羅秀惠
Project ID: C22-M001-03418
Report No.: AA-22-06839_ONC
Date Reported: Nov 23, 2022

ACT Onco® + Report

PATIENT		
Identifier: 羅秀惠		Patient ID: 41031769
Date of Birth: Jan 06, 1967		Gender: Female
Diagnosis: Ovarian cancer		
ORDERING PHYSICIAN		
Name: 陳志學醫師		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: S10813598B	Collection site: Pelvic	Type: FFPE tissue
Date received: Nov 11, 2022	Lab ID: AA-22-06839	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
DPYD	R74*	17.5%
TP53	Splice acceptor	75.4%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr11	*CHEK1*	Heterozygous deletion	1
Chr13	*BRCA2, RB1*	Heterozygous deletion	1
Chr15	*RAD51*	Heterozygous deletion	1
Chr17	*FLCN, NF1*	Heterozygous deletion	1
Chr4	*FBXW7*	Heterozygous deletion	1
Chr7	*KMT2C*	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)	1.3 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 74% 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.

VARIANT INTERPRETATION

DPYD R74*

Biological Impact

The DPYD gene encodes a pyrimidine catabolic enzyme, dihydropyrimidine dehydrogenase (DPD), which is the initial and rate-limiting factor in the pathway of uracil and thymine catabolism. DPD is responsible for the elimination of over 80% of systemic of 5-Fluorouracil (5-FU) and the oral 5-FU prodrug capecitabine[1][2]. Genetic variants, missense mutations, silent mutations, and nonsense mutations that result in DPD deficiency are significantly associated with thymine-uraciluria and an increased risk of toxicity with fluoropyrimidine chemotherapy treatments, such as fluorouracil[3][4][2].

R74* mutation results in a premature truncation of the DPYD protein at amino acid 74 (UniProtKB). This mutation is predicted to lead to a loss of DPYD function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

Under the fluoropyrimidine treatment, patients with DPD deficiency had an increased risk of developing severe (grade III/IV) adverse effects, including potential fetal neutropenia, mucositis, and diarrhea[5][6][7][8]. Recommendations of fluoropyrimidine dose reductions for cancer patients with variants associated with DPD deficiency were included in some pharmacogenetics guidelines[9][10].

TP53 Splice acceptor

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[11]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[12].

TP53 c.673-2A>G is a variant located at the splice acceptor region, which may result in the exon skipping.

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)[13].

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[14]. 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[15].

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[16][17][18]. 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)[19]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[20][21]. 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[22].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[23]. BRCA2 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[24]. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia[25]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[26].

Therapeutic and prognostic relevance

The U.S. FDA has approved olaparib in advanced ovarian cancer under several settings including (1) first-line maintenance treatment for patients with deleterious or suspected deleterious germline or somatic BRCA mutation who are in complete or partial response to first-line platinum-based chemotherapy[27]; (2) in combination with bevacizumab as first-line maintenance treatment for patients who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status[28]; (3) maintenance treatment for patients with recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy[29][30]. In addition, olaparib has also been approved in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative breast cancer who have been treated with chemotherapy in either neoadjuvant, adjuvant, or metastatic setting[31]and germline BRCA-mutated metastatic pancreatic cancer[32]. Of note, 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(NCT02987543)[33].

Rucaparib has been approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy[34]. NCCN guidelines recommend rucaparib as recurrence therapy for patients with BRCA-mutated ovarian cancer, who have been treated with two or more lines of chemotherapies[35]. In May 2020, the U.S. FDA also approved rucaparib to treat adult patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy (TRITON2, NCT02952534). Moreover, NCCN guidelines recommend rucaparib as maintenance therapy following prior platinum-based therapy for patients with metastatic pancreatic cancer harboring germline or somatic BRCA mutation.

The U.S. FDA has approved niraparib for the maintenance treatment of patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to first-line platinum-based chemotherapy and patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy[36][37]. Besides, NCCN guidelines recommend niraparib as maintenance therapy for ovarian cancer patients with BRCA mutations. The U.S. FDA also approved talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer[38].

CHEK1 Heterozygous deletion

Biological Impact

The checkpoint kinase 1 (CHEK1 or CHK1) gene encodes a protein kinase involved in transducing DNA damage signals and is required for both the intra-S phase and G2/M checkpoints[39]. CHEK1 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[40][41]. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors[42], and CHEK1 mutations are

extremely rare[39]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer[43], breast cancer[44], colorectal cancer[45], non-small cell lung (NSCLC) cancer[46], and nasopharyngeal cancer[47].

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 (NCT02987543)[33].

In addition, CHEK1 has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in advanced solid tumors (NCT03297606; CAPTUR trial), rucaparib efficacy in ovarian cancer (NCT01968213)[34], prostate cancer (NCT03533946), niraparib efficacy in pancreatic cancer (NCT03553004), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in lung cancer (NCT03377556), respectively.

Selective inhibitors for CHEK1 and CHEK2 alone or in combination with other agents are currently being investigated in clinical trials[48].

FBXW7 Heterozygous deletion

Biological Impact

The F-box/WD repeat-containing protein 7 (FBXW7) gene encodes a protein that belongs to the SCF (SKP1-CUL1-F-box protein) E3 ligase complex. FBXW7 is recognized as a tumor suppressor which is involved in the negative regulation of oncogenes such as c-Myc[49][50], c-Jun[51], cyclin E[52], Notch family members[53][54], Aurora-A[55], mTOR[56], KLF5[57], and MCL-1[58]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation[59]. FBXW7 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[57][58][60].

Therapeutic and prognostic relevance

Clinical efficacy of mTOR inhibitors was seen in patients harboring aberrations in the FBXW7 gene (one patient with refractory fibrolamellar hepatocellular carcinoma, and one patient with lung adenocarcinoma)[61][62]. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor[56].

Preclinical studies suggested that mutations or loss of FBXW7 were associated with regorafenib and oxaliplatin resistance in CRC cell lines and gefitinib resistance in lung cancer cells[63][64][65][66].

Retrospective studies have indicated that a relatively low expression level of FBXW7 is an independent prognostic marker of poor survival for patients with hepatocellular carcinoma, lung adenocarcinoma and squamous cell carcinoma[67][65].

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[68]. 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[69][70]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[71][72]. 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[73].

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[74]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[75].

KMT2C Heterozygous deletion

Biological Impact

Lysine methyltransferase 2C (KMT2C) gene encodes the histone methyltransferase MLL3, which methylates lysine residue four on the tail of histone H3 (H3K4)[76]and regulates the gene expression during development and hematopoiesis[77][78][79]. KMT2C is ubiquitously expressed, and its function is essential for normal embryonal development and cell proliferation[80]. Genetic deletion of the region containing KMT2C is the most common chromosomal abnormality in acute myeloid leukemia[81][82], and KMT2C mutation has been reported in breast cancer, cutaneous squamous cell carcinoma, and leukemia[83][84][85][86][87]. KMT2C was implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[88]. Animal studies revealed that MLL3 haploinsufficiency enhances hematopoietic stem cells (HSCs) self-renewal capacity and induces extensive division of HSCs (AACR; Cancer Res 2018;78(13 Suppl): Abstract nr 4996).

Therapeutic and prognostic relevance

Preclinical studies of cell lines and xenograft models demonstrated that cells with reduced KMT2C expression and activity are deficient in homologous recombination-mediated double-strand break DNA repair and therefore, are more sensitive to olaparib, a PARP1/2 inhibitor[89].

A meta-analysis indicated that low levels of KMT2C expression was associated with better overall survival in pancreatic ductal adenocarcinoma (PDAC) patients[90]. However, another study of ER-positive breast cancer patients (n = 401) demonstrated that low KMT2C expression was associated with worse overall survival[91].

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[92][93][94][95]. 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[96][97]. 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[98][99][100][101][102]. 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[103][104][105]. Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types[106], including myelodysplastic syndromes, melanomas, colon cancer[107], glioblastomas[108], lung cancer[109], ovarian cancer, and breast cancer[103].

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

NF1 depletion has been associated with drug resistance to RAF and EGFR inhibitors, tamoxifen, and retinoic acid[106][111]. 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[112][113][114]. Loss of NF1 in patients with BRAF-mutated melanomas was also suggested conferring resistance to BRAF inhibitors[115][116][117][118].

Notably, preclinical studies further revealed that the addition of a MEK inhibitor could restore the sensitivity to erlotinib[112]. Also, 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 and lapatinib resistance could be overcome with a combination of HER2 and MEK/ERK inhibitors[119].A case study had reported that MEK inhibitor, trametinib, was effective in a treatment-refractory neurofibromatosis type I-associated glioblastoma[120]. Various preclinical data had also supported the activity of MEK and mTOR inhibitors in NF1-deficient tumors[121][122][123][124][125][126]. In an NGS-based study, patients harboring mutations in the mTOR pathway, including mTOR, TSC1, TSC2, NF1, PIK3CA, and PIK3CG responded to everolimus[127].

RAD51 Heterozygous deletion

Biological Impact

The RAD51 gene encodes a recombinase that is crucial for homologous recombination (HR)-mediated repair of double-strand DNA breaks (DSBs) by forming complexes with known tumor suppressors including BRCA1, BRCA2, and PALB2[128][129][130]. RAD51 has been characterized as a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[131]. Overexpression of RAD51 has been observed in many cancer cells, including pancreatic cancer and breast cancer and its hyperexpression is implicated in drug resistance[132][133][134][135][136][137][138]. Germline mutations in RAD51 are associated with increased susceptibility to breast cancer[139][140][141][142].

Therapeutic and prognostic relevance

RAD51 loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer[143]; rucaparib efficacy in solid tumor (NCT04171700); talazoparib efficacy in lung cancer (NCT03377556); niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate cancer) (NCT03207347).

Preclinical studies showed that decreased RAD51 expression could sensitize cells to olaparib-induced tumor cell cytotoxicity[144][145].

RB1 Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[146]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[147]. RB1 has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[148][149][150]. Deletion or inactivating mutation of RB1 is found in a number of tumors, including lung, prostate, bladder, breast cancers and sarcomas. RB1 mutations are found in approximately half of all retinoblastoma cases[151].

ACT Onco® + Report

Therapeutic and prognostic relevance

A deleterious mutation in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response and better overall survival to cisplatin-based chemotherapy for muscle-invasive bladder cancer patients[152]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytoxan (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy[153].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[154][155].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[156]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[157].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[158][159]. Analyses of repeat biopsy samples from patients with EGFR-mutant adenocarcinoma that had transformed to the SCLC subtype have revealed that 100% of these patients have loss of RB1 and may be the alteration that induces this non-small-cell to small-cell transformation[155][160].

US FDA-APPROVED DRUG(S)

Binimetinib (MEKTOVI)

Binimetinib is an oral kinase inhibitor that targets MEK. Binimetinib is developed and marketed by Array BioPharma under the trade name MEKTOVI.

- FDA Approval Summary of Binimetinib (MEKTOVI)

MEKTOVI[161] NCT01909453	**Melanoma** (Approved on 2018/06/27) **BRAF V600E/K** Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3]

Cobimetinib (COTELLIC)

Cobimetinib is a reversible inhibitor which targets MEK1 and MEK2. Cobimetinib is developed by Exelixis and Genentech, and marketed by Genentech under the trade name COTELLIC.

- FDA Approval Summary of Cobimetinib (COTELLIC)

coBRIM[162] NCT01689519	**Melanoma** (Approved on 2015/11/10) **BRAF V600E/K** Cobimetinib + vemurafenib vs. Placebo + vemurafenib [PFS(M): 12.3 vs. 7.2]

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[163] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26) - Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[164] 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[165] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05) - Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[166] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29) - Everolimus vs. Placebo [ORR(%): 35.0]

RECORD-1[167] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30) - Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

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)

PRIMA NCT02655016	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2020/04/29) - Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
NOVA[37] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27) - Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

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)

OlympiA NCT02032823	**HER2-negative high-risk early breast cancer** (Approved on 2022/03/11) **HER2-/gBRCA mutation** Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound[33] NCT02987543	**Prostate cancer** (Approved on 2020/05/19) **HRR genes mutation** Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1[28] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08) **HRD+** Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[32] NCT02184195	**Pancreatic adenocarcinoma** (Approved on 2019/12/27) **gBRCA mutation** Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1[27] NCT01844986	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19) **gBRCA mutation or sBRCA mutation** Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD[31] NCT02000622	**Breast cancer** (Approved on 2018/02/06) **HER2-/gBRCA mutation** Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[168] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17) **gBRCA mutation** Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]

Study19[169] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

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 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[34] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	-
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]

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 NCT01362803	**Plexiform neurofibromas** (Approved on 2020/04/10)
	-
	Selumetinib [ORR(%): 66.0]

Talazoparib (TALZENNA)

Talazoparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2. Talazoparib is developed and marketed by Pfizer under the trade name TALZENNA.

- FDA Approval Summary of Talazoparib (TALZENNA)

EMBRACA[38] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

ACT Onco® + Report

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)

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

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, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060, NCT02124772	**Cancer** (Approved on 2022/06/22)
	BRAF V600E
	Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0]
BRF117019[171] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[172] NCT01336634	**Non-small cell lung cancer** (Approved on 2017/06/22)
	BRAF V600E
	Trametinib + dabrafenib vs. Dabrafenib [ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9]
COMBI-d[173] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[174] NCT01245062	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

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

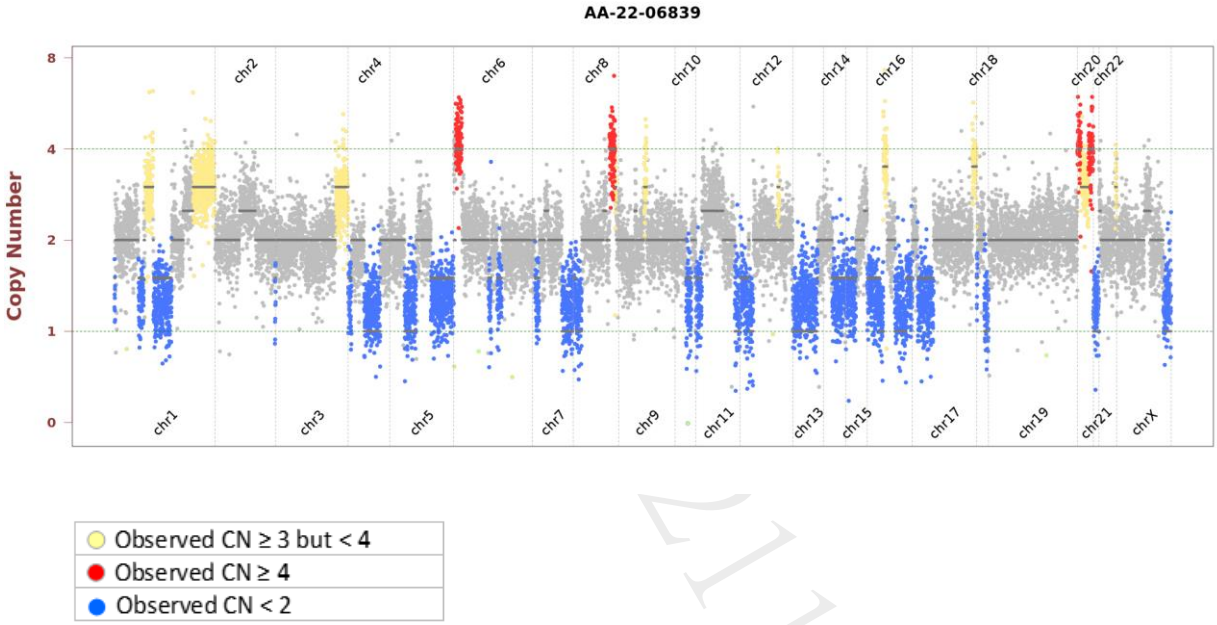
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
DPYD	R74*	3	c.220C>T	NM_000110	-	17.5%	389
TP53	Splice acceptor	-	c.673-2A>G	NM_000546	COSM6908	75.4%	1224

- 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
BIRC2	R241Q	2	c.722G>A	NM_001166	-	36.2%	1441
CDKN1A	P79R	2	c.236C>G	NM_000389	-	34.4%	567
DTX1	Splice region	-	c.1549-6_1549-5delinsTG	NM_004416	-	88.9%	1475
ERBB4	I658F	17	c.1972A>T	NM_005235	-	50.0%	76
FANCA	G304A	11	c.911G>C	NM_000135	-	79.0%	353
LRP1B	T294N	7	c.881C>A	NM_018557	-	37.8%	1018
MUC16	P4444H	3	c.13331C>A	NM_024690	-	34.0%	644
RAD51D	V66M	3	c.196G>A	NM_002878	-	26.0%	682
TBX3	H23L	1	c.68A>T	NM_016569	-	38.8%	765
TGFBR2	R193W	4	c.577C>T	NM_003242	-	52.5%	1099

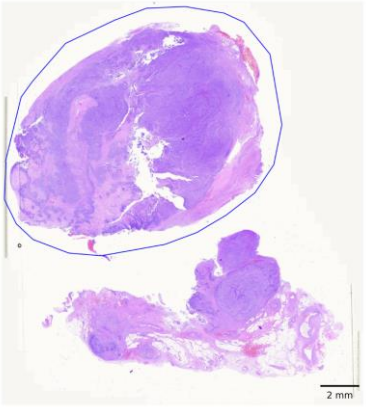
Note:

- 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.

ACTOnco®+ Report

TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Mar 28, 2019
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S10813598B
- Collection site: Pelvic
- Examined by: Dr. Yun-An Chen
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 70%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 85%
  3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 10%
  4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 15%
  5. Additional comment: N/A
- 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: 719x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 37

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.

ACT Onco® + Report

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

RNA test

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

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.

ACT Onco® + Report

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

Yehn

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*

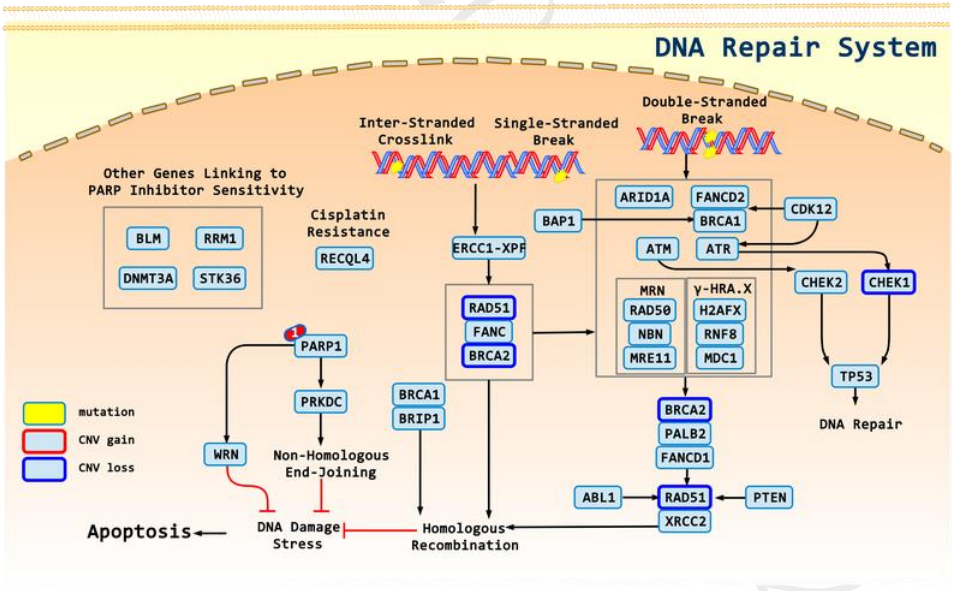
ACT Onco® + Report

APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

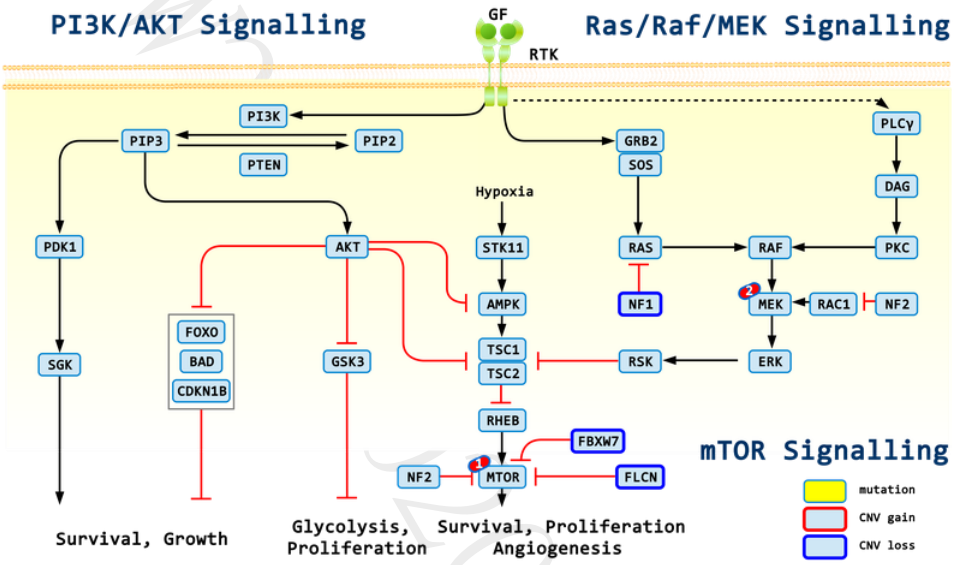
Gene	Therapies	Possible effect
NF1	Binimetinib, Cobimetinib, Everolimus, Selumetinib, Temsirolimus, Trametinib	**sensitive**
FBXW7	Everolimus, Temsirolimus	**sensitive**
FLCN	Everolimus, Temsirolimus	**sensitive**
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
KMT2C	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RAD51	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RB1	Abemaciclib, Palbociclib, Ribociclib	**resistant**
NF1	Afatinib, Cetuximab, Erlotinib, Gefitinib, Lapatinib, Trastuzumab, Vemurafenib	**resistant**
FBXW7	Gefitinib, Regorafenib	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

ACT Onco® + Report



1: Everolimus, Temsirolimus; 2: Trametinib, Selumetinib, Binimetinib, Cobimetinib

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: 16163233; 2004, Clin Adv Hematol Oncol;2(8):527-32
Dihydropyrimidine dehydrogenase deficiency: impact of pharmacogenetics on 5-fluorouracil therapy.

2. PMID: 31052357; 2019, Pharmaceutics;11(5):
DPYD and Fluorouracil-Based Chemotherapy: Mini Review and Case Report.

3. PMID: 11156223; 2000, Clin Cancer Res;6(12):4705-12
Clinical implications of dihydropyrimidine dehydrogenase (DPD) deficiency in patients with severe 5-fluorouracil-associated toxicity: identification of new mutations in the DPD gene.

4. PMID: 26603944; 2015, Lancet Oncol;16(16):1574-6
DPD deficiency in patients treated with fluorouracil.

5. PMID: 10537327; 1999, Clin Cancer Res;5(10):2672-3
Dihydropyrimidine dehydrogenase: its role in 5-fluorouracil clinical toxicity and tumor resistance.

6. PMID: 18299612; 2008, J Clin Oncol;26(13):2131-8
Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: a prospective clinical trial by the German 5-FU Toxicity Study Group.

7. PMID: 19104657; 2008, PLoS One;3(12):e4003
Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients.

8. PMID: 21498394; 2011, Clin Cancer Res;17(10):3455-68
Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer.

9. PMID: 21412232; 2011, Clin Pharmacol Ther;89(5):662-73
Pharmacogenetics: from bench to byte--an update of guidelines.

10. PMID: 29486921; 2018, Bull Cancer;105(4):397-407
[Dihydropyrimidine déhydrogenase (DPD) deficiency screening and securing of fluoropyrimidine-based chemotherapies: Update and recommendations of the French GPCO-Unicancer and RNPGx networks].

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

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

13. 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.

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

15. 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.

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

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

ACT Onco® + Report

containing therapy.

18. 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.

19. 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.

20. 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.

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

22. 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.

23. PMID: 11239455; 2001, Mol Cell;7(2):263-72
BRCA2 is required for homology-directed repair of chromosomal breaks.

24. PMID: 17597348; 2007, Ann Surg Oncol;14(9):2510-8
Heterogenic loss of the wild-type BRCA allele in human breast tumorigenesis.

25. PMID: 22193408; 2011, Nat Rev Cancer;12(1):68-78
BRCA1 and BRCA2: different roles in a common pathway of genome protection.

26. PMID: 27283171; 2016, J Natl Compr Canc Netw;14(6):795-806
The Relevance of Hereditary Cancer Risks to Precision Oncology: What Should Providers Consider When Conducting Tumor Genomic Profiling?

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

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

29. PMID: 28884698; 2017, Lancet Oncol;18(9):e510
Correction to Lancet Oncol 2017; 18: 1274-84.

30. PMID: 22452356; 2012, N Engl J Med;366(15):1382-92
Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.

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

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

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

34. 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.

35. PMID: 28882436; 2017, Gynecol Oncol;147(2):267-275
Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2.

36. PMID: 31562799; 2019, N Engl J Med;381(25):2391-2402

ACT Onco® + Report

Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.

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

38. PMID: 30110579; 2018, N Engl J Med;379(8):753-763
Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation.

39. PMID: 12781359; 2003, Cancer Cell;3(5):421-9
Chk1 and Chk2 kinases in checkpoint control and cancer.

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

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

42. PMID: 15459660; 2004, Nat Rev Mol Cell Biol;5(10):792-804
Checking on DNA damage in S phase.

43. PMID: 22585575; 2012, J Clin Invest;122(6):2165-75
CHK1 targets spleen tyrosine kinase (L) for proteolysis in hepatocellular carcinoma.

44. PMID: 17638866; 2007, Cancer Res;67(14):6574-81
The E2F-regulated gene Chk1 is highly expressed in triple-negative estrogen receptor /progesterone receptor /HER-2 breast carcinomas.

45. PMID: 17848589; 2007, Mol Cell Proteomics;6(12):2150-64
A proteomics analysis of cell signaling alterations in colorectal cancer.

46. PMID: 24418519; 2014, J Surg Res;187(1):6-13
Checkpoint kinase 1 protein expression indicates sensitization to therapy by checkpoint kinase 1 inhibition in non-small cell lung cancer.

47. PMID: 15297395; 2004, Clin Cancer Res;10(15):4944-58
Global gene expression profile of nasopharyngeal carcinoma by laser capture microdissection and complementary DNA microarrays.

48. PMID: 21458083; 2011, Trends Pharmacol Sci;32(5):308-16
Anticancer therapy with checkpoint inhibitors: what, where and when?

49. PMID: 15498494; 2004, Curr Biol;14(20):1852-7
A nucleolar isoform of the Fbw7 ubiquitin ligase regulates c-Myc and cell size.

50. PMID: 15103331; 2004, EMBO J;23(10):2116-25
Phosphorylation-dependent degradation of c-Myc is mediated by the F-box protein Fbw7.

51. PMID: 16023596; 2005, Cancer Cell;8(1):25-33
The v-Jun point mutation allows c-Jun to escape GSK3-dependent recognition and destruction by the Fbw7 ubiquitin ligase.

52. PMID: 11533444; 2001, Science;294(5540):173-7
Phosphorylation-dependent ubiquitination of cyclin E by the SCFFbw7 ubiquitin ligase.

53. PMID: 11461910; 2001, J Biol Chem;276(38):35847-53
The Notch intracellular domain is ubiquitinated and negatively regulated by the mammalian Sel-10 homolog.

54. PMID: 11425854; 2001, J Biol Chem;276(37):34371-8
Functional interaction between SEL-10, an F-box protein, and the nuclear form of activated Notch1 receptor.

55. PMID: 16863506; 2006, Cancer Sci;97(8):729-36
Fbxw7 contributes to tumor suppression by targeting multiple proteins for ubiquitin-dependent degradation.

56. PMID: 18787170; 2008, Science;321(5895):1499-502

FBXW7 targets mTOR for degradation and cooperates with PTEN in tumor suppression.

57. PMID: 20484041; 2010, Cancer Res;70(11):4728-38
The Fbw7 tumor suppressor targets KLF5 for ubiquitin-mediated degradation and suppresses breast cell proliferation.

58. PMID: 21368833; 2011, Nature;471(7336):104-9
SCF(FBW7) regulates cellular apoptosis by targeting MCL1 for ubiquitylation and destruction.

59. PMID: 18094723; 2008, Nat Rev Cancer;8(2):83-93
FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation.

60. PMID: 23032637; 2012, Cancer Inform;11():157-71
Haploinsufficiency of Tumor Suppressor Genes is Driven by the Cumulative Effect of microRNAs, microRNA Binding Site Polymorphisms and microRNA Polymorphisms: An In silico Approach.

61. PMID: 24586741; 2014, PLoS One;9(2):e89388
FBXW7 mutations in patients with advanced cancers: clinical and molecular characteristics and outcomes with mTOR inhibitors.

62. PMID: 24360397; 2014, Lung Cancer;83(2):300-1
Temsirolimus therapy in a patient with lung adenocarcinoma harboring an FBXW7 mutation.

63. PMID: 27399335; 2017, Oncogene;36(6):787-796
FBW7 mutations mediate resistance of colorectal cancer to targeted therapies by blocking Mcl-1 degradation.

64. PMID: 25860929; 2015, Oncotarget;6(11):9240-56
FBXW7-mutated colorectal cancer cells exhibit aberrant expression of phosphorylated-p53 at Serine-15.

65. PMID: 29633504; 2018, Mol Oncol;12(6):883-895
FBXW7 deletion contributes to lung tumor development and confers resistance to gefitinib therapy.

66. PMID: 28522751; 2017, Cancer Res;77(13):3527-3539
Targeting FBW7 as a Strategy to Overcome Resistance to Targeted Therapy in Non-Small Cell Lung Cancer.

67. PMID: 24884509; 2014, Mol Cancer;13():110
Fbxw7 is an independent prognostic marker and induces apoptosis and growth arrest by regulating YAP abundance in hepatocellular carcinoma.

68. 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.

69. 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.

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

71. 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.

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

73. 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.

74. 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.

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

76. PMID: 25998713; 2015, Nat Rev Cancer;15(6):334-46
Hijacked in cancer: the KMT2 (MLL) family of methyltransferases.

77. PMID: 24081332; 2013, Mol Cell Biol;33(23):4745-54
The MLL3/MLL4 branches of the COMPASS family function as major histone H3K4 monomethylases at enhancers.

78. PMID: 23166019; 2012, Genes Dev;26(23):2604-20
Enhancer-associated H3K4 monomethylation by Trithorax-related, the Drosophila homolog of mammalian Mll3/Mll4.

79. PMID: 27926873; 2016, Cell Rep;17(10):2715-2723
FOXA1 Directs H3K4 Monomethylation at Enhancers via Recruitment of the Methyltransferase MLL3.

80. PMID: 17021013; 2006, Proc Natl Acad Sci U S A;103(42):15392-7
Coactivator as a target gene specificity determinant for histone H3 lysine 4 methyltransferases.

81. PMID: 11891048; 2002, Gene;284(1-2):73-81
MLL3, a new human member of the TRX/MLL gene family, maps to 7q36, a chromosome region frequently deleted in myeloid leukaemia.

82. PMID: 22234698; 2012, Blood;119(10):e67-75
High-resolution genomic profiling of adult and pediatric core-binding factor acute myeloid leukemia reveals new recurrent genomic alterations.

83. PMID: 25537518; 2015, Oncotarget;6(4):2466-82
Genetic alterations of histone lysine methyltransferases and their significance in breast cancer.

84. PMID: 25303977; 2014, Clin Cancer Res;20(24):6582-92
Mutational landscape of aggressive cutaneous squamous cell carcinoma.

85. PMID: 25151357; 2014, Nat Genet;46(10):1097-102
Genetic landscape of esophageal squamous cell carcinoma.

86. PMID: 28801450; 2017, Blood;130(14):1644-1648
Genomic analysis of hairy cell leukemia identifies novel recurrent genetic alterations.

87. PMID: 25794446; 2015, Cancer Genet;208(5):178-91
The cancer COMPASS: navigating the functions of MLL complexes in cancer.

88. PMID: 24794707; 2014, Cancer Cell;25(5):652-65
MLL3 is a haploinsufficient 7q tumor suppressor in acute myeloid leukemia.

89. PMID: 30665945; 2019, EMBO Rep;20(3):
The lysine-specific methyltransferase KMT2C/MLL3 regulates DNA repair components in cancer.

90. PMID: 27280393; 2016, Cancer Res;76(16):4861-71
Reduced Expression of Histone Methyltransferases KMT2C and KMT2D Correlates with Improved Outcome in Pancreatic Ductal Adenocarcinoma.

91. PMID: 27986439; 2017, Clin Breast Cancer;17(3):e135-e142
Expression Levels of KMT2C and SLC20A1 Identified by Information-theoretical Analysis Are Powerful Prognostic Biomarkers in Estrogen Receptor-positive Breast Cancer.

92. 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.

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

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

ACT Onco® + Report

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

96. 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.

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

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

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

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

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

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

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

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

105. 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.

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

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

108. 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.

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

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

111. 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.

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

113. 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.

ACT Onco® + Report

114. 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.

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

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

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

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

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

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

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

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

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

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

125. 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.

126. 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.

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

128. PMID: 20930833; 2010, Nature;467(7316):667-8
DNA repair: A protein giant in its entirety.

129. PMID: 20729858; 2010, Nat Struct Mol Biol;17(10):1263-5
The breast cancer tumor suppressor BRCA2 promotes the specific targeting of RAD51 to single-stranded DNA.

130. PMID: 20729832; 2010, Nature;467(7316):678-83
Purified human BRCA2 stimulates RAD51-mediated recombination.

131. PMID: 22305526; 2012, Am J Hum Genet;90(2):301-7
RAD51 haploinsufficiency causes congenital mirror movements in humans.

132. PMID: 18243065; 2008, DNA Repair (Amst);7(5):686-93
The consequences of Rad51 overexpression for normal and tumor cells.

133. PMID: 24811120; 2014, Oncotarget;5(10):3261-72
Rad51 supports triple negative breast cancer metastasis.

134. PMID: 26317153; 2015, Cell Cycle;14(19):3190-202
High levels of RAD51 perturb DNA replication elongation and cause unscheduled origin firing due to impaired CHK1 activation.

135. PMID: 21807066; 2011, Biochim Biophys Acta;1816(2):209-18
RAD51 as a potential biomarker and therapeutic target for pancreatic cancer.

136. PMID: 10851081; 2000, Oncogene;19(23):2791-5
DNA repair and recombination factor Rad51 is over-expressed in human pancreatic adenocarcinoma.

137. PMID: 24741789; 2014, Rev Med Chir Soc Med Nat Iasi;118(1):133-40
Rad51 overexpression and resistance to genotoxic agents. A study in the fission yeast Schizosaccharomyces pombe.

138. PMID: 18618591; 2009, Mol Carcinog;48(2):105-9
Rad51 overexpression rescues radiation resistance in BRCA2-defective cancer cells.

139. PMID: 10807537; 2000, J Hum Genet;45(3):133-7
Identification of Rad51 alteration in patients with bilateral breast cancer.

140. PMID: 26108708; 2015, Sci Rep;5():11588
RAD51 135G>C substitution increases breast cancer risk in an ethnic-specific manner: a meta-analysis on 21,236 cases and 19,407 controls.

141. PMID: 11248061; 2001, Proc Natl Acad Sci U S A;98(6):3232-6
A single nucleotide polymorphism in the RAD51 gene modifies cancer risk in BRCA2 but not BRCA1 carriers.

142. PMID: 17999359; 2007, Am J Hum Genet;81(6):1186-200
RAD51 135G-->C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies.

143. PMID: 30353044; 2018, Br J Cancer;119(11):1401-1409
Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes.

144. PMID: 24577941; 2014, Mol Cancer Ther;13(5):1170-80
The use of Olaparib (AZD2281) potentiates SN-38 cytotoxicity in colon cancer cells by indirect inhibition of Rad51-mediated repair of DNA double-strand breaks.

145. PMID: 28759753; 2017, Biomed Pharmacother;94():165-168
Inhibition of Rad51 sensitizes breast cancer cells with wild-type PTEN to olaparib.

146. PMID: 22293180; 2012, J Clin Invest;122(2):425-34
Understanding pRb: toward the necessary development of targeted treatments for retinoblastoma.

147. PMID: 6320372; 1984, Science;223(4640):1028-33
Retinoblastoma: clues to human oncogenesis.

148. PMID: 27308386; 2015, Mol Cell Oncol;2(1):e968069
Conditional haploinsufficiency of the retinoblastoma tumor suppressor gene.

149. PMID: 23687339; 2013, Cancer Res;73(14):4247-55
Rb1 haploinsufficiency promotes telomere attrition and radiation-induced genomic instability.

150. PMID: 28169375; 2017, Sci Rep;7():42056
The Rb1 tumour suppressor gene modifies telomeric chromatin architecture by regulating TERRA expression.

151. PMID: 15884040; 2005, Hum Mutat;25(6):566-74
Sensitive multistep clinical molecular screening of 180 unrelated individuals with retinoblastoma detects 36 novel mutations in the RB1 gene.

152. PMID: 26238431; 2015, Eur Urol;68(6):959-67
Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy in Muscle-invasive Bladder Cancer.

153. PMID: 22811582; 2012, Clin Cancer Res;18(18):5110-22

RB-pathway disruption is associated with improved response to neoadjuvant chemotherapy in breast cancer.

154. PMID: 21358261; 2011, Cell Cycle;10(6):956-62
A non-functional retinoblastoma tumor suppressor (RB) pathway in premenopausal breast cancer is associated with resistance to tamoxifen.

155. PMID: 17160137; 2007, J Clin Invest;117(1):218-28
The retinoblastoma tumor suppressor modifies the therapeutic response of breast cancer.

156. PMID: 29236940; 2018, Ann Oncol;29(3):640-645
Polyclonal RB1 mutations and acquired resistance to CDK 4/6 inhibitors in patients with metastatic breast cancer.

157. PMID: 29483214; 2018, Mol Cancer Ther;17(5):897-907
Preclinical Activity of Abemaciclib Alone or in Combination with Antimitotic and Targeted Therapies in Breast Cancer.

158. PMID: 22941188; 2012, Nat Genet;44(10):1104-10
Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer.

159. PMID: 22941189; 2012, Nat Genet;44(10):1111-6
Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer.

160. PMID: 25846096; 2015, Lancet Oncol;16(4):e165-72
Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin.

161. PMID: 29573941; 2018, Lancet Oncol;19(5):603-615
Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial.

162. PMID: 27480103; 2016, Lancet Oncol;17(9):1248-60
Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial.

163. 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.

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

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

166. 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.

167. 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.

168. 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.

169. 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.

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

171. PMID: 29072975; 2018, J Clin Oncol;36(1):7-13

ACT Onco® + Report

Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer.

172. 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.

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

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