs. 0.9] |

| | |
|---|---|
| **CORRECT**[118] NCT01103323 | **Colorectal cancer** (Approved on 2012/09/27) |
| | - |
| | Regorafenib vs. Placebo [OS(M): 6.4 vs. 5] |

## 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**[119] NCT00984282 | **Differentiated thyroid carcinoma** (Approved on 2013/11/22) |
| | - |
| | Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8] |
| **SHARP**[120] NCT00105443 | **Hepatocellular carcinoma** (Approved on 2007/11/16) |
| | - |
| | Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9] |
| **TARGET**[121] 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)

| | |
|---|---|
| [122][123][124] NCT00428597 | **Pancreatic cancer** (Approved on 2011/05/20) |
| | - |
| | Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4] |

| | |
|---|---|
| [125][126][127]<br>NCT00077974 | **Renal cell carcinoma** (Approved on 2007/02/02)<br>-<br>Sunitinib<br>[ORR(%): 34.0] |
| [126][127]<br>NCT00054886 | **Renal cell carcinoma** (Approved on 2007/02/02)<br>-<br>Sunitinib<br>[ORR(%): 36.5] |
| [128][127]<br>NCT00083889 | **Renal cell carcinoma** (Approved on 2007/02/02)<br>-<br>Sunitinib vs. Ifn-α<br>[PFS(W): 47.3 vs. 22] |
| [129]<br>NCT00075218 | **Gastrointestinal stromal tumor** (Approved on 2006/01/26)<br>-<br>Sunitinib vs. Placebo<br>[TTP(W): 27.3 vs. 6.4] |

d=day; w=week; m=month

## ONGOING CLINICAL TRIALS

Clinical trials shown below were selected 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.

## DETAILED TEST RESULTS

### SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

| Gene | Chr | Exon | Accession Number | cDNA Change | Amino Acid Change | Coverage | Allele Frequency | COSMIC ID |
|---|---|---|---|---|---|---|---|---|
| *ADAMTS9* | 3 | 29 | NM_182920 | c.4376G>A | R1459Q | 739 | 72.7% | COSM7662835 |
| *BRAF* | 7 | 13 | NM_004333 | c.1540C>A | L514I | 670 | 51.9% | COSM6475282 |
| *CALR* | 19 | 3 | NM_004343 | c.200A>G | Q67R | 1689 | 55.4% | - |
| *MET* | 7 | 15 | NM_001127500 | c.3253C>A | Q1085K | 937 | 48.1% | - |
| *PRKCA* | 17 | 14 | NM_002737 | c.1600G>A | G534R | 1411 | 11.1% | COSM2797066 |
| *RAD51D* | 17 | - | NM_002878 | c.144+3G>T | Splice region | 758 | 55.7% | - |
| *SPEN* | 1 | 11 | NM_015001 | c.7696C>T | P2566S | 340 | 45.3% | - |
| *ZNF217* | 20 | 1 | NM_006526 | c.776C>T | P259L | 744 | 73.9% | - |

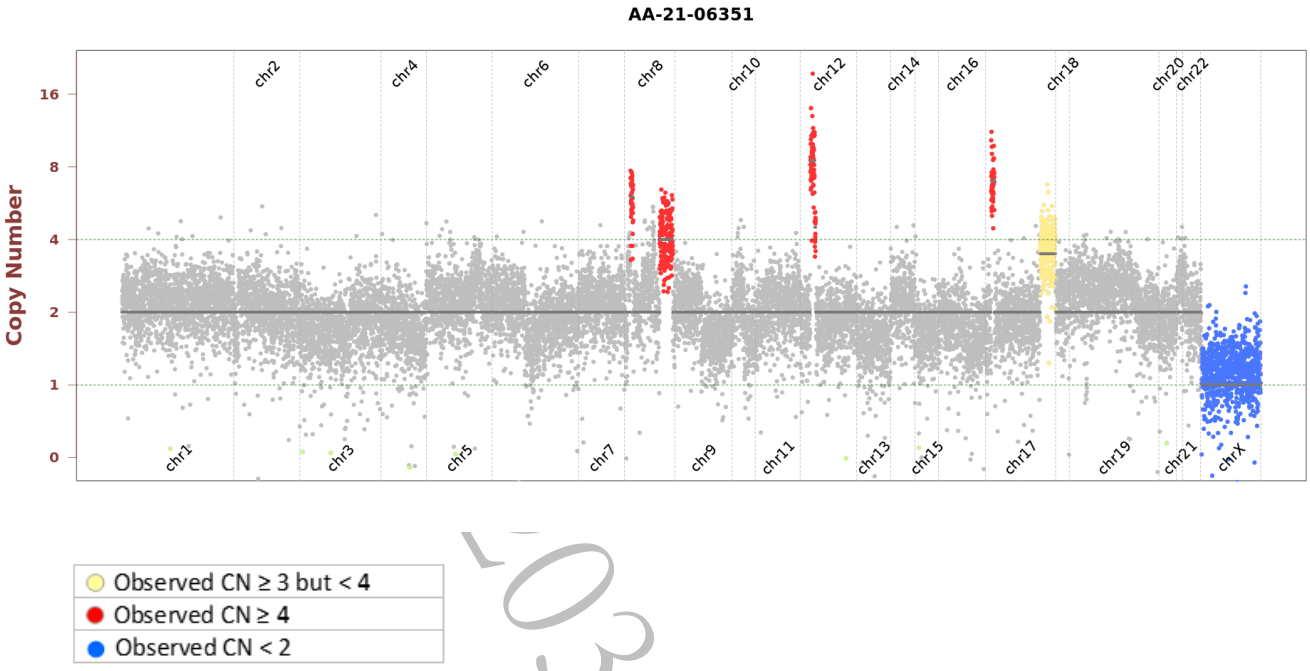
Mutations with clinical relevance are highlighted in red.

斯湯堡

Project ID: C21-M001-01618
Report No.: AA-21-06351_ONC
Date Reported: Jan 03, 2022

## COPY NUMBER VARIANTS (CNVS)

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.



## HOTSPOT GENOTYPES

Listed variants are biomarkers or hotspots that are recommended as standard care by the NCCN or other expert panels and not necessarily FDA-recognized for a particular indication. The genotypes have been manually checked to ensure sufficient coverage for each hotspot of the target gene.

| Gene | Variant | Genotype Detected |
|---|---|---|
| *BRAF* | V600X | Not detected |
| *EGFR* | A763_Y764insFQEA, E709K, E709_T710delinsD, Exon 19 deletion, Exon 19 insertion, Exon 20 insertion, G719A/C/D/S, L747P, L833V, L858R, L861Q/R, S768I, T790M | Not detected |
| *IDH2* | R140Q, R172G/K/M/S | Not detected |
| *KIT* | A502_Y503dup, D419del, D579del, D816F/V/Y, D820A/E/G/Y, E554_I571del, E554_K558del, E554_V559del, Exon 11 mutation, F522C, H697Y, I563_L576del, I653T, K550_W557del, K558N, K558_E562del, K558_V559del, K558delinsNP, K642E, M552_W557del, N505I, N564_Y578del, N822H/I/K/Y, P551_M552del, P573_D579del, P577_D579del, P577_W582delinsPYD, P838L, Q556_K558del, T417_D419delinsI, T417_D419delinsRG, T574_Q575insTQLPYD, V530I, V555_L576del, V555_V559del, V559A/C/D/G, V559_V560del, V559del, V560D/G, V560del, V569_L576del, V654A, W557G/R, W557_K558del, Y553N, Y553_K558del, Y570H, Y578C | Not detected |
| *KRAS* | A146T/V/P, G12X, G13X, Q61X | Not detected |
| *MET* | D1028H/N/Y | Not detected |
| *NRAS* | G12X, G13X, Q61X | Not detected |
| *PDGFRA* | A633T, C450_K451insMIEWMI, C456_N468del, C456_R481del, D568N, D842I/V, D842_H845del, D842_M844del, D846Y, E311_K312del, G853D, H650Q, H845Y, H845_N848delinsP, I843del, N659K/R/S, N848K, P577S, Q579R, R560_V561insER, R748G, R841K, S566_E571delinsR, S584L, V469A, V536E, V544_L545insAVLVLLVIVIISLI, V561A/D, V561_I562insER, V658A, W559_R560del, Y375_K455del, Y555C, Y849C/S | Not detected |
| *PIK3CA* | C420R, E542K/V, E545A/D/G/K, H1047X, Q546E/R | Not detected |

V600X= any mutation in the valine (V) at amino acid 600 being replaced by a different amino acid.
G12X = any mutation in the glycine (G) at amino acid 12 being replaced by a different amino acid.
G13X= any mutation in the glycine (G) at amino acid 13 being replaced by a different amino acid.
Q61X = any mutation in the glutamine (Q) at amino acid 61 being replaced by a different amino acid.
H1047X = any mutation in the histidine (H) at amino acid 1047 being replaced by a different amino acid.

| Gene | Copy Number Detected |
|---|---|
| *CDK4* | 2 |
| *EGFR* | 2 |
| *ERBB2* | 2 |
| *MET* | 2 |

Copy number ≥ 8 is considered amplification

**Other known alterations that are associated with sensitivity, resistance, and toxicity to therapies.**

| Gene | Variant | Genotype Detected |
|---|---|---|
| *AKT1* | E17K | Not detected |
| *ALK* | C1156Y, D1203N, G1202R, L1152R, S1206Y, T1151_L1152insT | Not detected |
| *BRAF* | K601E, L597V/Q/R/S | Not detected |
| *DPYD* | D949V, I560S, splice-site mutation | Not detected |
| *EGFR* | A750P, C797S/Y, S492R | Not detected |
| *ERBB2* | V659E | Not detected |
| *ESR1* | D538G, E380Q, L469V, L536H/P/Q/R, S432L, S463P, V422del, V534E, Y537C/N/S | Not detected |
| *FGFR3* | G370C, G380R, K650E/N/R/M/T/Q, R248C, S249C, S371C, Y373C | Not detected |
| *IDH1* | R132C/G/H/L/Q/S | Not detected |
| *MAP2K1* | D67N, E203K, F53L, K57E/N, P124S, Q56P, Q56_V60del, R47Q, R49L, S222D | Not detected |
| *PTEN* | R130*/fs/G/L/P/Q | Not detected |
| *TPMT* | A154T, Y240C | Not detected |

| Gene | Copy Number Detected |
|---|---|
| *FGFR1* | **12** |
| *MDM2* | 2 |
| *MDM4* | 2 |

Copy number ≥ 8 is considered amplification

# TEST DETAILS

## 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 variations (CNVs).

See ACTOnco®+ Gene List' Section for details of gene sequenced.

## DATABASE USED

- Reference genome: human genome sequence hg19
- COSMIC v.92
- Genome Aggregation database r2.1.1
- ClinVar (version 20210208)
- ACT Genomics in-house database

## NEXT-GENERATION SEQUENCING (NGS) METHODS

Extracted genomic DNA was amplified using four pools of primer pairs targeting coding exons of analyzed genes. Amplicons were ligated with barcoded adaptors. Quality and quantity of amplified library were determined using the fragment analyzer (AATI) and Qubit (Invitrogen). Barcoded libraries were subsequently conjugated with sequencing beads by emulsion PCR and enriched using Ion Chef system (Thermo Fisher Scientific) according to the Ion PI Hi-Q Chef Kit protocol (Thermo Fisher Scientific) or Ion 540 Kit-Chef protocol (Thermo Fisher Scientific). Sequencing was performed on the Ion Proton or Ion S5 sequencer (Thermo Fisher Scientific).

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite (version 5.10). 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 (version 5.10). The coverage was down-sampled to 4000. VEP (Variant Effect Predictor) (version 100) was used to annotate every variant using databases from Clinvar (version 20210208), COSMIC v.92 and Genome Aggregation database r2.1.1. Variants with coverage ≥ 25, 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 r2.1.1 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 variations (CNVs) 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 from samples in ACT Genomics in-house database.

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).

## STANDARD OPERATING PROCEDURES (SOPS)

Standard operating procedures (SOPs) are shown below:

- AG2-QP-15 Specimen Management Procedure
- AG3-QP16-03 SOP of Cancer Cell DNA and RNA Extraction
- AG3-QP16-07 SOP of Nucleic Acid Extraction with QIAsymphony SP
- AG3-QP16-08 SOP of FFPE Nucleic Acid Extraction
- AG3-QP16-10 SOP of HE Staining
- AG3-QP16-13 SOP of Library Construction and Preparation
- AG3-QP16-17 SOP of DNA Quantification with Qubit Fluorometer
- AG3-QP16-20 SOP of CE-Fragment Analysis
- AG3-QP16-22 SOP of Variant Calling
- AG3-QP16-24 SOP of Ion Torrent System Sequencing Reaction
- AG3-QP16-26 SOP of Ion Chef Preparation

- AG3-QP16-35 SOP of Variant Annotation
- AG3-QP16-96 SOP of Manual Inspection for SNVIndel Variant
- AG3-QP16-95 SOP of Manual Inspection for Copy Number Variant
- AG3-QP40-08 (02) Standard protocol for variant interpretation, curation and classification
- AG3-QP16-41 SOP of The user manual for clinical report system (CRS)

## LIMITATIONS

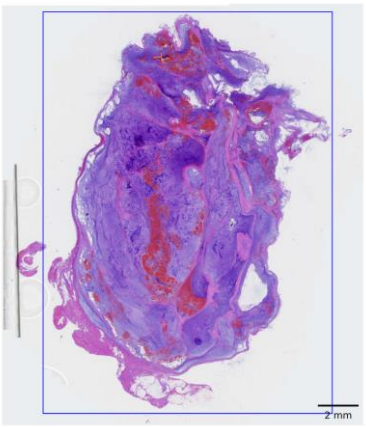
This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject to validation by Sanger or other technologies.

## NOTES

We do not exclude the possibility that pathogenic variants may not be reported by one or more of the tools and the parameters used.

## PATHOLOGY EVALUATION

- H&E-stained section No.: S11035749D
- Collection site: Sacrum
- Examined by: Dr. Yeh-Han Wang
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 70%
  The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 70%
  The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
  The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
  Additional comment: NA
- Manual macrodissection: Not performed




The outline highlights the area of malignant neoplasm annotated by a pathologist.

斯湯堡

Project ID: C21-M001-01618
Report No.: AA-21-06351_ONC
Date Reported: Jan 03, 2022

## SPECIMEN PHOTO(S)


- Collection date: Nov 2021
- Facility retrieved: 臺北榮總

## RUN QC

- Panel: ACTOnco®+
- Mean Depth: 618x
- Target Base Coverage at 100x: 92%

斯湯堡
Project ID: C21-M001-01618
Report No.: AA-21-06351_ONC
Date Reported: Jan 03, 2022

## ACTOnco®+ GENE LIST

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ABCB1* | AURKB | CBL | CDKN2B | E2F3 | FAT1 | GRIN2A | JAK2 | MED12 | NOTCH4 | PMS1 | RAD51D | SLCO1B3* | TNFRSF14 |
| ABCC2* | AXIN1 | CCNA1 | CDKN2C | EGFR | FBXW7 | GSK3B | JAK3 | MEF2B | NPM1 | PMS2 | RAD52 | SMAD2 | TNFSF11 |
| ABCG2* | AXIN2 | CCNA2 | CEBPA* | EP300 | FCGR2B | GSTP1* | JUN* | MEN1 | NQO1* | POLB | RAD54L | SMAD3 | TOP1 |
| ABL1 | AXL | CCNB1 | CHEK1 | EPCAM | FGF1* | GSTT1* | KAT6A | MET | NRAS | POLD1 | RAF1 | SMAD4 | TP53 |
| ABL2 | B2M | CCNB2 | CHEK2 | EPHA2 | FGF10 | HGF | KDM5A | MITF | NSD1 | POLE | RARA | SMARCA4 | TPMT* |
| ADAMTS1 | BAP1 | CCNB3 | CIC | EPHA3 | FGF14 | HIF1A | KDM5C | MLH1 | NTRK1 | PPARG | RB1 | SMARCB1 | TSC1 |
| ADAMTS13 | BARD1 | CCND1 | CREBBP | EPHA5 | FGF19* | HIST1H1C* | KDM6A | MPL | NTRK2 | PPP2R1A | RBM10 | SMO | TSC2 |
| ADAMTS15 | BCL10 | CCND2 | CRKL | EPHA7 | FGF23 | HIST1H1E* | KDR | MRE11 | NTRK3 | PRDM1 | RECQL4 | SOCS1* | TSHR |
| ADAMTS16 | BCL2* | CCND3 | CRLF2 | EPHB1 | FGF3 | HNF1A | KEAP1 | MSH2 | PAK3 | PRKAR1A | REL | SOX2* | TYMS |
| ADAMTS18 | BCL2L1 | CCNE1 | CSF1R | ERBB2 | FGF4* | HR | KIT | MSH6 | PALB2 | PRKCA | RET | SOX9 | U2AF1 |
| ADAMTS6 | BCL2L2* | CCNE2 | CTCF | ERBB3 | FGF6 | HRAS* | KMT2A | MTHFR* | PARP1 | PRKCB | RHOA | SPEN | UBE2A* |
| ADAMTS9 | BCL6 | CCNH | CTLA4 | ERBB4 | FGFR1 | HSP90AA1 | KMT2C | MTOR | PAX5 | PRKCG | RICTOR | SPOP | UBE2K |
| ADAMTSL1 | BCL9 | CD19 | CTNNA1 | ERCC1 | FGFR2 | HSP90AB1 | KMT2D | MUC16 | PAX8 | PRKCI | RNF43 | SRC | UBR5 |
| ADGRA2 | BCOR | CD274 | CTNNB1 | ERCC2 | FGFR3 | HSPA4 | KRAS | MUC4 | PBRM1 | PRKCQ | ROS1 | STAG2 | UGT1A1* |
| ADH1C* | BIRC2 | CD58 | CUL3 | ERCC3 | FGFR4 | HSPA5 | LCK | MUC6 | PDCD1 | PRKDC | RPPH1 | STAT3 | USH2A |
| AKT1 | BIRC3 | CD70* | CYLD | ERCC4 | FH | IDH1 | LIG1 | MUTYH | PDCD1LG2 | PRKN | RPTOR | STK11 | VDR* |
| AKT2 | BLM | CD79A | CYP1A1* | ERCC5 | FLCN | IDH2 | LIG3 | MYC | PDGFRA | PSMB8 | RUNX1 | SUFU | VEGFA |
| AKT3 | BMPR1A | CD79B | CYP2B6* | ERG | FLT1 | IFNL3* | LMO1 | MYCL | PDGFRB | PSMB9 | RUNX1T1 | SYK | VEGFB |
| ALDH1A1* | BRAF | CDC73 | CYP2C19* | ESR1 | FLT3 | IGF1 | LRP1B | MYCN | PDIA3 | PSME1 | RXRA | SYNE1 | VHL |
| ALK | BRCA1 | CDH1 | CYP2C8* | ESR2 | FLT4 | IGF1R | LYN | MYD88 | PGF | PSME2 | SDHA | TAF1 | WT1 |
| AMER1 | BRCA2 | CDK1 | CYP2D6 | ETV1 | FOXL2* | IGF2 | MALT1 | NAT2* | PHOX2B* | PSME3 | SDHB | TAP1 | XIAP |
| APC | BRD4 | CDK12 | CYP2E1* | ETV4 | FOXP1 | IKBKB | MAP2K1 | NBN | PIK3C2B | PTCH1 | SDHC | TAP2 | XPO1 |
| AR | BRIP1 | CDK2 | CYP3A4* | EZH2 | FRG1 | IKBKE | MAP2K2 | NEFH | PIK3C2G | PTEN | SDHD | TAPBP | XRCC2 |
| ARAF | BTG1* | CDK4 | CYP3A5* | FAM46C | FUBP1 | IKZF1 | MAP2K4 | NF1 | PIK3C3 | PTGS2 | SERPINB3 | TBX3 | ZNF217 |
| ARID1A | BTG2* | CDK5 | DAXX | FANCA | GATA1 | IL6 | MAP3K1 | NF2 | PIK3CA | PTPN11 | SERPINB4 | TEK | |
| ARID1B | BTK | CDK6 | DCUN1D1 | FANCC | GATA2 | IL7R | MAP3K7 | NFE2L2 | PIK3CB | PTPRD | SETD2 | TERT | |
| ARID2 | BUB1B | CDK7 | DDR2 | FANCD2 | GATA3 | INPP4B | MAPK1 | NFKB1 | PIK3CD | PTPRT | SF3B1 | TET1 | |
| ASXL1 | CALR | CDK8 | DICER1 | FANCE | GNA11 | INSR | MAPK3 | NFKBIA | PIK3CG | RAC1 | SGK1 | TET2 | |
| ATM | CANX | CDK9 | DNMT3A | FANCF | GNA13 | IRF4 | MAX | NKX2-1* | PIK3R1 | RAD50 | SH2D1A* | TGFBR2 | |
| ATR | CARD11 | CDKN1A | DOT1L | FANCG | GNAQ | IRS1 | MCL1 | NOTCH1 | PIK3R2 | RAD51 | SLC19A1* | TMSB4X* | |
| ATRX | CASP8 | CDKN1B | DPYD | FANCL | GNAS | IRS2* | MDM2 | NOTCH2 | PIK3R3 | RAD51B | SLC22A2* | TNF | |
| AURKA | CBFB | CDKN2A | DTX1 | FAS | GREM1 | JAK1 | MDM4 | NOTCH3 | PIM1 | RAD51C | SLCO1B1* | TNFAIP3 | |

*Analysis of copy number alteration not available.

## DISCLAIMER

**Legal Statement**

This test was developed by ACT Genomics and its performing characteristics were determined by ACT Genomics. This test result is to be used for clinical consultative purposes only and is not intended as a substitute for a clinical guidance of your doctor or another qualified medical practitioner. It should not be regarded as investigational or used for research.

The detection of genomic alterations does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; the detection of no genomic alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

**Treatment Decisions are the Responsibility of the Physician**

Decisions on clinical care and treatment should be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, including physical examinations, information from other diagnostics tests and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test, or the information contained in this report.

In terms of consulting a different treating physician, the patient must file an application and fulfill the listed criteria for ACT Genomics to provide the patient's report to the assigned physician. The report may not be copied or reproduced except in its totality.

**Genetic Alterations and Drugs Not Presented in Ranked Order**

In this report, neither any biomarker alteration nor any drug associated with a potential clinical benefit (or potential lack of clinical benefit), are ranked in order of potential or predicted efficacy.

**Level of Evidence Provided**

Drugs with a potential clinical benefit (or potential lack of clinical benefit) are evaluated for level of published evidence with at least one clinical efficacy case report or preclinical study. We endeavor to keep the information in the report up to date. However, customers must be aware that scientific understanding and technologies change over time, and we make no warranty as to the accuracy, suitability or currency of information provided in this report at any time.

**No Guarantee of Clinical Benefit**

This report makes no promises or guarantees about the effectiveness of a particular drug or any treatment procedure in any disease or in any patient. This report also makes no promises or guarantees that a drug without an association of reportable genomic alteration will, in fact, provide no clinical benefit.

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## 免責聲明

**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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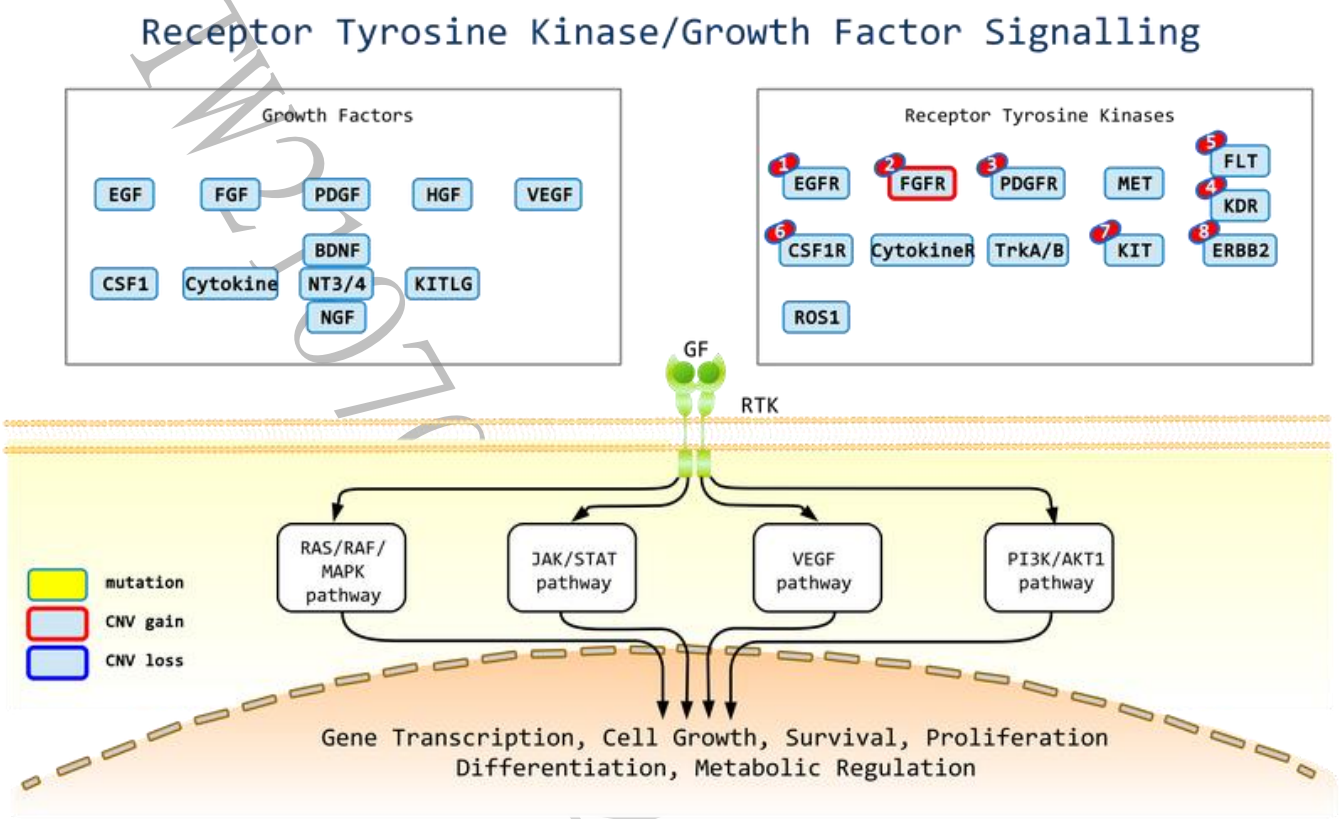
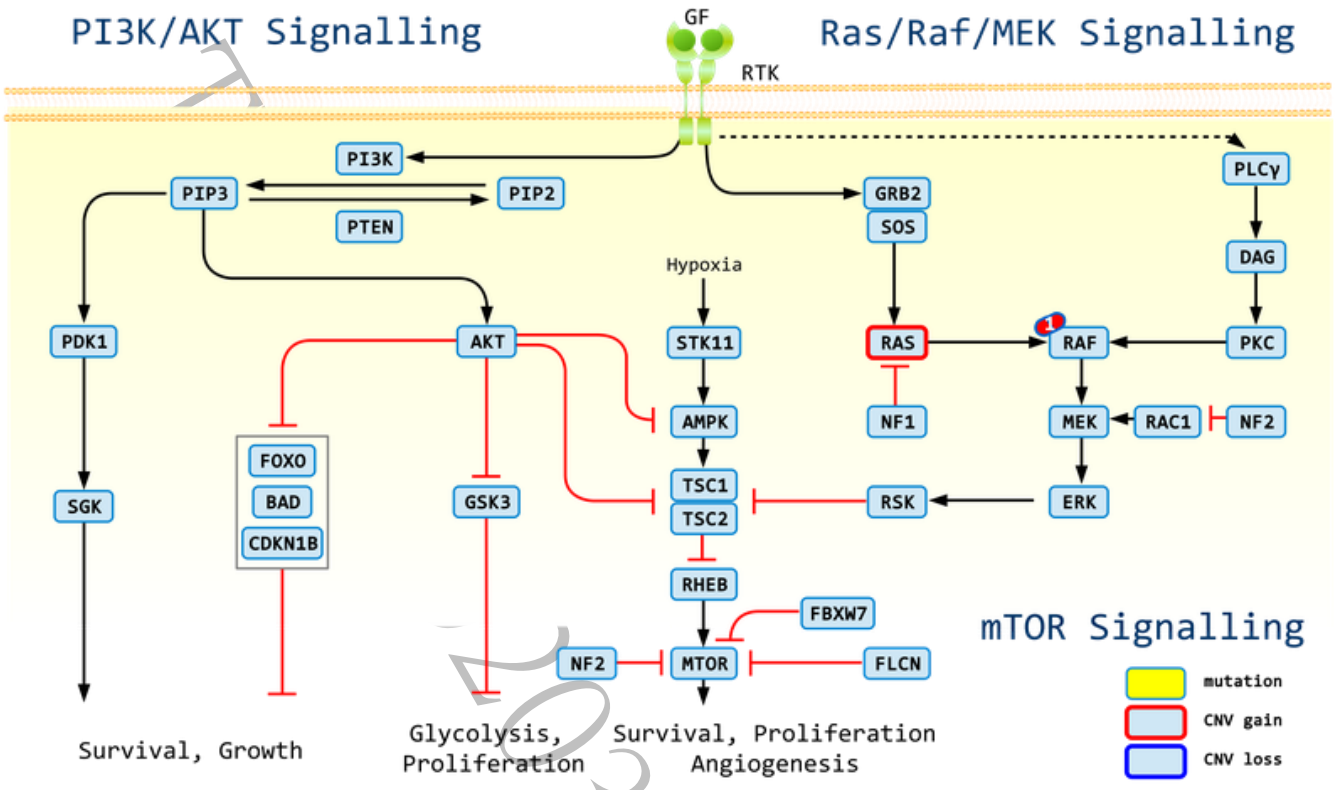
斯湯堡
Project ID: C21-M001-01618
Report No.: AA-21-06351_ONC
Date Reported: Jan 03, 2022

## SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS




**1: Afatinib; 2: Ponatinib, Lenvatinib, Erdafitinib, Infigratinib, Pazopanib; 3: Regorafenib, Pazopanib, Sunitinib, Ponatinib; 4: Ponatinib, Lenvatinib, Pazopanib, Sunitinib; 5: Lenvatinib, Pazopanib, Sunitinib, Ponatinib; 6: Sunitinib; 7: Ponatinib, Regorafenib, Lenvatinib, Pazopanib, Sunitinib, Sorafenib; 8: Afatinib**




**1: Sorafenib**

## REFERENCES

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# ACTFusion™ Report



| PATIENT | | |
|---|---|---|
| Name: 斯湯堡 | | Patient ID: 47679549 |
| Date of Birth: Dec 16, 1991 | | Gender: Male |
| Diagnosis: Myxoid chondrosarcoma | | |
| **ORDERING PHYSICIAN** | | |
| Name: 周德盈醫師 | | 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: S11035749D | Collection site: Sacrum | Date received: Dec 21, 2021 |
| Lab ID: AA-21-06351 | Type: FFPE tissue | D/ID: NA |

**ABOUT ACTFusion™**
The test is a next-generation sequencing (NGS) based in vitro diagnostic assay to detect fusion transcripts of 13 genes, including *ALK, BRAF, EGFR, FGFR1, FGFR2, FGFR3, MET, NRG1, NTRK1, NTRK2, NTRK3, RET,* and *ROS1*.

## TESTING RESULTS

### VARIANT(S) WITH CLINICAL RELEVANCE

### - Fusions

| Fusion Gene & Exon | Transcript ID |
|---|---|
| *SNTB1(1)-NRG1(6) fusion* | SNTB1(NM_021021.3), NRG1(NM_004495.3) |

Note:
- 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.

# ACTFusion™ Report



## THERAPEUTIC IMPLICATION

| Genomic Alterations | Therapies | Effect |
|---|---|---|
| **Level 3B** | | |
| ***SNTB1(1)-NRG1(6)*** fusion | Afatinib | **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 biomarker predictive of response to an FDA approved drug in this indication |
| 2 | | Standard care biomarker (recommended as standard care by the NCCN or other expert panels) predictive of response to an FDA approved drug in this indication |
| 3 | A | Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor |
| | B | Biomarkers that serve as inclusion criteria for clinical trials |
| 4 | | Biomarkers that show plausible therapeutic significance based on small studies, few case reports or preclinical studies |

# ACTFusion™ Report



## VARIANT INTERPRETATION

### *SNTB1(1)-NRG1(6)* fusion

#### Biological Impact

NRG1 (neuregulin 1) encodes a member of the neuregulin protein family which contains an epidermal growth factor (EGF)-like domain and acts as an ERBB3 and ERBB4-specific ligand. Upon binding, NRG1 promotes the dimerization with other ERBB receptors and results in the activation of the PI3K-AKT and MAPK pathways, which in turn regulates cell proliferation, differentiation, and survival[1][2][3]. Overexpression of NRG1 has been reported in ovarian cancer and gastric cancer[4][5].

#### Therapeutic and prognostic relevance

CD74-NRG1 and SDC4-NRG1 are commonly characterized NRG1 fusions and reported with clinical efficacy with afatinib treatment in lung cancer patients[6][7][8].

NRG1 fusions have been determined as an inclusion criterion for the TAPUR trial evaluating afatinib efficacy in advanced solid tumors (NCT02693535).

ACTFusion™ Report



## US FDA-APPROVED DRUG(S)

### Afatinib (GILOTRIF)

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

### - FDA Approval Summary of Afatinib (GILOTRIF)

| | |
|---|---|
| **LUX-Lung 8**[9]<br>NCT01523587 | **Non-small cell lung carcinoma** (Approved on 2016/04/15) |
| | **EGFR Del19/L858R** |
| | Afatinib vs. Erlotinib [PFS(M): 2.4 vs. 1.9] |
| **LUX-Lung 3**[10]<br>NCT00949650 | **Non-small cell lung carcinoma** (Approved on 2013/07/13) |
| | **EGFR Del19/L858R** |
| | Afatinib vs. Pemetrexed + cisplatin [PFS(M): 11.1 vs. 6.9] |

d=day; w=week; m=month

# ACT Fusion™ Report



## 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.

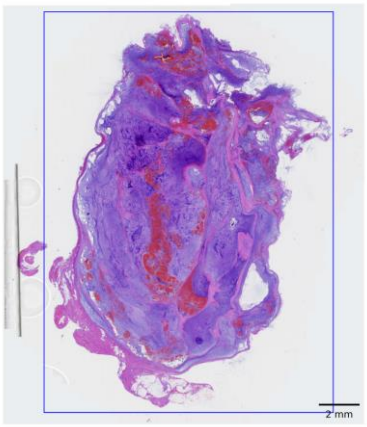
No trial has been found.

# ACTFusion™ Report



## TEST DETAILS

### SPECIMEN RECEIVED AND PATHOLOGY REVIEW


- Collection date: Nov 2021
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11035749D
- Collection site: Sacrum
- Examined by: Dr. Yeh-Han Wang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 70%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 70%
    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: No
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

### RUN QC

- Panel: ACTFusion™
- Total reads: 358491
- Average unique RNA Start Sites per control GSP2: 138

### LIMITATIONS

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.

# ACTFusion™ Report



## NEXT-GENERATION SEQUENCING (NGS) METHODS

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.

## STANDARD OPERATING PROCEDURES (SOPs)

- AG2-QP-15 Specimen Management Procedure
- AG3-QP16-08 SOP of FFPE Nucleic Acid Extraction
- AG3-QP16-10 SOP of HE Staining
- AG3-QP16-17 SOP of DNA Quantification with Qubit Fluorometer
- AG3-QP16-20 SOP of CE-Fragment Analysis
- AG3-QP16-24 SOP of Ion Torrent System Sequencing Reaction
- AG3-QP16-26 SOP of Ion Chef Preparation
- AG3-QP40-08 (02) Standard protocol for variant interpretation, curation and classification
- AG3-QP16-94 (01) SOP of ACTFusion v3 Library Construction and Preparation
- AG3-QP16-36(02) SOP of Fusion Gene Detection
- AG3-QP16-41 SOP of The user manual for clinical report system (CRS)

## DATABAES USED

- Quiver Gene Fusion Database version 5.1.18

## GENE LIST

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *ALK* | *BRAF* | *EGFR* | *FGFR1* | *FGFR2* | *FGFR3* | *MET* | *NRG1* |
| *NTRK1* | *NTRK2* | *NTRK3* | *RET* | *ROS1* | | | |

**Variant Analysis:**
醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

**Sign Off**
醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

# ACTFusion™ Report



## 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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# ACTFusion™ Report



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