ACTOnco® + Report

TW2107002032021121315132O

## REPORT SUMMARY



## REPORT DETAILS



## APPENDIX

## PATIENT AND SAMPLE INFORMATION

| PATIENT | SPECIMEN | ORDERING PHYSICIAN |
|---|---|---|
| Name: 許獻聰 | Type: FFPE tissue | Name: 顏厥全醫師 |
| Gender: Male | Date received: Dec 01, 2021 | Facility: 臺北榮總 |
| Date of Birth: Nov 21, 1963 | Collection site: Left pelvic | Tel: 886-228712121 |
| Patient ID: 45100274 | Specimen ID: S11031648A | Address: 臺北市北投區石牌路二段 201 號 |
| Diagnosis: Chondrosarcoma | Lab ID: AA-21-05913 | |
| | 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

| Gene | Amino Acid Change | Coverage | Allele Frequency | COSMIC ID |
|---|---|---|---|---|
| *IDH1* | R132S | 1094 | 28.0% | COSM28748 |
| *TP53* | R248Q | 1065 | 50.7% | COSM10662 |

### 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 **44%** tumor purity.

**Amplification (Copy number ≥ 8)**

| Chr | Gene | Copy Number |
|---|---|---|
| ND | ND | ND |

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

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

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

| Chr | Gene |
|---|---|
| chr9 | *CDKN2A* |
| chr17 | *NF1* |
| chr22 | *CHEK2, NF2* |

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:**
醫檢師黃靖婷 博士
Ching-Ting Huang Ph.D.
檢字第 016511 號

CT Huang

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

# THERAPEUTIC IMPLICATIONS

## TARGETED THERAPIES

| Genomic Alterations | Therapies | Effect |
|---|---|---|
| **Level 3A** | | |
| ***IDH1*** R132S | Ivosidenib | sensitive |
| **Level 3B** | | |
| ***CDKN2A*** Heterozygous deletion | Abemaciclib, Palbociclib, Ribociclib | sensitive |
| ***CHEK2*** Heterozygous deletion | Niraparib, Rucaparib | sensitive |
| ***NF1*** Heterozygous deletion | Selumetinib | sensitive |
| **Level 4** | | |
| ***IDH1*** R132S | Dasatinib, Sunitinib, Bevacizumab | sensitive |
| ***CHEK2*** Heterozygous deletion | Olaparib | sensitive |
| ***NF2*** Heterozygous deletion | Everolimus | sensitive |
| ***NF1*** Heterozygous deletion | Everolimus, Trametinib | sensitive |
| ***NF1*** Heterozygous deletion | Afatinib, Erlotinib, Gefitinib, Lapatinib, Vemurafenib, Cetuximab, Trastuzumab | 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 |
| 3 | 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

| Therapies | Genomic Alterations | Effect | Gene / Variant Level Evidence | Cancer Type |
|---|---|---|---|---|
| Platinum- and taxane-based regimens | ***TP53*** R248Q | less sensitive | Clinical | Ovarian cancer |

## HORMONAL THERAPIES

| Therapies | Genomic Alterations | Effect | Gene / Variant Level Evidence | Cancer Type |
|---|---|---|---|---|
| Tamoxifen | ***NF1*** Heterozygous deletion | less sensitive | Clinical | Breast cancer |

## OTHERS

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

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

W21-07520-20211213-151320

## VARIANT INTERPRETATION

### *IDH1* R132S

**Biological Impact**

IDH1 encodes the isocitrate dehydrogenase 1 (IDH1), an enzyme that catalyzes the conversion of isocitrate to alpha-ketoglutarate (alpha-KG), a crucial step in the tricarboxylic acid (TCA) cycle. Mutations in IDH1 convert alpha-KG to 2-HG, which is an oncogenic metabolite[1]. Missense mutations of IDH1/2, including the substitution of the amino acids arginine 132 in IDH1 and arginine 172 or 140 in IDH2, leads to accumulate intracellular D-2-hydroxyglutarate (D-2HG) and alter epigenetic regulation, cancer cell differentiation and metabolism[2][3][4][5]. Mutations in IDH1 and IDH2 have been reported a wide range of cancers, including prostate cancer[6], chondrosarcoma[7], glioma[8], cholangiocarcinoma[9] and acute myeloid leukemia (AML)[10].

**Therapeutic and prognostic relevance**

Ivosidenib, the IDH1 inhibitor has been approved by the U.S. Food and Drug Administration (U.S. FDA) for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) carrying a susceptible IDH1 mutation (R132C, R132H, R132G, R132S, and R132L) as detected by an FDA-approved test. Results of a Phase I clinical study showed that IDH305 and AG-120 (Ivosidenib), inhibitors explicitly targeting the mutated IDH1, demonstrate efficacy in patients AML harboring IDH1 R132 mutations[11]. In another clinical study (n=63), glioma patients harboring IDH1 R132 mutations showed favorable overall survival when treated with bevacizumab or sunitinib[12]. Of note, in August. 2021, U.S. FDA has also approved ivosidenib for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with IDH1 mutation (R132C, R132H, R132G, R132S, and R132L) based on the results of Study AG120-C-005 (NCT02989857)[13].

A combination therapy consists of vandetanib, a multi-tyrosine kinase inhibitor, temozolomide, and radiotherapy demonstrated a significant increased PFS and OS in glioblastoma patients harboring IDH1 R132H compared to glioblastoma patients without IDH1 R132H[14].

Preclinical studies in intrahepatic cholangiocarcinoma, glioma, sarcoma, and AML also demonstrated the sensitivity of R132C/H-mutant tumors to multi-kinase inhibitors such as saracatinib and dasatinib[15], PARP inhibitors[16][17], as well as IDH1 inhibitor AGI-5198[18][19]. Small molecule inhibitors of IDH1, which have shown activity in the preclinical settings in IDH1-mutant glioma and leukemia cells, are currently in clinical trials[18][4].

### *TP53* R248Q

**Biological Impact**

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[20]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[21].

R248Q is a missense mutation located in the DNA-binding domain (DBD) of the p53 protein (UniProtKB). This mutation causes oncogenic gain-of-function phenotypes in a breast cancer cell line[22] and has been reported to target the proteasome activator REG gamma to promote endometrial cancer progression[23].

**Therapeutic and prognostic relevance**

Despite having a high mutation rate in cancers, there are currently no approved targeted therapies for TP53 mutations. A phase II trial demonstrated that Wee1 inhibitor (AZD1775) in combination with carboplatin was well tolerated and showed promising anti-tumor activity in TP53-mutated ovarian cancer refractory or resistant (< 3 months) to standard first-line therapy (NCT01164995)[24].

In a retrospective study (n=19), advanced sarcoma patients with TP53 loss-of-function mutations displayed improved progression-free survival (208 days versus 136 days) relative to patients with wild-type TP53 when treated with pazopanib[25]. Results from another Phase I trial of advanced solid tumors (n=78) demonstrated that TP53 hotspot mutations are associated with better clinical response to the combination of pazopanib and vorinostat[26].

Advanced solid tumor and colorectal cancer patients harboring a TP53 mutation have been shown to be more sensitive to bevacizumab when compared with patients harboring wild-type TP53[27][28][29]. In a pilot trial (n=21), TP53-negative breast cancer patients demonstrated increased survival following treatment with bevacizumab in combination with chemotherapy agents, Adriamycin (doxorubicin) and Taxotere (docetaxel)[30]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[31][32]. In a retrospective study of non-small cell lung cancer (NSCLC), TP53 mutations were associated with high expression of VEGF-A, the primary target of bevacizumab, offering a mechanistic explanation for why patients exhibit improved outcomes after bevacizumab treatment when their tumors harbor mutant TP53 versus wild-type TP53[33].

TP53 oncomorphic mutations, including P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L and R282W have been shown to predict resistance to platinum- and taxane-based chemotherapy in advanced serous ovarian carcinoma patients[34].

## *CDKN2A* Heterozygous deletion

**Biological Impact**

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein[35][36] whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53[37]. CDKN2A has been reported as a haploinsufficient tumor suppressor with one copy loss that may lead to weak protein expression and is insufficient to execute its original physiological functions[38]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[39][40].

TW21070020320211213 151320

**Therapeutic and prognostic relevance**

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[41][42]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[43][44][45]. However, there are clinical studies that demonstrated CDKN2A nuclear expression, CDKN2A/CDKN2B co-deletion, or CDKN2A inactivating mutation was not associated with clinical benefit from CDK4/6 inhibitors, such as palbociclib and ribociclib, in RB-positive patients[46][47][48]. However, CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for the treatment of ER+ and HER2- breast cancer[42][49][50].

In a Phase I trial, a KRAS wild-type squamous non-small cell lung cancer (NSCLC) patient with CDKN2A loss had a partial response when treated with CDK4/6 inhibitor abemaciclib[44]. Administration of combined palbociclib and MEK inhibitor PD-0325901 yield promising progression-free survival among patients with KRAS mutant non-small cell lung cancer (NSCLC) (AACR 2017, Abstract CT046). Moreover, MEK inhibitor in combination with CDK4/6 inhibitor demonstrates significant anti-KRAS-mutant NSCLC activity and radiosensitizing effect in preclinical models[51].

A retrospective analysis demonstrated that concurrent deletion of CDKN2A with EGFR mutation in patients with non-small cell lung cancer (NSCLC), predicts worse overall survival after EGFR-TKI treatment[52].

## *CHEK2* Heterozygous deletion

**Biological Impact**

The checkpoint kinase 2 (CHEK2 or CHK2) gene encodes a serine/threonine protein kinase involved in transducing DNA damage signals that are required for both the intra-S phase and G2/M checkpoints[53]. CHEK2 heterozygosity has been shown to cause haploinsufficient phenotypes that can contribute to tumorigenesis through inappropriate S phase entry, accumulation of DNA damage during replication, and failure to restrain mitotic entry[54][55]. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers[56][57][58][59][60].

**Therapeutic and prognostic relevance**

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate[61].

TW21070020202111213 151320

In addition, CHEK2 has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer[62] or prostate cancer[63] (NCT03533946), niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

In a phase 2 trial, two prostate cancer patients harboring CHEK2 homozygous deletion was enrolled. One of the two patients had a response to olaparib[64].

## *NF1* Heterozygous deletion

**Biological Impact**

The neurofibromin 1 (NF1) gene encodes a GTPase activating protein (GAP) which is an important negative regulator of the Ras cellular proliferation pathways[65][66][67][68]. Besides, NF1 also physically interacts with the N-terminal domain of focal adhesion kinase (FAK) and involves in the regulation of cell adhesion, growth, and other pathways[69][70]. NF1 is considered a classical haploinsufficient tumor suppressor gene with loss of one allele through inherited or acquired mutation may lead to reduced protein expression and is insufficient to execute normal cellular functions contributing to tumor development[71][72][73][74][75]. NF1 syndrome is a germline condition resulting in a predisposition to several types of cancer such as neurofibromas, melanoma, lung cancer, ovarian cancer, breast cancer, colorectal cancer, hematological malignancies[76][77][78]. Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types[79], including myelodysplastic syndromes, melanomas, colon cancer[80], glioblastomas[81], lung cancer[82], ovarian cancer, and breast cancer[76].

**Therapeutic and prognostic relevance**

In April 2020, the U.S. FDA has approved selumetinib for pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

A phase II trial (NCT02664935, NLMT) demonstrated that selumetinib in combination with docetaxel resulted in a confirmed ORR of 28.5% (4/14), durable clinical benefit (DCB) rate of 50% (7/14), and mPFS of 5.3 months in lung adenocarcinoma patients harboring NF1 loss[83].

NF1 loss has been determined as an inclusion criterion for the trials evaluating selumetinib efficacies in lung cancer (NCT02664935) and NF1-associated tumors (NCT03326388).

A case study had reported that MEK inhibitor, trametinib, was effective in a treatment-refractory neurofibromatosis type I-associated glioblastoma[84]. Various preclinical data had also supported the activity of MEK and mTOR inhibitors in NF1-deficient tumors[85][86][87][88][89][90].

TW2107002020211213151320

In an NGS-based study, patients harboring mutations in the mTOR pathway, including mTOR, TSC1, TSC2, NF1, PIK3CA, and PIK3CG responded to everolimus[91].

NF1 depletion has been associated with drug resistance to RAF and EGFR inhibitors, tamoxifen, and retinoic acid[79][92]. For example, loss of NF1 was identified in patients with lung adenocarcinomas or colorectal cancer who presented resistance to anti-EGFR treatment, including erlotinib, gefitinib, afatinib, and cetuximab, respectively[93][94][95]. Notably, preclinical studies further revealed that the addition of a MEK inhibitor could restore the sensitivity to erlotinib[93].

In a liquid biopsy-based ctDNA profiling study of HER2-positive metastatic gastric cancer, NF1 loss (either induced by mutation or deletion) was suggested as a novel mechanism contributes to trastuzumab resistance. The cell-based study also showed that the trastuzumab resistance could be overcome with a combination of HER2 and MEK/ERK inhibitors[96].

Loss of NF1 in patients with BRAF-mutated melanomas was suggested conferring resistance to BRAF inhibitors[97][98][99][100].

## *NF2* Heterozygous deletion

**Biological Impact**

The neurofibromin (NF2) gene encodes the protein Merlin, a tumor suppressor that functions as a negative regulator of the PI3K/AKT/mTOR pathway[101][102][103]. NF2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[104]. Inactivation germline mutations in the NF2 are associated with the hereditary neurofibromatosis type 2, a disorder characterized by the growth of noncancerous tumors in the nervous system[101][105]. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas[106], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers[107].

**Therapeutic and prognostic relevance**

Genomic alterations with activating effects on the mTOR signaling pathway have been identified to confer sensitivity to everolimus across multiple cancer types[108][109][110][91]. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer[111] and urothelial carcinoma[112], both harboring NF2 truncating mutations. Preclinical evidence has shown the efficacy of MEK1/2 inhibitor selumetinib in KRAS-mutant thyroid cancer model with NF2 loss[113].

Analysis of afatinib-plus-cetuximab-resistant biopsy specimens revealed a loss-of-function alteration in genes that modulate mTOR signaling pathway, including NF2 and TSC1[114].

TW21070020320211213151320

# US FDA-APPROVED DRUG(S)

## Abemaciclib (VERZENIO)

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

### FDA Approval Summary of Abemaciclib (VERZENIO)

| | |
|---|---|
| **monarchE**<br>NCT03155997 | **Breast cancer** (Approved on 2021/10/12)<br>**HR-positive, HER2-negative**<br>Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor<br>[IDFS at 36 months(%): 86.1 vs. 79.0] |
| **MONARCH 3**[115]<br>NCT00246621 | **Breast cancer** (Approved on 2018/02/26)<br>**HR-positive, HER2-negative**<br>Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole<br>[PFS(M): 28.2 vs. 14.8] |
| **MONARCH 1**[116]<br>NCT02102490 | **Breast cancer** (Approved on 2017/09/28)<br>**HR-positive, HER2-negative**<br>Abemaciclib<br>[ORR(%): 19.7 vs. 17.4] |
| **MONARCH 2**[50]<br>NCT02107703 | **Breast cancer** (Approved on 2017/09/28)<br>**HR-positive, HER2-negative**<br>Abemaciclib + fulvestrant vs. Placebo + fulvestrant<br>[PFS(M): 16.4 vs. 9.3] |

## 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**<br>NCT03434379 | **Hepatocellular carcinoma** (Approved on 2020/05/29)<br>-<br>Atezolizumab plus bevacizumab vs. Sorafenib<br>[PFS(M): 6.8 vs. 4.3, OS(M): NR vs. 13.2] |
| **GOG-0213**[117]<br>NCT00565851 | **Peritoneal carcinoma, Ovary epithelial cancer, Fallopian tube cancer** (Approved on 2016/12/06)<br>-<br>Bevacizumab + carboplatin + paclitaxel vs. Carboplatin + paclitaxel<br>[OS(M): 42.6 vs. 37.3] |

| | |
|---|---|
| **OCEANS[118]**<br>NCT00434642 | **Peritoneal carcinoma, Ovary epithelial cancer, Fallopian tube cancer** (Approved on 2016/12/06)<br>-<br>Bevacizumab + carboplatin + gemcitabine vs. Carboplatin + gemcitabine<br>[PFS(M): 12.4 vs. 8.4] |
| **AURELIA [119]**<br>NCT00976911 | **Peritoneal carcinoma, Ovary epithelial cancer, Fallopian tube cancer** (Approved on 2014/11/14)<br>-<br>Bevacizumab + chemotherapy vs. Chemotherapy<br>[PFS(M): 6.8 vs. 3.4] |
| **GOG-0240[120]**<br>NCT00803062 | **Cervical cancer** (Approved on 2014/08/14)<br>-<br>Bevacizumab + chemotherapy vs. Chemotherapy<br>[OS(M): 16.8 vs. 12.9] |
| **ML18147[121]**<br>NCT00700102 | **Colorectal cancer** (Approved on 2013/01/23)<br>-<br>Bevacizumab + chemotherapy vs. Chemotherapy<br>[OS(M): 11.2 vs. 9.8] |
| **BO17705[122]**<br>NCT00738530 | **Renal cell carcinoma** (Approved on 2009/07/31)<br>-<br>Bevacizumab + IFN-α2a vs. IFN-α2a<br>[PFS(M): 10.2 vs. 5.4] |
| **AVF3708g[123]**<br>NCT00345163 | **Glioblastoma multiforme** (Approved on 2009/05/06)<br>-<br>Bevacizumab + irinotecan vs. Bevacizumab<br>[ORR(%): 25.9] |
| **E4599[124]**<br>NCT00021060 | **Non-small cell lung carcinoma** (Approved on 2006/10/11)<br>-<br>Bevacizumab + paclitaxel + carboplatin vs. Paclitaxel + carboplatin<br>[OS(M): 12.3 vs. 10.3] |
| **E3200[125]**<br>NCT00025337 | **Colorectal cancer** (Approved on 2006/06/20)<br>-<br>Bevacizumab + oxaliplatin + fluorouracil + leucovorin vs. Oxaliplatin + fluorouracil + leucovorin<br>[OS(M): 13 vs. 10.8] |

0700020211213151320

| | |
|---|---|
| **AVF2107g**[126]<br>NCT00109070 | **Colorectal cancer** (Approved on 2004/02/26) |
| | - |
| | Bevacizumab + irinotecan+5-FU + leucovorin vs. Irinotecan + 5-FU + leucovorin<br>[OS(M): 20.3 vs. 15.6] |

## 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**[127]<br>NCT00481247 | **Chronic myeloid leukemia** (Approved on 2010/10/28) |
| | - |
| | Dasatinib vs. Imatinib<br>[ORR(%): 76.8 vs. 66.2] |
| [128]<br>NCT00123474 | **Chronic myeloid leukemia** (Approved on 2007/11/08) |
| | - |
| | Dasatinib<br>[ORR(%): 63.0] |
| [129]<br>NCT00123487 | **Acute lymphocytic leukemia** (Approved on 2006/06/28) |
| | - |
| | Dasatinib<br>[ORR(%): 38.0] |

## Everolimus (AFINITOR)

Everolimus, a derivative of sirolimus, works as an inhibitor of mammalian target of rapamycin complex 1 (mTORC1) and blocks mTORC1-mediated downstream signals for cell growth, proliferation, and survival. Everolimus is developed and marketed by Novartis under the trade name AFINITOR.

### FDA Approval Summary of Everolimus (AFINITOR)

| | |
|---|---|
| **RADIANT-4**[130]<br>NCT01524783 | **Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26) |
| | - |
| | Everolimus vs. Placebo<br>[PFS(M): 11 vs. 3.9] |
| **BOLERO-2**[131]<br>NCT00863655 | **Breast cancer** (Approved on 2012/07/20) |
| | **ER+/HER2-** |
| | Everolimus + exemestane vs. Placebo + exemestane<br>[PFS(M): 7.8 vs. 3.2] |

M107002032021121315132

| | |
|---|---|
| **RADIANT-3**[132]<br>NCT00510068 | **Pancreatic neuroendocrine tumor** (Approved on 2011/05/05) |
| | - |
| | Everolimus vs. Placebo<br>[PFS(M): 11 vs. 4.6] |
| **EXIST-1**[133]<br>NCT00789828 | **Subependymal giant cell astrocytoma** (Approved on 2010/10/29) |
| | - |
| | Everolimus vs. Placebo<br>[ORR(%): 35.0] |
| **RECORD-1**[134]<br>NCT00410124 | **Renal cell carcinoma** (Approved on 2009/05/30) |
| | - |
| | Everolimus vs. Placebo<br>[PFS(M): 4.9 vs. 1.9] |

## Ivosidenib (TIBSOVO)

Ivosidenib is an isocitrate dehydrogenase-1 (IDH1) inhibitor. Ivosidenib is developed and marketed by Agios under the trade name TIBSOVO.

### FDA Approval Summary of Ivosidenib (TIBSOVO)

| | |
|---|---|
| **Study AG120-C-005**[13]<br>NCT02989857 | **Cholangiocarcinoma** (Approved on 2021/08/25) |
| | **IDH1 mutation (R132C/H/G/S/L)** |
| | Ivosidenib vs. Placebo<br>[PFS(M): 2.7 vs. 1.4] |
| **AG120-C-001**[11]<br>NCT02074839 | **Acute myeloid leukemia** (Approved on 2018/07/20) |
| | **IDH1 mutation (R132C/H/G/S/L)** |
| | Ivosidenib<br>[pCR(%): 42.9] |

## Niraparib (ZEJULA)

Niraparib is an oral, small molecule inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1 and -2 (PARP-1, -2). Niraparib is developed and marketed by Tesaro under the trade name ZEJULA.

### FDA Approval Summary of Niraparib (ZEJULA)

| | |
|---|---|
| **QUADRA**[135]<br>NCT02354586 | **Ovarian cancer** (Approved on 2019/10/23) |
| | **HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)** |
| | Niraparib<br>[ORR(%): 24.0, DOR(M): 8.3] |

0700203202112131513320

| | |
|---|---|
| **NOVA**[136] NCT01847274 | **Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27) |
| | **gBRCA+ CR/PR to platinum-based chemotherapy** |
| | Niraparib vs. Placebo [PFS(M): 21 vs. 5.5] |
| **NOVA**[136] NCT01847274 | **Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27) |
| | **gBRCA- CR/PR to platinum-based chemotherapy** |
| | Niraparib vs. Placebo [PFS(M): 9.3 vs. 3.9] |

## Olaparib (LYNPARZA)

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

### FDA Approval Summary of Olaparib (LYNPARZA)

| | |
|---|---|
| **PROfound**[61] NCT02987543 | **Prostate cancer** (Approved on 2020/05/19) |
| | **ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm, RAD54Lm** |
| | Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5] |
| **PAOLA-1**[137] NCT02477644 | **Ovarian cancer** (Approved on 2020/05/08) |
| | **HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)** |
| | Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7] |
| **POLO**[138] NCT02184195 | **Pancreatic adenocarcinoma** (Approved on 2019/12/27) |
| | **Germline BRCA mutation (deleterious/suspected deleterious)** |
| | Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8] |
| **SOLO-1**[139] NCT01844986 | **Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19) |
| | **Germline or somatic BRCA-mutated (gBRCAm or sBRCAm)** |
| | Olaparib vs. Placebo [PFS(M): NR vs. 13.8] |

| | |
|---|---|
| **OlympiAD[140]**<br>NCT02000622 | **Breast cancer** (Approved on 2018/02/06)<br>**Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative**<br>Olaparib vs. Chemotherapy<br>[PFS(M): 7 vs. 4.2] |
| **SOLO-2/ENGOT-Ov21[141]**<br>NCT01874353 | **Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)<br>**gBRCA+**<br>Olaparib vs. Placebo<br>[PFS(M): 19.1 vs. 5.5] |
| **Study19[142]**<br>NCT00753545 | **Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)<br>**-**<br>Olaparib vs. Placebo<br>[PFS(M): 8.4 vs. 4.8] |
| **Study 42[143]**<br>NCT01078662 | **Ovarian cancer** (Approved on 2014/12/19)<br>**Germline BRCA mutation (deleterious/suspected deleterious)**<br>Olaparib<br>[ORR(%): 34.0, DOR(M): 7.9] |

## Palbociclib (IBRANCE)

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

### FDA Approval Summary of Palbociclib (IBRANCE)

| | |
|---|---|
| **PALOMA-2[144]**<br>NCT01740427 | **Breast cancer** (Approved on 2017/03/31)<br>**ER+, HER2-**<br>Palbociclib + letrozole vs. Placebo + letrozole<br>[PFS(M): 24.8 vs. 14.5] |
| **PALOMA-3[145]**<br>NCT01942135 | **Breast cancer** (Approved on 2016/02/19)<br>**ER+, HER2-**<br>Palbociclib + fulvestrant vs. Placebo + fulvestrant<br>[PFS(M): 9.5 vs. 4.6] |

0700202211213151320

## Ribociclib (KISQALI)

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

### FDA Approval Summary of Ribociclib (KISQALI)

| | |
|---|---|
| **MONALEESA-2**[49]<br>NCT01958021 | **Breast cancer** (Approved on 2017/03/13)<br>**HR+, HER2-**<br>Ribociclib vs. Letrozole<br>[PFS(M): NR vs. 14.7] |

## Rucaparib (RUBRACA)

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

### FDA Approval Summary of Rucaparib (RUBRACA)

| | |
|---|---|
| **TRITON2**<br>NCT02952534 | **Prostate cancer** (Approved on 2020/05/15)<br>**gBRCA+, sBRCA**<br>Rucaparib<br>[ORR(%): 44.0, DOR(M): NE] |
| **ARIEL3**[62]<br>NCT01968213 | **Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)<br>**All\|HRD\|tBRCA**<br>Rucaparib vs. Placebo<br>[PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4] |
| **ARIEL2**[146]<br>NCT01482715, NCT01891344 | **Ovarian cancer** (Approved on 2016/12/19)<br>**Germline and/or somatic BRCA mutation**<br>Rucaparib<br>[ORR(%): 54.0] |

TW2017092032021213 151320

## Selumetinib (KOSELUGO)

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

### FDA Approval Summary of Selumetinib (KOSELUGO)

| | |
|---|---|
| **SPRINT**<br>NCT01362803 | **Plexiform neurofibromas** (Approved on 2020/04/10)<br>**Neurofibromatosis type 1**<br>Selumetinib<br>[ORR(%): 66.0] |

## 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)

| | |
|---|---|
| [147][148][149]<br>NCT00428597 | **Pancreatic cancer** (Approved on 2011/05/20)<br>-<br>Sunitinib vs. Placebo<br>[PFS(M): 10.2 vs. 5.4] |
| [150][151][152]<br>NCT00077974 | **Renal cell carcinoma** (Approved on 2007/02/02)<br>-<br>Sunitinib<br>[ORR(%): 34.0] |
| [151][152]<br>NCT00054886 | **Renal cell carcinoma** (Approved on 2007/02/02)<br>-<br>Sunitinib<br>[ORR(%): 36.5] |
| [153][152]<br>NCT00083889 | **Renal cell carcinoma** (Approved on 2007/02/02)<br>-<br>Sunitinib vs. IFN-α<br>[PFS(W): 47.3 vs. 22] |

TW070020211213 151320

| | |
|---|---|
| [154]<br>NCT00075218 | **Gastrointestinal stromal tumor** (Approved on 2006/01/26) |
| | - |
| | Sunitinib vs. Placebo<br>[TTP(W): 27.3 vs. 6.4] |

## Trametinib (MEKINIST)

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

### FDA Approval Summary of Trametinib (MEKINIST)

| | |
|---|---|
| **BRF117019**[155]<br>NCT02034110 | **Anaplastic thyroid cancer** (Approved on 2018/05/04) |
| | **BRAF V600E** |
| | Dabrafenib + trametinib<br>[ORR(%): 61.0] |
| **BRF113928**[156]<br>NCT01336634 | **Non-small cell lung cancer** (Approved on 2017/06/22) |
| | **BRAF V600E** |
| | Trametinib + dabrafenib vs. Dabrafenib<br>[ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9] |
| **COMBI-d**[157]<br>NCT01584648 | **Melanoma** (Approved on 2014/01/10) |
| | **BRAF V600E/K** |
| | Trametinib + dabrafenib vs. Dabrafenib + placebo<br>[PFS(M): 9.3 vs. 8.8] |
| **METRIC**[158]<br>NCT01245062 | **Melanoma** (Approved on 2013/05/29) |
| | **BRAF V600E/K** |
| | Trametinib vs. Dacarbazine or paclitaxel<br>[PFS(M): 4.8 vs. 1.5] |

d=day; w=week; m=month

M10700220211213151320

## 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.

TW2107002032021213 15132

# DETAILED TEST RESULTS

## SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS

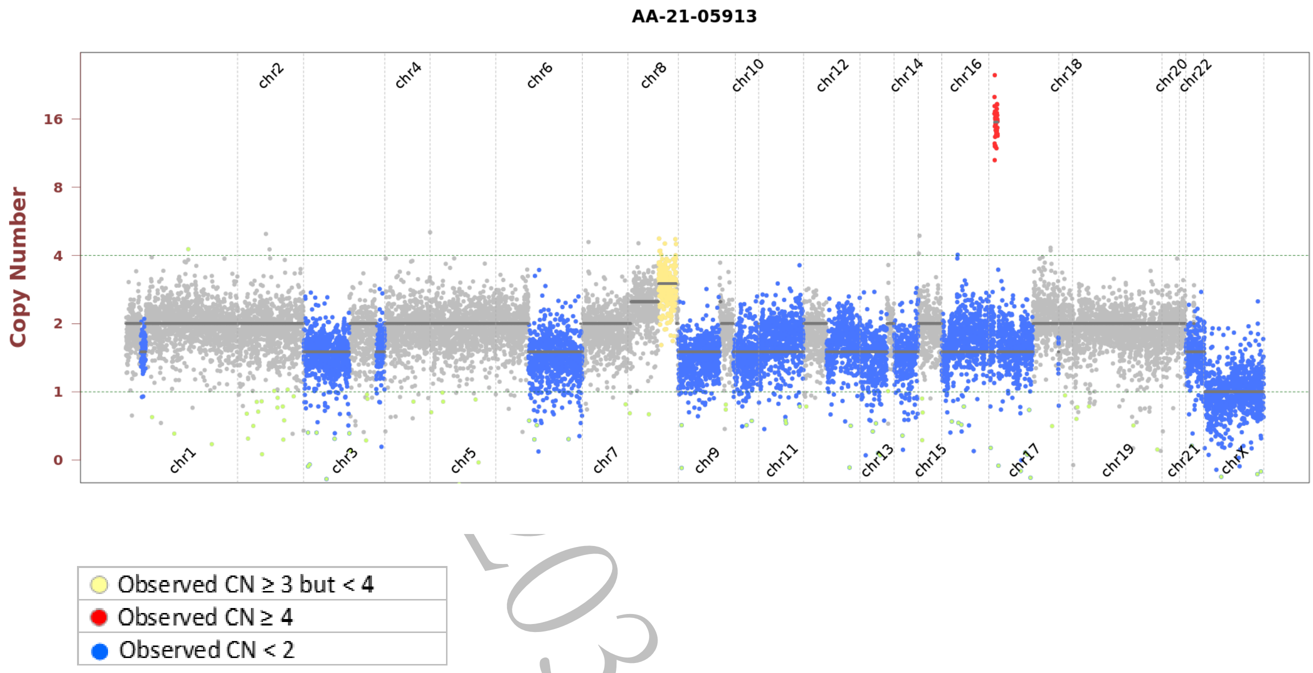
| Gene | Chr | Exon | Accession Number | cDNA Change | Amino Acid Change | Coverage | Allele Frequency | COSMIC ID |
|---|---|---|---|---|---|---|---|---|
| *ADAMTS16* | 5 | 19 | NM_139056 | c.2870G>A | R957Q | 767 | 53.1% | - |
| *ADGRA2* | 8 | - | NM_032777 | c.719-3C>T | Splice region | 614 | 38.8% | - |
| *FANCA* | 16 | 43 | NM_000135 | c.4294G>T | V1432L | 733 | 50.8% | - |
| *FLT3* | 13 | 3 | NM_004119 | c.190G>A | G64R | 1862 | 29.4% | COSM3786160 |
| ***IDH1*** | **2** | **4** | **NM_005896** | **c.394C>A** | **R132S** | **1094** | **28.0%** | **COSM28748** |
| *JAK1* | 1 | 22 | NM_002227 | c.2989C>T | R997W | 1637 | 29.9% | COSM3790207 |
| *KMT2C* | 7 | 43 | NM_170606 | c.10063A>G | I3355V | 1441 | 51.7% | - |
| *MAP3K1* | 5 | 17 | NM_005921 | c.4019C>G | A1340G | 805 | 14.2% | - |
| *MEN1* | 11 | 10 | NM_130802 | c.1813_1814del | L605fs | 515 | 24.5% | - |
| *MUC16* | 19 | 19 | NM_024690 | c.37181T>A | F12394Y | 1916 | 50.0% | - |
| *MUC16* | 19 | 3 | NM_024690 | c.30688C>T | P10230S | 1151 | 47.1% | - |
| *NOTCH2* | 1 | - | NM_024408 | c.2480-4C>G | Splice region | 788 | 49.2% | - |
| *NSD1* | 5 | 23 | NM_022455 | c.7421A>C | Q2474P | 945 | 49.0% | - |
| *PRKDC* | 8 | 27 | NM_006904 | c.3089G>T | G1030V | 1473 | 41.5% | - |
| *SYNE1* | 6 | 48 | NM_182961 | c.7168G>A | E2390K | 773 | 70.8% | COSM9354463 |
| *TAP2* | 6 | 11 | NM_018833 | c.1932C>T | Splice region | 1956 | 46.3% | - |
| ***TP53*** | **17** | **7** | **NM_000546** | **c.743G>A** | **R248Q** | **1065** | **50.7%** | **COSM10662** |

Mutations with clinical relevance are highlighted in red.

F12100020320211213151320

## 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.




20211213 151320

## 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* | 1 |
| *MET* | 2 |

Copy number ≥ 8 is considered amplification

TW2021121315320

**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 | **R132S** |
| *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* | 2 |
| *MDM2* | 2 |
| *MDM4* | 2 |

Copy number ≥ 8 is considered amplification

TW2100020320211213 151320

# 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

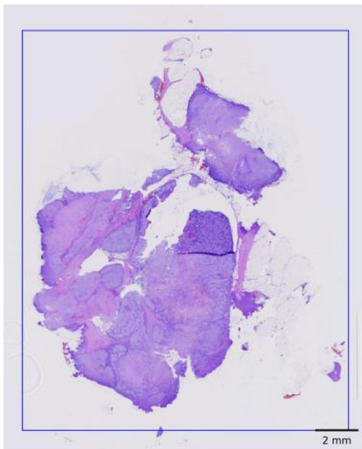
This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject 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.: S11031648A
- Collection site: Left pelvic
- Examined by: Dr. Yeh-Han Wang
- Estimated neoplastic nuclei (whole sample): The percentage of viable tumor cells in total cells in the whole slide (%): 60%
  The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 60%
  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.

151320

## SPECIMEN PHOTO(S)


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

## RUN QC

- Panel: ACTOnco®+
- Mean Depth: 907x
- Target Base Coverage at 100x: 94%

## 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

TW2107002032021121315 1320

**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.

**Liability**

ACT Genomics is not affiliated with any medical facility or medical practitioner. We provide information for informational purposes only, therefore, ACT Genomics and their employees cannot be held responsible for any direct, indirect, special, incidental or consequential damages that may arise from the use of information provided in the report.

## 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**

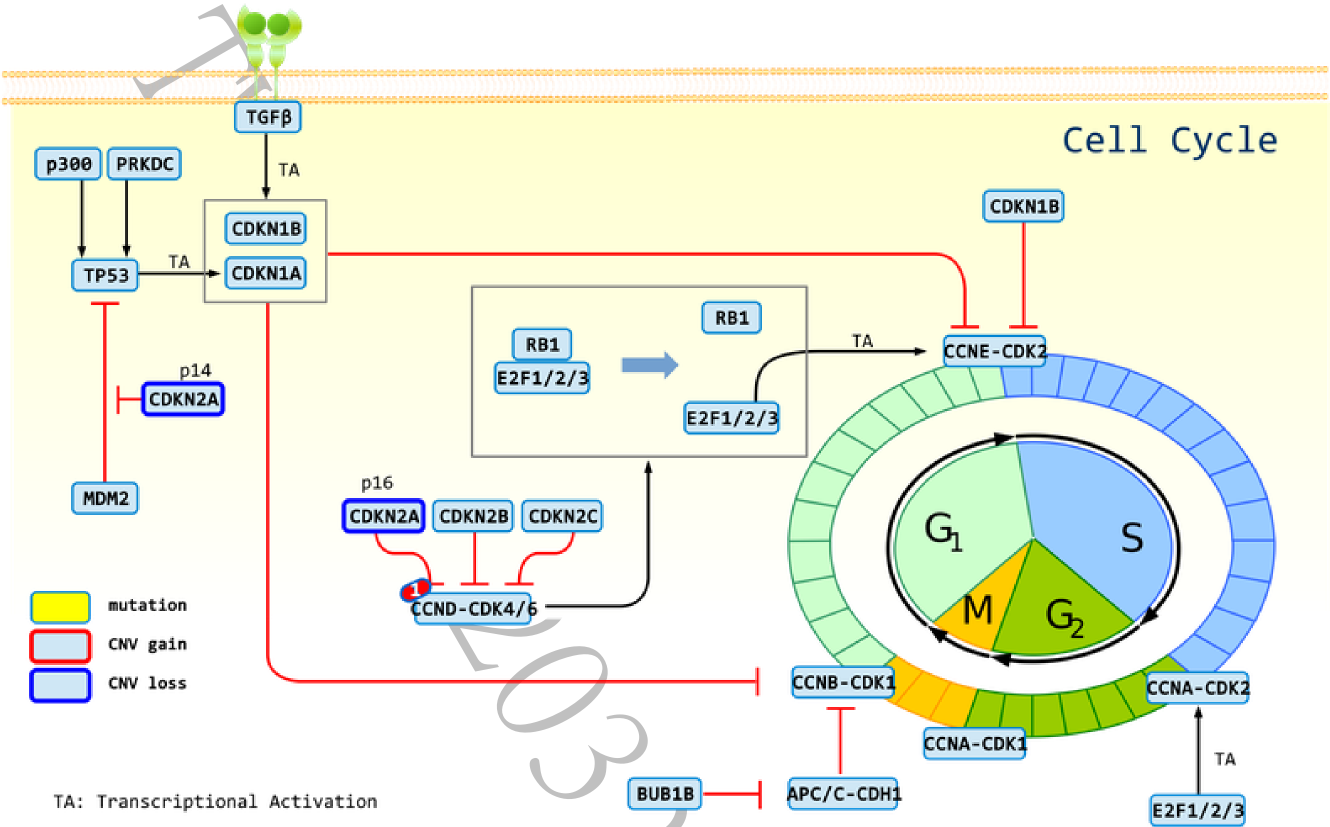
藥物潛在臨床效益(或缺乏潛在臨床效益)的實證證據是依據至少一篇臨床療效個案報告或臨床前試驗做為評估。本公司盡力提供適時及準確之資料，但由於醫學科技之發展日新月異，本公司不就本報告提供的資料是否為準確、適宜或最新作保證。

**責任**

本檢驗報告僅提供專業醫療參考，本公司及其員工不對任何由使用本報告之內容引起的直接、間接、特殊、連帶或衍生的損失或損害承擔責任。

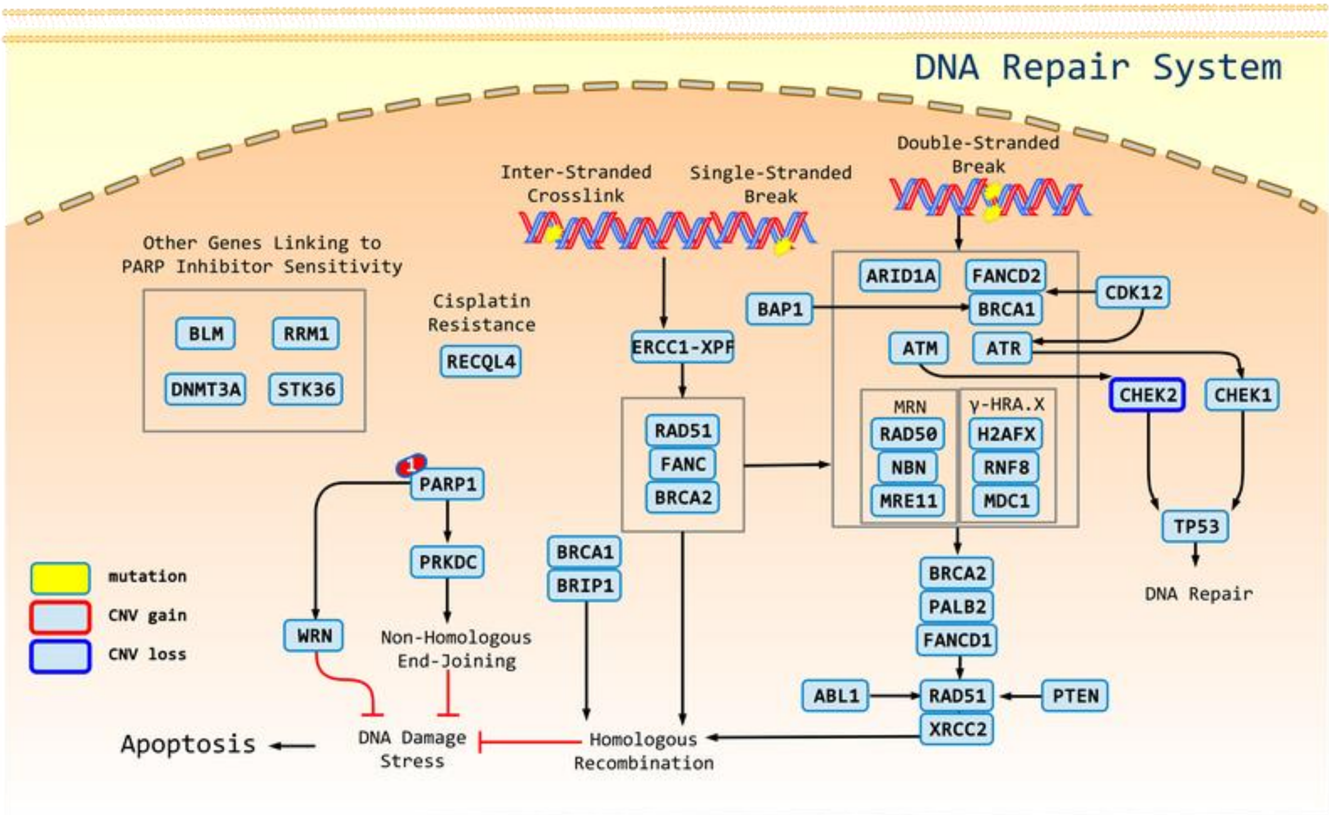
TW2101002020211213 151320

## SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



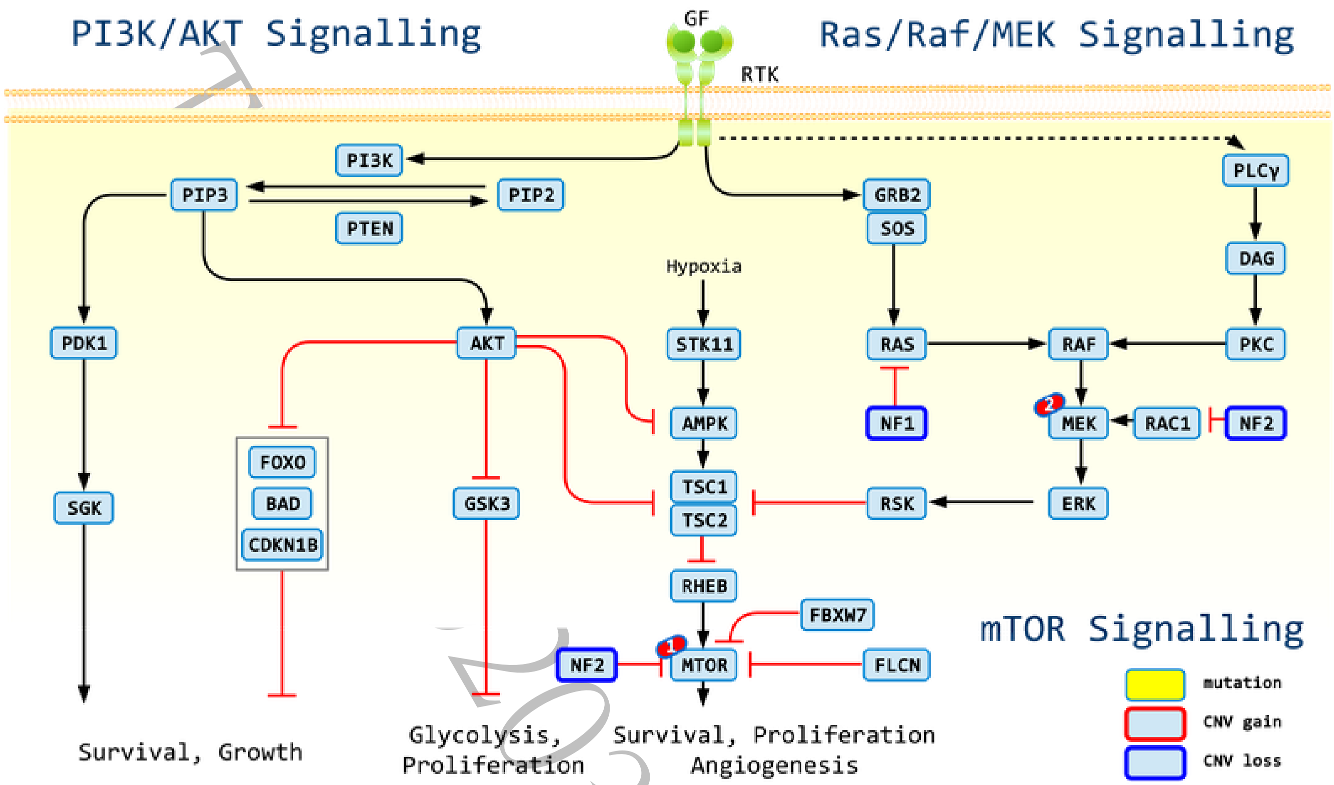

1: Abemaciclib, Palbociclib, Ribociclib

T2032021213 151320




1: Olaparib, Niraparib, Rucaparib

20211213 151320




1: Everolimus; 2: Trametinib, Selumetinib

## REFERENCES


1. PMID: 23999441; 2013, J Clin Invest;123(9):3672-7
   Isocitrate dehydrogenase mutations in leukemia.

2. PMID: 21130701; 2010, Cancer Cell;18(6):553-67
   Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation.

3. PMID: 22343901; 2012, Nature;483(7390):474-8
   IDH mutation impairs histone demethylation and results in a block to cell differentiation.

4. PMID: 23558173; 2013, Science;340(6132):622-6
   Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation.

5. PMID: 27956631; 2016, Proc Natl Acad Sci U S A;113(52):15084-15089
   The IDH2 R172K mutation associated with angioimmunoblastic T-cell lymphoma produces 2HG in T cells and impacts lymphoid development.

6. PMID: 19378339; 2009, Int J Cancer;125(2):353-5
   Mutational analysis of IDH1 codon 132 in glioblastomas and other common cancers.

7. PMID: 21598255; 2011, J Pathol;224(3):334-43
   IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours.

8. PMID: 19246647; 2009, Am J Pathol;174(4):1149-53
   IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas.

9. PMID: 22180306; 2012, Oncologist;17(1):72-9
   Frequent mutation of isocitrate dehydrogenase (IDH)1 and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping.

10. PMID: 19657110; 2009, N Engl J Med;361(11):1058-66
    Recurring mutations found by sequencing an acute myeloid leukemia genome.

11. PMID: 29860938; 2018, N Engl J Med;378(25):2386-2398
    Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML.

12. PMID: 22199315; 2011, Anticancer Res;31(12):4457-63
    Correlation between IDH1 gene mutation status and survival of patients treated for recurrent glioma.

13. PMID: 32416072; 2020, Lancet Oncol;21(6):796-807
    Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study.

14. PMID: 25910950; 2015, Clin Cancer Res;21(16):3610-8
    A Multicenter, Phase II, Randomized, Noncomparative Clinical Trial of Radiation and Temozolomide with or without Vandetanib in Newly Diagnosed Glioblastoma Patients.

15. PMID: 27231123; 2016, Cancer Discov;6(7):727-39
    Isocitrate Dehydrogenase Mutations Confer Dasatinib Hypersensitivity and SRC Dependence in Intrahepatic Cholangiocarcinoma.

16. PMID: 28148839; 2017, Sci Transl Med;9(375):
    2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces

PARP inhibitor sensitivity.

17. PMID: 29339439; 2018, Clin Cancer Res;24(7):1705-1715
<i>IDH1/2</i> Mutations Sensitize Acute Myeloid Leukemia to PARP Inhibition and This Is Reversed by IDH1/2-Mutant Inhibitors.

18. PMID: 23558169; 2013, Science;340(6132):626-30
An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells.

19. PMID: 28232670; 2017, Leukemia;31(10):2020-2028
Pan-mutant-IDH1 inhibitor BAY1436032 is highly effective against human IDH1 mutant acute myeloid leukemia in vivo.

20. PMID: 24739573; 2014, Nat Rev Cancer;14(5):359-70
Unravelling mechanisms of p53-mediated tumour suppression.

21. PMID: 21125671; 2011, J Pathol;223(2):137-46
Haplo-insufficiency: a driving force in cancer.

22. PMID: 26703669; 2015, Int J Environ Res Public Health;13(1):ijerph13010022
Hot Spot Mutation in TP53 (R248Q) Causes Oncogenic Gain-of-Function Phenotypes in a Breast Cancer Cell Line Derived from an African American patient.

23. PMID: 25697482; 2015, Cancer Lett;360(2):269-79
Mutant p53 (p53-R248Q) functions as an oncogene in promoting endometrial cancer by up-regulating REGγ.

24. PMID: 27998224; 2016, J Clin Oncol;34(36):4354-4361
Phase II Study of WEE1 Inhibitor AZD1775 Plus Carboplatin in Patients With TP53-Mutated Ovarian Cancer Refractory or Resistant to First-Line Therapy Within 3 Months.

25. PMID: 26646755; 2016, Ann Oncol;27(3):539-43
TP53 mutational status is predictive of pazopanib response in advanced sarcomas.

26. PMID: 25669829; 2015, Ann Oncol;26(5):1012-8
Phase I study of pazopanib and vorinostat: a therapeutic approach for inhibiting mutant p53-mediated angiogenesis and facilitating mutant p53 degradation.

27. PMID: 27466356; 2016, Mol Cancer Ther;15(10):2475-2485
TP53 Alterations Correlate with Response to VEGF/VEGFR Inhibitors: Implications for Targeted Therapeutics.

28. PMID: 23670029; 2013, Oncotarget;4(5):705-14
P53 mutations in advanced cancers: clinical characteristics, outcomes, and correlation between progression-free survival and bevacizumab-containing therapy.

29. PMID: 17145525; 2006, Semin Oncol;33(5 Suppl 10):S8-14
Bevacizumab in combination with chemotherapy: first-line treatment of patients with metastatic colorectal cancer.

30. PMID: 21399868; 2011, Int J Oncol;38(5):1445-52
p53, HER2 and tumor cell apoptosis correlate with clinical outcome after neoadjuvant bevacizumab plus chemotherapy in breast cancer.

31. PMID: 20549698; 2011, Int J Cancer;128(8):1813-21
p53 status influences response to tamoxifen but not to fulvestrant in breast cancer cell lines.

32. PMID: 10786679; 2000, Cancer Res;60(8):2155-62
Complete sequencing of TP53 predicts poor response to systemic therapy of advanced breast cancer.

33. PMID: 25672981; 2015, Cancer Res;75(7):1187-90
VEGF-A Expression Correlates with TP53 Mutations in Non-Small Cell Lung Cancer: Implications for Antiangiogenesis Therapy.

34. PMID: 25385265; 2015, Int J Oncol;46(2):607-18
TP53 oncomorphic mutations predict resistance to platinum- and taxane- based standard chemotherapy in patients diagnosed with advanced serous ovarian carcinoma.

35. PMID: 17055429; 2006, Cell;127(2):265-75
The regulation of INK4/ARF in cancer and aging.

36. PMID: 8521522; 1995, Cell;83(6):993-1000
Alternative reading frames of the INK4a tumor suppressor gene encode two unrelated proteins capable of inducing cell cycle arrest.

37. PMID: 9529249; 1998, Cell;92(6):725-34
ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways.

38. PMID: 16115911; 2005, Clin Cancer Res;11(16):5740-7
Comprehensive analysis of CDKN2A status in microdissected urothelial cell carcinoma reveals potential haploinsufficiency, a high frequency of homozygous co-deletion and associations with clinical phenotype.

39. PMID: 7550353; 1995, Nat Genet;11(2):210-2
Frequency of homozygous deletion at p16/CDKN2 in primary human tumours.

40. PMID: 24089445; 2013, Clin Cancer Res;19(19):5320-8
The cell-cycle regulator CDK4: an emerging therapeutic target in melanoma.

41. PMID: 27849562; 2017, Gut;66(7):1286-1296
Palbociclib (PD-0332991), a selective CDK4/6 inhibitor, restricts tumour growth in preclinical models of hepatocellular carcinoma.

42. PMID: 25524798; 2015, Lancet Oncol;16(1):25-35
The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.

43. PMID: 28283584; 2017, Oncologist;22(4):416-421
Clinical Benefit in Response to Palbociclib Treatment in Refractory Uterine Leiomyosarcomas with a Common CDKN2A Alteration.

44. PMID: 27217383; 2016, Cancer Discov;6(7):740-53
Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non-Small Cell Lung Cancer, and Other Solid Tumors.

45. PMID: 26715889; 2015, Curr Oncol;22(6):e498-501
Does CDKN2A loss predict palbociclib benefit?

46. PMID: 25501126; 2015, Clin Cancer Res;21(5):995-1001
CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment.

47. PMID: 27542767; 2016, Clin Cancer Res;22(23):5696-5705
A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas.

48. PMID: 24797823; 2014, Oncologist;19(6):616-22
Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel.

49. PMID: 27717303; 2016, N Engl J Med;375(18):1738-1748
Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer.

50. PMID: 28580882; 2017, J Clin Oncol;35(25):2875-2884
MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy.

51. PMID: 26728409; 2016, Clin Cancer Res;22(1):122-33
Coadministration of Trametinib and Palbociclib Radiosensitizes KRAS-Mutant Non-Small Cell Lung Cancers In Vitro and In Vivo.

52. PMID: 31401335; 2019, Transl Oncol;12(11):1425-1431
Concomitant Genetic Alterations are Associated with Worse Clinical Outcome in EGFR Mutant NSCLC Patients Treated with Tyrosine Kinase Inhibitors.

53. PMID: 21088254; 2011, Clin Cancer Res;17(3):401-5
Tumor suppressor CHK2: regulator of DNA damage response and mediator of chromosomal stability.

54. PMID: 15261141; 2004, Cancer Cell;6(1):45-59
Chk1 is haploinsufficient for multiple functions critical to tumor suppression.

55. PMID: 15539958; 2005, Cell Cycle;4(1):131-9
Chk1 is essential for tumor cell viability following activation of the replication checkpoint.

56. PMID: 23296741; 2013, Fam Cancer;12(3):473-8
The risk of gastric cancer in carriers of CHEK2 mutations.

57. PMID: 24713400; 2014, Hered Cancer Clin Pract;12(1):10
A risk of breast cancer in women - carriers of constitutional CHEK2 gene mutations, originating from the North - Central Poland.

58. PMID: 25583358; 2015, Int J Cancer;137(3):548-52
CHEK2 mutations and the risk of papillary thyroid cancer.

59. PMID: 12052256; 2002, Breast Cancer Res;4(3):R4
Mutation analysis of the CHK2 gene in breast carcinoma and other cancers.

60. PMID: 15125777; 2004, Mol Cancer;3():14
CHK2 kinase expression is down-regulated due to promoter methylation in non-small cell lung cancer.

61. PMID: 32343890; 2020, N Engl J Med;382(22):2091-2102
Olaparib for Metastatic Castration-Resistant Prostate Cancer.

62. PMID: 28916367; 2017, Lancet;390(10106):1949-1961
Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial.

63. PMID: 32086346; 2020, Clin Cancer Res;26(11):2487-2496
Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: Analysis From the Phase II TRITON2 Study.

64. PMID: 26510020; 2015, N Engl J Med;373(18):1697-708
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer.

65. PMID: 8563751; 1996, Nat Genet;12(2):144-8
Loss of NF1 results in activation of the Ras signaling pathway and leads to aberrant growth in haematopoietic cells.

66. PMID: 1946382; 1991, Proc Natl Acad Sci U S A;88(21):9658-62
Identification of the neurofibromatosis type 1 gene product.

67. PMID: 2116237; 1990, Cell;62(3):599-608
The neurofibromatosis type 1 gene encodes a protein related to GAP.

68. PMID: 2121370; 1990, Cell;63(4):843-9
The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21.

69. PMID: 14502561; 2003, J Cell Physiol;197(2):214-24
NF1 modulates the effects of Ras oncogenes: evidence of other NF1 function besides its GAP activity.

70. PMID: 19479903; 2009, Mol Carcinog;48(11):1005-17
Neurofibromin physically interacts with the N-terminal domain of focal adhesion kinase.

71. PMID: 28680740; 2017, Adv Med Biol;118():83-122
Haploinsufficient tumor suppressor genes.

72. PMID: 10442636; 1999, Oncogene;18(31):4450-9
Haploinsufficiency for the neurofibromatosis 1 (NF1) tumor suppressor results in increased astrocyte proliferation.

73. PMID: 16288202; 2006, Oncogene;25(16):2297-303
Nf1 haploinsufficiency augments angiogenesis.

74. PMID: 18089636; 2008, Hum Mol Genet;17(7):936-48
Rac1 mediates the osteoclast gains-in-function induced by haploinsufficiency of Nf1.

75. PMID: 7920653; 1994, Nat Genet;7(3):353-61
Tumour predisposition in mice heterozygous for a targeted mutation in Nf1.

76. PMID: 25026295; 2014, Oncotarget;5(15):5873-92
The NF1 gene revisited - from bench to bedside.

77. PMID: 29892687; 2018, Gynecol Oncol Rep;23():41-44
Clonal lineage of high grade serous ovarian cancer in a patient with neurofibromatosis type 1.

78. PMID: 29926297; 2018, Breast Cancer Res Treat;171(3):719-735
Breast cancer in women with neurofibromatosis type 1 (NF1): a comprehensive case series with molecular insights into its aggressive phenotype.

79. PMID: 28637487; 2017, Hum Genomics;11(1):13
The NF1 somatic mutational landscape in sporadic human cancers.

80. PMID: 15840687; 2005, Gut;54(8):1129-35
NF1 gene loss of heterozygosity and expression analysis in sporadic colon cancer.

81. PMID: 20129251; 2010, Cancer Cell;17(1):98-110
Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1.

82. PMID: 27158780; 2016, Nat Genet;48(6):607-16
Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas.

83. PMID: 32669708; 2020, Nature;583(7818):807-812
The National Lung Matrix Trial of personalized therapy in lung cancer.

84. PMID: 26936308; 2016, J Clin Pharm Ther;41(3):357-359
Prolonged disease control with MEK inhibitor in neurofibromatosis type I-associated glioblastoma.

85. PMID: 22573716; 2012, Cancer Res;72(13):3350-9
Sensitivity of glioblastomas to clinically available MEK inhibitors is defined by neurofibromin 1 deficiency.

86. PMID: 19727076; 2009, Nature;461(7262):411-4
Response and resistance to MEK inhibition in leukaemias initiated by hyperactive Ras.

87. PMID: 23858101; 2013, Mol Cancer Ther;12(9):1906-17
NF1 deletion generates multiple subtypes of soft-tissue sarcoma that respond to MEK inhibition.

88. PMID: 23221341; 2013, J Clin Invest;123(1):340-7
MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors.

89. PMID: 18483311; 2008, Mol Cancer Ther;7(5):1237-45
Effective in vivo targeting of the mammalian target of rapamycin pathway in malignant peripheral nerve sheath tumors.

90. PMID: 23209032; 2013, Clin Cancer Res;19(2):450-61
Prognostic significance of AKT/mTOR and MAPK pathways and antitumor effect of mTOR inhibitor in NF1-related and sporadic malignant peripheral nerve sheath tumors.

91. PMID: 26859683; 2016, Oncotarget;7(9):10547-56
Next-generation sequencing reveals somatic mutations that confer exceptional response to everolimus.

92. PMID: 21482774; 2012, Proc Natl Acad Sci U S A;109(8):2730-5
Genome-wide functional screen identifies a compendium of genes affecting sensitivity to tamoxifen.

93. PMID: 24535670; 2014, Cancer Discov;4(5):606-19
Reduced NF1 expression confers resistance to EGFR inhibition in lung cancer.

94. PMID: 29703253; 2018, BMC Cancer;18(1):479
SMAD4 and NF1 mutations as potential biomarkers for poor prognosis to cetuximab-based therapy in Chinese metastatic colorectal cancer patients.

95. PMID: 30858928; 2019, Oncotarget;10(14):1440-1457
CRISPR-induced RASGAP deficiencies in colorectal cancer organoids reveal that only loss of NF1 promotes resistance to EGFR inhibition.

96. PMID: 30269082; 2019, Gut;68(7):1152-1161
Liquid biopsies to track trastuzumab resistance in metastatic HER2-positive gastric cancer.

97. PMID: 24576830; 2014, Cancer Res;74(8):2340-50
Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence.

98. PMID: 23171796; 2013, Cancer Discov;3(3):338-49
Elucidating distinct roles for NF1 in melanomagenesis.

99. PMID: 23288408; 2013, Cancer Discov;3(3):350-62
A genome-scale RNA interference screen implicates NF1 loss in resistance to RAF inhibition.

100. PMID: 24265153; 2014, Cancer Discov;4(1):94-109
The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma.

101. PMID: 25893302; 2016, Oncogene;35(5):537-48
Role of Merlin/NF2 inactivation in tumor biology.

102. PMID: 19451229; 2009, Mol Cell Biol;29(15):4235-49
Loss of the tumor suppressor gene NF2, encoding merlin, constitutively activates integrin-dependent mTORC1 signaling.

103. PMID: 19451225; 2009, Mol Cell Biol;29(15):4250-61
NF2/merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with meningioma and schwannoma growth.

104. PMID: 17655741; 2007, Brain Pathol;17(4):371-6
Role of NF2 haploinsufficiency in NF2-associated polyneuropathy.

105. PMID: 19545378; 2009, Orphanet J Rare Dis;4():16
Neurofibromatosis type 2 (NF2): a clinical and molecular review.

106. PMID: 21642991; 2011, Nat Genet;43(7):668-72
The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma.

107. PMID: 24393766; 2014, Oncotarget;5(1):67-77
NF2/merlin in hereditary neurofibromatosis 2 versus cancer: biologic mechanisms and clinical associations.

108. PMID: 27091708; 2016, J Clin Oncol;34(18):2115-24
Molecular Alterations and Everolimus Efficacy in Human Epidermal Growth Factor Receptor 2-Overexpressing Metastatic Breast Cancers: Combined Exploratory Biomarker Analysis From BOLERO-1 and BOLERO-3.

109. PMID: 26503204; 2016, J Clin Oncol;34(5):419-26
Correlative Analysis of Genetic Alterations and Everolimus Benefit in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From BOLERO-2.

110. PMID: 24833916; 2014, Breast Cancer (Dove Med Press);6():43-57
Use of mTOR inhibitors in the treatment of breast cancer: an evaluation of factors that influence patient outcomes.

111. PMID: 22923433; 2012, Science;338(6104):221
Genome sequencing identifies a basis for everolimus sensitivity.

112. PMID: 25630452; 2015, Eur Urol;67(6):1195-1196
Exceptional Response on Addition of Everolimus to Taxane in Urothelial Carcinoma Bearing an NF2 Mutation.

113. PMID: 26359368; 2015, Cancer Discov;5(11):1178-93
NF2 Loss Promotes Oncogenic RAS-Induced Thyroid Cancers via YAP-Dependent Transactivation of RAS Proteins and Sensitizes Them to MEK Inhibition.

114. PMID: 24813888; 2014, Cell Rep;7(4):999-1008
Acquired resistance of EGFR-mutant lung adenocarcinomas to afatinib plus cetuximab is associated with activation of mTORC1.

115. PMID: 28968163; 2017, J Clin Oncol;35(32):3638-3646
MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer.

116. PMID: 28533223; 2017, Clin Cancer Res;23(17):5218-5224
MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer.

117. PMID: 28438073; 2018, Cogn Emot;32(7):1499-1513
The meaning profiles of anxiety and depression: similarities and differences in two age groups.

118. PMID: 22529265; 2012, J Clin Oncol;30(17):2039-45
OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer.

119. PMID: 24637997; 2014, J Clin Oncol;32(13):1302-8
Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial.

120. PMID: 24552320; 2014, N Engl J Med;370(8):734-43
Improved survival with bevacizumab in advanced cervical cancer.

121. PMID: 23168366; 2013, Lancet Oncol;14(1):29-37
Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial.

122. PMID: 18156031; 2007, Lancet;370(9605):2103-11
Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial.

123. PMID: 19720927; 2009, J Clin Oncol;27(28):4733-40
Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.

124. PMID: 17167137; 2006, N Engl J Med;355(24):2542-50
Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.

125. PMID: 17442997; 2007, J Clin Oncol;25(12):1539-44
Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200.

126. PMID: 15175435; 2004, N Engl J Med;350(23):2335-42
Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.

127. PMID: 20525995; 2010, N Engl J Med;362(24):2260-70
Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.

128. PMID: 18541900; 2008, J Clin Oncol;26(19):3204-12
Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia.

129. PMID: 17496201; 2007, Blood;110(7):2309-15
Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study.

130. PMID: 26703889; 2016, Lancet;387(10022):968-977
Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study.

131. PMID: 22149876; 2012, N Engl J Med;366(6):520-9
Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.

132. PMID: 21306238; 2011, N Engl J Med;364(6):514-23
Everolimus for advanced pancreatic neuroendocrine tumors.

133. PMID: 23158522; 2013, Lancet;381(9861):125-32
Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial.

134. PMID: 18653228; 2008, Lancet;372(9637):449-56
Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial.

135. PMID: 30948273; 2019, Lancet Oncol;20(5):636-648
Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial.

136. PMID: 27717299; 2016, N Engl J Med;375(22):2154-2164
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer.

137. PMID: 31851799; 2019, N Engl J Med;381(25):2416-2428
Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer.

138. PMID: 31157963; 2019, N Engl J Med;381(4):317-327
Maintenance Olaparib for Germline <i>BRCA</i>-Mutated Metastatic Pancreatic Cancer.

139. PMID: 30345884; 2018, N Engl J Med;379(26):2495-2505
Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.

140. PMID: 28578601; 2017, N Engl J Med;377(6):523-533
Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation.

141. PMID: 28754483; 2017, Lancet Oncol;18(9):1274-1284
Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial.

142. PMID: 27617661; 2016, Lancet Oncol;17(11):1579-1589
Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial.

143. PMID: 25366685; 2015, J Clin Oncol;33(3):244-50
Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation.

144. PMID: 27959613; 2016, N Engl J Med;375(20):1925-1936
Palbociclib and Letrozole in Advanced Breast Cancer.

145. PMID: 26030518; 2015, N Engl J Med;373(3):209-19
Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer.

146. PMID: 27908594; 2017, Lancet Oncol;18(1):75-87
Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial.

147. PMID: 27924459; 2016, Target Oncol;11(6):815-824
Patient-Reported Outcomes and Quality of Life with Sunitinib Versus Placebo for Pancreatic Neuroendocrine Tumors: Results From an International Phase III Trial.

148. PMID: 27836885; 2017, Ann Oncol;28(2):339-343
Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study.

149. PMID: 21306237; 2011, N Engl J Med;364(6):501-13
Sunitinib malate for the treatment of pancreatic neuroendocrine tumors.

150. PMID: 16757724; 2006, JAMA;295(21):2516-24
Sunitinib in patients with metastatic renal cell carcinoma.

151. PMID: 25577718; 2015, Eur Urol;67(5):952-8
Depth of remission is a prognostic factor for survival in patients with metastatic renal cell carcinoma.

152. PMID: 27238653; 2016, Eur Urol;70(6):1006-1015
Early Tumour Shrinkage: A Tool for the Detection of Early Clinical Activity in Metastatic Renal Cell Carcinoma.

153. PMID: 17227905; 2007, Oncologist;12(1):107-13
Food and Drug Administration drug approval summary: Sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma.

154. PMID: 17046465; 2006, Lancet;368(9544):1329-38
Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial.

155. PMID: 29072975; 2018, J Clin Oncol;36(1):7-13
Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer.

156. PMID: 27080216; 2016, Lancet Oncol;17(5):642-50
Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial.

157. PMID: 25265492; 2014, N Engl J Med;371(20):1877-88
Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma.

158. PMID: 22663011; 2012, N Engl J Med;367(2):107-14
Improved survival with MEK inhibition in BRAF-mutated melanoma.

.213 151320

# ACTFusion™ Report

TW1D/002021213 1513

| PATIENT | | |
|---|---|---|
| Name: 許獻聰 | | Patient ID: 45100274 |
| Date of Birth: Nov 21, 1963 | | Gender: Male |
| Diagnosis: Chondrosarcoma | | |
| **ORDERING PHYSICIAN** | | |
| Name: 顏厥全醫師 | | Tel: 886-228712121 |
| Facility: 臺北榮總 | | |
| Address: 臺北市北投區石牌路二段 201 號 | | |
| **SPECIMEN** | | |
| Specimen ID: S11031648A | Collection site: Left pelvic | Date received: Dec 01, 2021 |
| Lab ID: AA-21-05913 | 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 |
|---|---|
| No fusion gene detected in this sample. | |

# ACTFusion™ Report

TW21070020320211213 1513

## THERAPEUTIC IMPLICATION

Not Applicable.

## VARIANT INTERPRETATION

Not Applicable.

## US FDA-APPROVED DRUG(S)

Not Applicable.

# ACTFusion™ Report

TW21070020320211213 1513

## ONGOING CLINICAL TRIALS

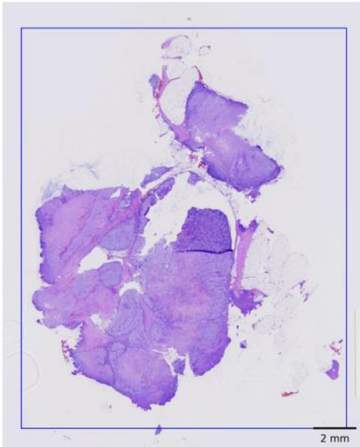
Trials were searched by applying filters: study status, patient's diagnosis, intervention, location and/or biomarker(s). Please visit https://clinicaltrials.gov to search and view for a complete list of open available and updated matched trials.

No trial has been found.

# ACTFusion™ Report

## TEST DETAILS

### SPECIMEN RECEIVED AND PATHOLOGY REVIEW


- Collection date: Oct 2021
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11031648A
- Collection site: Left pelvic
- Examined by: Dr. Yeh-Han Wang
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 60%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 60%
  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: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

### RUN QC

- Panel: ACTFusion™
- Total reads: 503940
- Average unique RNA Start Sites per control GSP2: 140

### 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

TW2107000320211213 15:3

## 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:**
醫檢師黃靖婷 博士
Ching-Ting Huang Ph.D.
檢字第 016511 號

CT Huang

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

# ACT Fusion™ Report

TW2107002032021213 1513

## 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。

### 責任

本檢驗報告僅提供專業醫療參考，本公司及其員工不對任何由使用本報告之內容引起的直接、間接、特殊、連帶或衍生的損失或損害承擔責任。

# ACTFusion™ Report

TW2107002032021213 1513

## REFERENCE

Not Applicable.