陳明珠
Project ID: C23-M001-01299
Report No.: AA-23-02587_ONC
Date Reported: May 15, 2023

# ACT Onco® + Report

| PATIENT | | |
|---|---|---|
| Identifier: 陳明珠 | | Patient ID: 49347480 |
| Date of Birth: Mar 20, 1955 | | Gender: Female |
| Diagnosis: Cholangiocarcinoma | | |
| **ORDERING PHYSICIAN** | | |
| Name: 姜乃榕醫師 | | 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: S11217984A | Collection site: Liver | Type: FFPE tissue |
| Date received: May 02, 2023 | Lab ID: AA-23-02587 | D/ID: NA |

**ABOUT ACTOnco®+**

The test is a next-generation sequencing (NGS)-based assay developed for efficient and comprehensive genomic profiling of cancers. This test interrogates coding regions of 440 genes associated with cancer treatment, prognosis and diagnosis. Genetic mutations detected by this test include small-scale mutations like single nucleotide variants (SNVs), small insertions and deletions (InDels) (≤ 15 nucleotides) and large-scale genomic alterations like copy number alterations (CNAs). The test also includes an RNA test, detecting fusion transcripts of 13 genes.

## SUMMARY FOR ACTIONABLE VARIANTS

### VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

| Genomic Alterations/Biomarkers | Probable Effects in Patient's Cancer Type | | Probable Sensitive in Other Cancer Types |
|---|---|---|---|
| | Sensitive | Resistant | |
| Not detected | | | |

### VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

| Genomic Alterations/Biomarkers | Possibly Sensitive | Possibly Resistant |
|---|---|---|
| Not detected | | |

**Note:**

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

# ACT Onco® + Report

## TESTING RESULTS

### VARIANT(S) WITH CLINICAL RELEVANCE

#### - Single Nucleotide and Small InDel Variants

| Gene | Amino Acid Change | Allele Frequency |
|---|---|---|
| *JAK2* | E845* | 37.2% |
| *MTOR* | F1888L | 47.4% |
| *SERPINB4* | E361K | 66.8% |
| *TP53* | Q331* | 32.2% |

#### - Copy Number Alterations

| Chromosome | Gene | Variation | Copy Number |
|---|---|---|---|
| Chr17 | *FLCN, TP53* | Heterozygous deletion | 1 |

#### - Fusions

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

#### - Immune Checkpoint Inhibitor (ICI) Related Biomarkers

| Biomarker | Results |
|---|---|
| Tumor Mutational Burden (TMB) | 5.7 muts/Mb |
| Microsatellite Instability (MSI) | Microsatellite stable (MSS) |

Note:
- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 47% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- 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%.

ACT Onco® + Report



# THERAPEUTIC IMPLICATIONS

## TARGETED THERAPIES

Not Applicable.

## IMMUNE CHECKPOINT INHIBITORS (ICIs)

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

## - Other Biomarkers with Potential Clinical Effects for ICIs

| Genomic Alterations | Potential Clinical Effects |
|---|---|
| Not detected | |

Note: Tumor non-genomic factors, such as patient germline genetics, PDL1 expression, tumor microenvironment, epigenetic alterations or other factors not provided by this test may affect ICI response.

## CHEMOTHERAPIES

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

## HORMONAL THERAPIES

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

## OTHERS

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

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

ACT Onco® + Report



## VARIANT INTERPRETATION

### *JAK2* E845*

#### Biological Impact

The JAK2 (Janus kinase 2) gene encodes one of four members of the JAK family of non-receptor tyrosine kinases and is involved in the interferon-alpha/beta/gamma pathway and is a member of the JAK/STAT signaling pathway[1][2]. JAK2 signaling is required for the normal production of blood cells such as erythrocytes and thrombocytes[3].

E845* mutation results in a premature truncation of the JAK2 protein at amino acid 845 (UniProtKB). This mutation is predicted to lead to a loss of JAK2 function, despite not having characterized in the literature.

#### Therapeutic and prognostic relevance

Biallelic inactivation of JAK1/2 was associated with primary and acquired resistance to PD-1 blockade due to defects in the pathways involved in interferon-receptor signaling[4][5].

### *MTOR* F1888L

#### Biological Impact

The MTOR gene encodes for an intracellular serine–threonine kinase that involved in the regulation of cell growth, protein synthesis and metabolism[6][7]. Missense mutations of the MTOR gene have been report in a wide range of cancers, such as clear cell renal cell carcinoma, lung cancer, endometrial carcinomas, and colorectal cancer[8].

MTOR F1888L is located within the central FAT domain of the MTOR protein (UniProtKB). F1888L confers a gain of function to the MTOR protein as demonstrated by activation of signaling and phosphorylation of downstream targets in vitro[9][10].

#### Therapeutic and prognostic relevance

MTOR can become an oncokinase as a result of amino acid substitutions, and that the transforming activity of this oncokinase is sensitive to rapamycin[10][11][12].

### *SERPINB4* E361K

#### Biological Impact

SERPINB4 encodes a protein of the serpin family of serine protease inhibitors. SERPINB4 is a close human homolog of SERPINB3 with which shares 92% protein sequence identity. SERPINB3 and SERINB4 proteins have overlapping functions and are involved in both oncogenesis and immunity[13][14].

#### Therapeutic and prognostic relevance

Results from a clinical study showed that somatic mutations in SERPINB3 and SERPINB4 predicted improved survival from treatment with anti-CTLA4 therapy in two independent cohorts of patients with melanoma (n=174)[15].

### *TP53* Q331*, Heterozygous deletion

#### Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[16]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[17].

Q331* mutation results in a premature truncation of the p53 protein at amino acid 331 (UniProtKB). This mutation is predicted to lead to a loss of p53 function, despite not having characterized in the literature.

Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

### 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)[18].

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[19]. 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[20].

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[21][22][23]. 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)[24]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[25][26]. 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[27].

## *FLCN* Heterozygous deletion

### Biological Impact

The FLCN gene encodes the tumor suppressor, Folliculin, a GTPase activating protein (GAP) for RagC/D GTPase proteins involved in amino acid sensing and signaling to mTORC1[28]. FLCN has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[29][30]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[31][32]. Germline mutation of the FLCN gene causes the Birt-Hogg-Dubé syndrome, a rare disorder that is characterized by benign hamartomatous skin lesions and an increased risk of pneumothorax and renal tumors[33].

### Therapeutic and prognostic relevance

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTC) patients who had PI3K/mTOR/AKT alterations, including TSC2, FLCN or NF1, showed impressive progression-free survival (PFS) of 15.2 months after receiving everolimus[34]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[35].

ACT Onco® + Report



## US FDA-APPROVED DRUG(S)

### 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**[36] NCT01524783 | **Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26) |
| | - |
| | Everolimus vs. Placebo [PFS(M): 11 vs. 3.9] |
| **BOLERO-2**[37] NCT00863655 | **Breast cancer** (Approved on 2012/07/20) |
| | **ER+/HER2-** |
| | Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2] |
| **EXIST-2** NCT00790400 | **Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma** (Approved on 2012/04/26) |
| | - |
| | Everolimus vs. Placebo [ORR(%): 41.8 vs. 0] |
| **RADIANT-3**[38] NCT00510068 | **Pancreatic neuroendocrine tumor** (Approved on 2011/05/05) |
| | - |
| | Everolimus vs. Placebo [PFS(M): 11 vs. 4.6] |
| **EXIST-1**[39] NCT00789828 | **Subependymal giant cell astrocytoma** (Approved on 2010/10/29) |
| | - |
| | Everolimus vs. Placebo [ORR(%): 35.0] |
| **RECORD-1**[40] NCT00410124 | **Renal cell carcinoma** (Approved on 2009/05/30) |
| | - |
| | Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9] |

### Temsirolimus (TORISEL)

Temsirolimus is a soluble ester of sirolimus (rapamycin, brand-name drug Rapamune) and functions as an inhibitor of mammalian target of rapamycin complex (mTORC). The inhibitory molecular mechanism is similar to Everolimus. Temsirolimus is developed by Wyeth Pharmaceuticals and marketed by Pfizer under the trade name TORISEL.

### - FDA Approval Summary of Temsirolimus (TORISEL)

| | |
|---|---|
| [41] NCT00065468 | **Renal cell carcinoma** (Approved on 2007/05/30) |
| | - |
| | Temsirolimus vs. Ifn-α [OS(M): 10.9 vs. 7.3] |

D=day; W=week; M=month

ACT Onco® + 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.

# ACT Onco® + Report

## SUPPLEMENTARY INFORMATION OF TESTING RESULTS

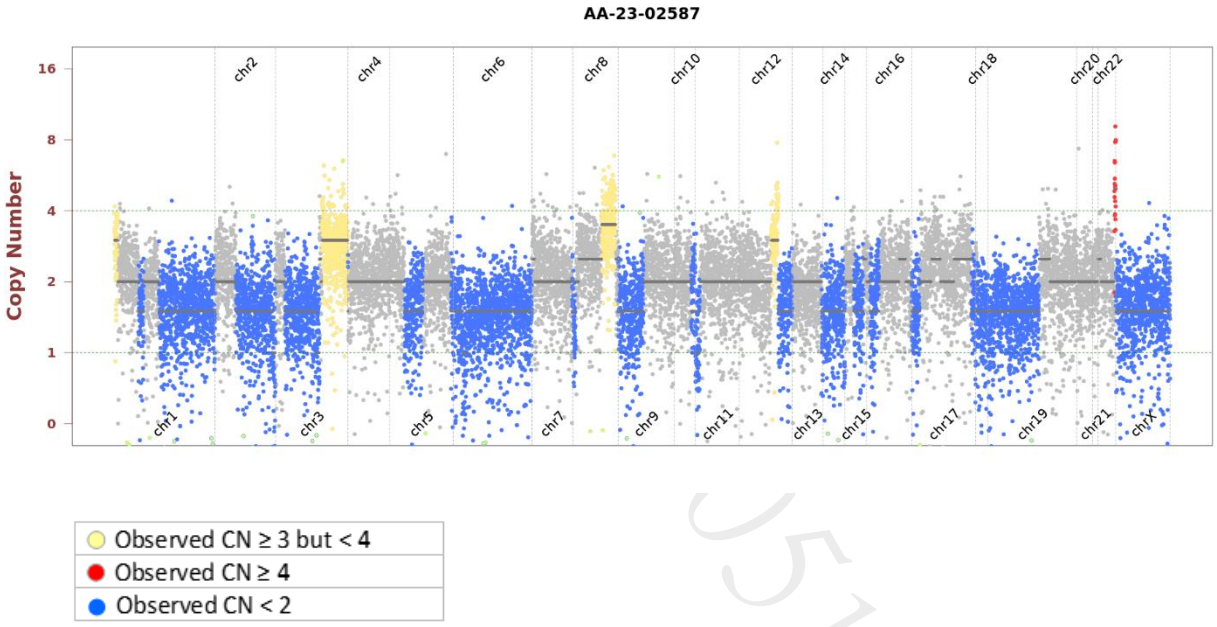
### DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

#### - Single Nucleotide and Small InDel Variants

| Gene | Amino Acid Change | Exon | cDNA Change | Accession Number | COSMIC ID | Allele Frequency | Coverage |
|---|---|---|---|---|---|---|---|
| JAK2 | E845* | 19 | c.2533G>T | NM_004972 | - | 37.2% | 282 |
| MTOR | F1888L | 40 | c.5664C>G | NM_004958 | COSM462604 | 47.4% | 684 |
| SERPINB4 | E361K | 8 | c.1081G>A | NM_002974 | COSM3527019 | 66.8% | 1109 |
| TP53 | Q331* | 9 | c.991C>T | NM_000546 | COSM11354 | 32.2% | 671 |

#### - Copy Number Alterations

Observed copy number (CN) for each evaluated position is shown on the y-axis. Regions referred to as amplification or deletion are shown in color. Regions without significant changes are represented in gray.



# ACT Onco® + Report

## OTHER DETECTED VARIANTS

| Gene | Amino Acid Change | Exon | cDNA Change | Accession Number | COSMIC ID | Allele Frequency | Coverage |
|---|---|---|---|---|---|---|---|
| ADAMTS18 | H359R | 7 | c.1076A>G | NM_199355 | - | 18.8% | 505 |
| AMER1 | S42* | 2 | c.125C>G | NM_152424 | - | 30.2% | 658 |
| BCOR | D1752N | 15 | c.5254G>A | NM_001123385 | - | 65.8% | 380 |
| FCGR2B | P47S | 3 | c.139C>T | NM_004001 | - | 83.7% | 263 |
| GRIN2A | Splice acceptor | - | c.1652-1G>A | NM_000833 | COSM6924157 | 23.3% | 498 |
| HR | Splice region | - | c.2846+3G>A | NM_005144 | - | 31.5% | 305 |
| IKBKB | M83V | 4 | c.247A>G | NM_001556 | - | 58.2% | 395 |
| INSR | K294R | 3 | c.881A>G | NM_000208 | COSM2728577 | 37.5% | 403 |
| KEAP1 | E41K | 2 | c.121G>A | NM_203500 | - | 25.9% | 147 |
| KMT2C | E336G | 7 | c.1007A>G | NM_170606 | COSM5482468 | 14.3% | 4000 |
| LMO1 | Splice region | - | c.240-8C>A | NM_002315 | - | 16.6% | 535 |
| PDIA3 | V125I | 4 | c.373G>A | NM_005313 | - | 49.0% | 537 |
| PRKCQ | Q299E | 9 | c.895C>G | NM_006257 | - | 24.2% | 670 |
| PRKN | M80I | 3 | c.240G>C | NM_004562 | - | 27.5% | 710 |
| PTPRD | S180L | 12 | c.539C>T | NM_002839 | COSM4499314 | 32.3% | 954 |
| RECQL4 | D1049N | 19 | c.3145G>A | NM_004260 | - | 21.2% | 330 |
| ROS1 | Q1409E | 26 | c.4225C>G | NM_002944 | - | 36.6% | 525 |
| ROS1 | Y2173N | 41 | c.6517T>A | NM_002944 | - | 70.0% | 727 |
| RPTOR | V1147I | 29 | c.3439G>A | NM_020761 | COSM6769672 | 32.5% | 553 |
| SMO | T179M | 2 | c.536C>T | NM_005631 | COSM6927006 | 52.1% | 507 |
| XIAP | A321G | 3 | c.962C>G | NM_001167 | - | 64.3% | 580 |

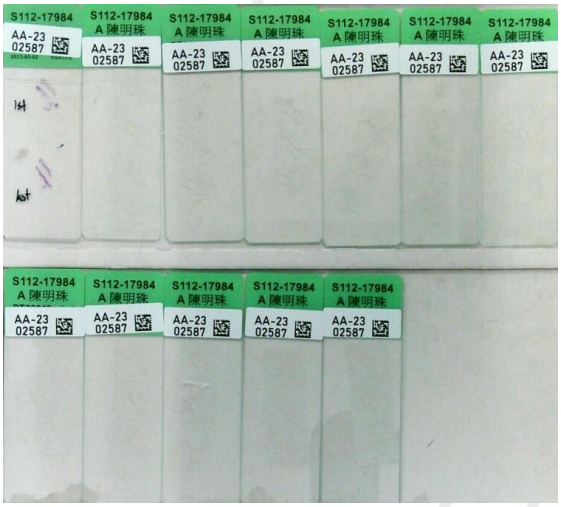
Note:

- This table enlists variants detected by the panel other than those with clinical relevance (reported in Testing Result section). The clinical impact of a genetic variant is determined according to ACT Genomics in-house clinical knowledge database. A negative result does not necessarily indicate absence of biological effect on the tumor. Some variants listed here may possibly have preclinical data or may show potential clinical relevance in the future.

# ACT Onco® + Report

## TEST DETAILS

### SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: Apr 24, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11217984A
- Collection site: Liver
- Examined by: Dr. Yun-An Chen
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 30%
    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: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

### RUN QC

- Panel: ACTOnco®+

**DNA test**

- Mean Depth: 616x
- Target Base Coverage at 100x: 93%

**RNA test**

- Average unique RNA Start Sites per control GSP2: 150

# ACT Onco® + Report



## LIMITATIONS

1. This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject to validation by Sanger or other technologies.
2. The possibility cannot be excluded that certain pathogenic variants detected by other sequencing tools may not be reported in the test because of technical limitation of bioinformatics algorithm or the NGS sequencing platform, e.g. low coverage.
3. This test has been designed to detect fusions in 13 genes sequenced. Therefore, fusion in genes not covered by this test would not be reported. For novel fusions detected in this test, Sanger sequencing confirmation is recommended if residue specimen is available.

## NEXT-GENERATION SEQUENCING (NGS) METHODS

**DNA test**

Extracted genomic DNA was amplified using primers targeting coding exons of analyzed genes and subjected to library construction. Barcoded libraries were subsequently conjugated with sequencing beads by emulsion PCR and enriched using Ion Chef system. Sequencing was performed according to Ion Proton or Ion S5 sequencer protocol (Thermo Fisher Scientific).

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite. Coverage depth was calculated using Torrent Coverage Analysis plug-in. Single nucleotide variants (SNVs) and short insertions/deletions (InDels) were identified using the Torrent Variant Caller plug-in. VEP (Variant Effect Predictor) was used to annotate every variant using databases from Clinvar, COSMIC and Genome Aggregation database. Variants with coverage ≥ 20, allele frequency ≥ 5% and actionable variants with allele frequency ≥ 2% were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at 100x ≥ 85% with a mean coverage ≥ 500x.

Variants reported in Genome Aggregation database with > 1% minor allele frequency (MAF) were considered as polymorphisms. ACT Genomics in-house database was used to determine technical errors. Clinically actionable and biologically significant variants were determined based on the published medical literature.

The copy number alterations (CNAs) were predicted as described below:
Amplicons with read counts in the lowest 5th percentile of all detectable amplicons and amplicons with a coefficient of variation ≥ 0.3 were removed. The remaining amplicons were normalized to correct the pool design bias. ONCOCNV (an established method for calculating copy number aberrations in amplicon sequencing data by Boeva et al., 2014) was applied for the normalization of total amplicon number, amplicon GC content, amplicon length, and technology-related biases, followed by segmenting the sample with a gene-aware model. The method was used as well for establishing the baseline of copy number variations.

Tumor mutational burden (TMB) was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The TMB calculation predicted somatic variants and applied a machine learning model with a cancer hotspot correction. TMB may be reported as “TMB-High”, “TMB-Low” or “Cannot Be Determined”. TMB-High corresponds to ≥ 7.5 mutations per megabase (Muts/Mb); TMB-Low corresponds to < 7.5 Muts/Mb. TMB is reported as “Cannot Be Determined” if the tumor purity of the sample is < 30%.

Classification of microsatellite instability (MSI) status is determined by a machine learning prediction algorithm. The change of a number of repeats of different lengths from a pooled microsatellite stable (MSS) baseline in > 400 genomic loci are used as the features for the algorithm. The final output of the results is either microsatellite Stable (MSS) or microsatellite instability high (MSI-H).

# ACT Onco® + Report



**RNA test**

Extracted RNA was reverse-transcribed and subjected to library construction. Sequencing was performed according to Ion Proton or Ion S5 sequencer protocol (Thermo Fisher Scientific). To ensure sequencing quality for fusion variant analysis, the average unique RNA Start Sites (SS) per control Gene Specific Primer 2 (GSP 2) should be ≥ 10.

The fusion analysis pipeline aligned sequenced reads to the human reference genome, identified regions that map to noncontiguous regions of the genome, applied filters to exclude probable false-positive events and, annotated previously characterized fusion events according to Quiver Gene Fusion Database, a curated database owned and maintained by ArcherDX. In general, samples with detectable fusions need to meet the following criteria: (1) Number of unique start sites (SS) for the GSP2 ≥ 3; (2) Number of supporting reads spanning the fusion junction ≥ 5; (3) Percentage of supporting reads spanning the fusion junction ≥ 10%; (4) Fusions annotated in Quiver Gene Fusion Database.

## DATABASE USED

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

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

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

# ACT Onco® + Report



## GENE LIST

### SNV & CNV

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

*Analysis of copy number alterations NOT available.

### FUSION

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

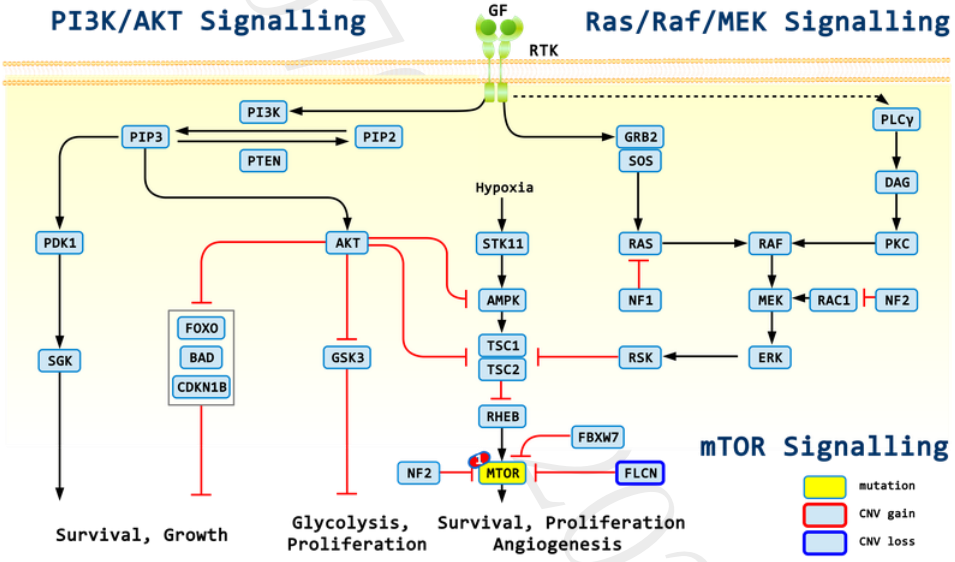
# ACT Onco® + Report

## APPENDIX

### POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

| Gene | Therapies | Possible effect |
|---|---|---|
| *FLCN* | Everolimus, Temsirolimus | **sensitive** |

### SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS




**1: Everolimus, Temsirolimus**

ACT Onco® + 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。

## 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。

ACT Onco® + Report

## REFERENCE

1. PMID: 25057888; 2014, Biochem J;462(1):1-13
The molecular regulation of Janus kinase (JAK) activation.

2. PMID: 15575979; 2004, Genome Biol;5(12):253
The Janus kinases (Jaks).

3. PMID: 9590173; 1998, Cell;93(3):385-95
Jak2 is essential for signaling through a variety of cytokine receptors.

4. PMID: 27903500; 2017, Cancer Discov;7(2):188-201
Primary Resistance to PD-1 Blockade Mediated by JAK1/2 Mutations.

5. PMID: 27433843; 2016, N Engl J Med;375(9):819-29
Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma.

6. PMID: 22500797; 2012, Cell;149(2):274-93
mTOR signaling in growth control and disease.

7. PMID: 21157483; 2011, Nat Rev Mol Cell Biol;12(1):21-35
mTOR: from growth signal integration to cancer, diabetes and ageing.

8. PMID: 24132290; 2013, Nature;502(7471):333-339
Mutational landscape and significance across 12 major cancer types.

9. PMID: 27482884; 2016, J Clin Invest;126(9):3526-40
Mechanistically distinct cancer-associated mTOR activation clusters predict sensitivity to rapamycin.

10. PMID: 24631838; 2014, Cancer Discov;4(5):554-63
A diverse array of cancer-associated MTOR mutations are hyperactivating and can predict rapamycin sensitivity.

11. PMID: 24625776; 2014, Cancer Discov;4(5):546-53
Activating mTOR mutations in a patient with an extraordinary response on a phase I trial of everolimus and pazopanib.

12. PMID: 24622468; 2014, Clin Cancer Res;20(7):1955-64
Tumor genetic analyses of patients with metastatic renal cell carcinoma and extended benefit from mTOR inhibitor therapy.

13. PMID: 25111616; 2015, J Invest Dermatol;135(1):160-169
SERPINB3/B4 contributes to early inflammation and barrier dysfunction in an experimental murine model of atopic dermatitis.

14. PMID: 24759783; 2014, Nat Commun;5():3729
Oncogenic Ras induces inflammatory cytokine production by upregulating the squamous cell carcinoma antigens SerpinB3/B4.

15. PMID: 27668655; 2016, Nat Genet;48(11):1327-1329
Recurrent SERPINB3 and SERPINB4 mutations in patients who respond to anti-CTLA4 immunotherapy.

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

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

18. 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.

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

20. 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.

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

22. 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.

23. 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.

24. 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.

25. 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.

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

27. 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.

28. PMID: 24095279; 2013, Mol Cell;52(4):495-505
The folliculin tumor suppressor is a GAP for the RagC/D GTPases that signal amino acid levels to mTORC1.

29. PMID: 26342594; 2016, Fam Cancer;15(1):127-32
Birt-Hogg-Dubé syndrome: novel FLCN frameshift deletion in daughter and father with renal cell carcinomas.

30. PMID: 23223565; 2013, J Clin Pathol;66(3):178-86
Birt-Hogg-Dube syndrome: clinicopathological features of the lung.

31. PMID: 19850877; 2009, Proc Natl Acad Sci U S A;106(44):18722-7
Homozygous loss of BHD causes early embryonic lethality and kidney tumor development with activation of mTORC1 and mTORC2.

32. PMID: 24908670; 2014, Hum Mol Genet;23(21):5706-19
Folliculin (Flcn) inactivation leads to murine cardiac hypertrophy through mTORC1 deregulation.

33. PMID: 15956655; 2005, J Natl Cancer Inst;97(12):931-5
High frequency of somatic frameshift BHD gene mutations in Birt-Hogg-Dubé-associated renal tumors.

34. PMID: 29301825; 2018, Clin Cancer Res;24(7):1546-1553
Genomic Correlates of Response to Everolimus in Aggressive Radioiodine-refractory Thyroid Cancer: A Phase II Study.

35. PMID: 26418749; 2015, Oncotarget;6(32):32761-73
Flcn-deficient renal cells are tumorigenic and sensitive to mTOR suppression.

36. 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.

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

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

ACT Onco® + Report



39. 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.

40. 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.

41. PMID: 17538086; 2007, N Engl J Med;356(22):2271-81
Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma.