ACT Onco® + Report

PATIENT		
Identifier: 詹益飛		Patient ID: 49655110
Date of Birth: Oct 16, 2015		Gender: Male
Diagnosis: Lymphangioma		
ORDERING PHYSICIAN		
Name: 顏秀如醫師		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: S11237349A	Collection site: Skin	Type: FFPE tissue
Date received: Aug 10, 2023	Lab ID: AA-23-05252	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	
GOPC(4)-ROS1(36) fusion	-	-	Ceritinib, Crizotinib, Entrectinib, Lorlatinib

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
GOPC(4)-ROS1(36) fusion	Brigatinib, Cabozantinib	Osimertinib

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
Not detected		

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr11	*MUC6*	Homozygous deletion	0
Chr13	*BRCA2*	Heterozygous deletion	1

- Fusions

Fusion Gene & Exon	Transcript ID
GOPC(4)-ROS1(36) fusion	GOPC(NM_020399.3), ROS1(NM_002944.2)

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	0.1 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 30% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- The fusion gene reported above is confirmed to be in-frame and includes the kinase/functional domain. Such alteration may indicate potential benefits from kinase inhibitors. However, for a novel fusion, its functional significance and response to kinase inhibitors are undetermined.
- 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%.

THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3A		
GOPC(4)-ROS1(36) fusion	Ceritinib, Crizotinib, Entrectinib, Lorlatinib	**sensitive**
Level 3B		
GOPC(4)-ROS1(36) fusion	Brigatinib, Cabozantinib	**sensitive**
Level 4		
GOPC(4)-ROS1(36) fusion	Osimertinib	**resistant**

Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence in professional guidelines or peer-reviewed journals.

Level	Description
1	FDA-recognized biomarkers predictive of response or resistance to FDA approved drugs in this indication
2	Standard care biomarkers (recommended by the NCCN guideline) predictive of response or resistance to FDA approved drugs in this indication
3A	Biomarkers predictive of response or resistance to therapies approved by the FDA or NCCN guideline in a different cancer type
3B	Biomarkers that serve as inclusion criteria for clinical trials (minimal supportive data required)
4	Biomarkers that show plausible therapeutic significance based on small studies, few case reports, or preclinical studies

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

GOPC(4)-ROS1(36) fusion

Biological Impact

The ROS1 gene encodes a receptor tyrosine kinase[1]. ROS1 gene rearrangements, which the kinase domain is retained[2], are implicated in a range of human epithelial cancers including cholangiocarcinoma[3], ovarian carcinoma[4], gastric carcinoma[5], angiosarcoma[6], and most commonly non-small cell lung cancer[7].

GOPC-ROS1 (also referred to as FIG-ROS1) results from the fusion of GOPC and ROS1, leading to constitutive ROS1 activation, cell transformation, and tumorigenesis in vitro and in vivo[8][9]. GOPC-ROS1 fusion has been identified in lung cancer, biliary tract carcinoma, glioma, melanoma, breast cancer, and ovarian cancer (DOI: 10.1158/1538-7445.AM2019-1317)[10][11][12][13][14].

Therapeutic and prognostic relevance

Crizotinib and entrectinib are FDA-approved for ROS1-positive metastatic NSCLC. The NCCN guidelines recommend ceritinib, crizotinib, and entrectinib in the first-line setting for patients with advanced ROS1-rearranged NSCLC, and lorlatinib and entrectinib for subsequent therapy.

Lorlatinib, ceritinib, cabozantinib, brigatinib, and DS-6051b have shown clinical activity and efficacy in patients with ROS1-rearranged lung cancer[15][16][17][18].

In a clinical study of pemetrexed-based chemotherapy efficacy, patients with ROS1-rearranged lung cancer had a better overall response rate compared with patients who carry other driver mutations, including EGFR mutations, KRAS mutations, and EML4-ALK fusion[19].

In a case report, GOPC-ROS1 was identifed in a patient with lung adenocarcinoma harboring EGFR exon 19 deletion and T790M when the disease progressed on osimertinib treatment. Combination of crizotinib and osimertinib treatment resulted in a partial response[20]. Another case report demonstrated that a patient with chemotherapy-resistant high-grade serous ovarian carcinoma harboring GOPC-ROS1 fusion showed rapid clinical response to crizotinib treatment, achieving a partial response at one month[14]. Furthermore, a case study presented an ER/PR-positive, HER2-negative breast cancer patient harboring GOPC-ROS1 fusion who was sensitive to crizotinib treatment, as demonstrated by imaging response as well as decreased expression of tumor markers. This patient switched to ceritinib treatment due to crizotinib-related pneumonitis and continued to have good response following six months of anti-ROS1 treatment (DOI: 10.1158/1538-7445.AM2019-1317).

In a phase I/II trial (STARTRK-NG; NCT02650401), a pediatric patient with K27-mutant diffuse midline glioma harboring GOPC-ROS1 fusion achieved a complete response to entrectinib treatment lasting for 22.2 months[21]. Another pediatric patient with glioma harboring GOPC-ROS1 resulted in a partial response to entrectinib treatment lasting for at least 3.8 months. In a clinical study analyzing combined results from two phase 1 trials (ALKA-372-001 and STARTRK-1), a patient with melanoma harboring GOPC-ROS1 fusion resulted in a partial response to entrectinib treatment in the first-line setting[13]. Another case study demosntrated that a heavily pre-treated patient with acral lentiginous melanoma harboring GOPC-ROS1 achieved dramatic and durable resposne (parital response) to entrectinib treatment, with a 38% decrease in tumor size at 3 months and 55% decrease at 11 months. The patient remained progression-free at 11 months[22].

In preclinical studies, transformed cells harboring GOPC-ROS1 fusion were sensitive to brigatinib, crizotinib, cabozantinib, lorlatinib, ceritinib, and entrectinib, as demosntrated by inhibition of ROS1 phosphorylation, downstream signaling, and cell growth in vitro[23][8][24]. Additionally, lorlatinib inhibited tumor growth and prolonged survival in mice xenograft model[24].

ACT Onco® + Report

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[25]. 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[26]. 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[27]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[28].

Therapeutic and prognostic relevance

Multiple PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have been approved by the U.S. FDA for the treatment of cancer. Olaparib is approved for multiple settings in advanced ovarian cancer, metastatic breast cancer with BRCA mutations, metastatic pancreatic cancer, and mCRPC with BRCA mutations or HRR gene mutations, including BRCA mutations. Rucaparib is approved for maintenance treatment of recurrent ovarian cancer with BRCA mutations and mCRPC with BRCA mutations. Niraparib is approved for maintenance treatment of advanced ovarian cancer and recurrent ovarian cancer with BRCA mutations, and mCRPC with BRCA mutations in combination with abiraterone acetate. Talazoparib is approved for locally advanced or metastatic breast cancer with BRCA mutations and mCRPC with HRR gene mutations, including BRCA2.

According to the NCCN guidelines, rucaparib is recommended as recurrence therapy for patients with BRCA-mutated ovarian cancer who have been treated with multiple lines of chemotherapy. It is also recommended as maintenance therapy for patients with metastatic pancreatic cancer who have undergone prior platinum-based therapy and harbor germline or somatic BRCA mutations. Additionally, niraparib is recommended as maintenance therapy for ovarian cancer patients with BRCA mutations.

MUC6 Homozygous deletion

Biological Impact

MUC6 encodes a secretory mucin glycoprotein that is physiologically expressed in the digestive tract. Abnormal MUC6 expression has been found in various human cancers arising in the stomach, duodenum, breast, pancreas, endometrium, colorectum and lung[29]. Overexpression of MUC6 has been shown to inhibit tumor proliferation and invasion in vitro[30][31]. In Wilms tumor, MUC6 overexpression suppresses the expression of β-catenin and its target genes via autophagy-dependent mechanism, while MUC6 knock-down leads to the opposite effects, supporting a possible tumor suppressor role[31].

Therapeutic and prognostic relevance

Lack of MUC6 expression was associated with shorter overall survival in patients with well- to moderately-differentiated gallbladder cancer[32]. MUC6-expressing pulmonary invasive mucinous adenocarcinoma demonstrated superior survival to MUC6-negative cases[33]. In colorectal cancer, high MUC6 expression was associated with improved progression-free and cancer-specific survival[34].

US FDA-APPROVED DRUG(S)

Brigatinib (ALUNBRIG)

Brigatinib is a potent dual inhibitor of anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR). Brigatinib is developed and marketed by Takeda under the trade name ALUNBRIG.

- FDA Approval Summary of Brigatinib (ALUNBRIG)

ALTA 1L NCT02737501	**Non-small cell lung carcinoma** (Approved on 2020/05/22)
	ALK+
	Brigatinib vs. Crizotinib [PFS(M): 24 vs. 11]
ALTA NCT02094573	**Non-small cell lung carcinoma** (Approved on 2017/04/28)
	ALK+
	Brigatinib [ORR (90mg)(%): 48.0, ORR (90→180mg)(%): 53.0]

Cabozantinib (COMETRIQ)

Cabozantinib is a small molecule inhibitors of multiple tyrosine kinases, including RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, and TIE-2. Cabozantinib is developed and marketed by Exelixis under the trade names COMETRIQ (capsule) and CABOMETYX (tablet).

- FDA Approval Summary of Cabozantinib (COMETRIQ)

EXAM[35] NCT00704730	**Thyroid cancer** (Approved on 2012/11/29)
	-
	Cabozantinib vs. Placebo [PFS(M): 11.2 vs. 4]

Cabozantinib (CABOMETYX)

Cabozantinib is a small molecule inhibitors of multiple tyrosine kinases, including RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, and TIE-2. Cabozantinib is developed and marketed by Exelixis under the trade names COMETRIQ (capsule) and CABOMETYX (tablet).

- FDA Approval Summary of Cabozantinib (CABOMETYX)

COSMIC-311 NCT03690388	**Differentiated thyroid cancer (dtc)** (Approved on 2021/09/17)
	-
	Cabozantinib vs. Placebo [PFS(M): 11 vs. 1.9, ORR(%): 18.0 vs. 0]
CHECKMATE-9ER NCT03141177	**Renal cell carcinoma** (Approved on 2021/01/22)
	-
	Nivolumab + cabozantinib vs. Sunitinib [ORR(%): 55.7 vs. 27.1, PFS(M): 16.6 vs. 8.3, OS(M): NR vs. NR]
CELESTIAL [36] NCT01908426	**Hepatocellular carcinoma** (Approved on 2019/01/14)
	-
	Cabozantinib vs. Placebo [OS(M): 10.2 vs. 8]
CABOSUN[37] NCT01835157	**Renal cell carcinoma** (Approved on 2017/12/09)
	-
	Cabozantinib vs. Sunitinib [PFS(M): 8.6 vs. 5.3]

METEOR[38] NCT01865747	**Renal cell carcinoma** (Approved on 2016/04/25)
	-
	Cabozantinib vs. Everolimus [PFS(M): 7.4 vs. 3.8]

Ceritinib (ZYKADIA)

Ceritinib is a small molecule inhibitor of anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase which, after genetic rearrangement, acts as an oncogenic driver. Ceritinib is developed and marketed by Novartis under the trade name ZYKADIA.

- FDA Approval Summary of Ceritinib (ZYKADIA)

ASCEND-4[39] NCT01828099	**Non-small cell lung carcinoma** (Approved on 2017/05/26)
	ALK+
	Ceritinib vs. Pemetrexed + cisplatin| pemetrexed + carboplatin [ORR(%): 73.0 vs. 27.0]
ASCEND-1[40] NCT01685060	**Non-small cell lung carcinoma** (Approved on 2014/04/29)
	ALK+
	Ceritinib [ORR(%): 43.6]

Crizotinib (XALKORI)

Crizotinib is an inhibitor of the tyrosine kinases anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1), by competitively binding with the ATP-binding pocket. Crizotinib is developed and marketed by Pfizer under the trade name XALKORI.

- FDA Approval Summary of Crizotinib (XALKORI)

ADVL0912, A8081013 NCT00939770, NCT01121588	**Inflammatory myofibroblastic tumor** (Approved on 2022/08/05)
	ALK+
	Crizotinib [ORR(pediatric patients)(%): 86.0, ORR(adult patients)(%): 71.0]
ADVL0912 NCT00939770	**Alk fusion-positive anaplastic large cell lymphoma (alcl)** (Approved on 2021/01/14)
	ALK fusion
	Crizotinib [ORR(%): 88.0, DOR(M): 39 (maintained response for at least 6 months) vs. 22 (maintained response for at least 12 months)]
PROFILE 1001[41] NCT00585195	**Non-small cell lung carcinoma** (Approved on 2016/03/11)
	ROS1+
	Crizotinib [ORR(%): 66.0]
PROFILE 1014[42] NCT01154140	**Non-small cell lung carcinoma** (Approved on 2015/03/20)
	ALK+
	Crizotinib vs. Pemetrexed + cisplatin or pemetrexed + carboplatin [PFS(M): 10.9 vs. 7]
PROFILE 1007[43] NCT00932893	**Non-small cell lung carcinoma** (Approved on 2013/11/20)
	ALK+
	Crizotinib vs. Pemetrexed or docetaxel [PFS(M): 7.7 vs. 3]

ACT Onco® + Report

Entrectinib (ROZLYTREK)

Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2, and NTRK3, respectively), proto-oncogene tyrosine-protein kinase ROS1 (ROS1), and anaplastic lymphoma kinase (ALK) with IC50 values of 0.1 to 2 nM. Entrectinib is developed and marketed by Genentech under the tradename ROZLYTREK.

- FDA Approval Summary of Entrectinib (ROZLYTREK)

ALKA, STARTRK-1, STARTRK-2 [44] NCT02097810, NCT02568267	**Cancer** (Approved on 2019/08/15)
	NTRK fusion
	Entrectinib [ORR(%): 57.0]
ALKA, STARTRK-1, STARTRK-2 [45] NCT02097810, NCT02568267	**Non-small cell lung carcinoma** (Approved on 2019/08/15)
	ROS1+
	Entrectinib [ORR(%): 78.0]

Lorlatinib (LORBRENA)

Lorlatinib is a kinase inhibitor with in vitro activity against ALK and ROS1 as well as TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK. Lorlatinib demonstrated in vitro activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on crizotinib and other ALK inhibitors. Lorlatinib is developed and marketed by Pfizer under the trade name LORBRENA.

- FDA Approval Summary of Lorlatinib (LORBRENA)

Study B7461006 (CROWN) NCT03052608	**Non-small cell lung carcinoma** (Approved on 2021/03/03)
	ALK+
	Lorlatinib vs. Crizotinib [PFS(M): NR vs. 9.3]
Study B7461001[46] NCT01970865	**Non-small cell lung carcinoma** (Approved on 2018/11/02)
	ALK+
	Lorlatinib [ORR(%): 48, ORR (intracranial)(%): 60]

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)

MAGNITUDE NCT03748641	**Prostate cancer** (Approved on 2023/08/11)
	BRCA mutation
	Niraparib and abiraterone acetate plus prednisone vs. placebo and abiraterone acetate plus prednisone [rPFS(M): 16.6 vs. 10.9]
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[47] 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)

PROpel NCT03732820	**Prostate cancer** (Approved on 2023/05/31)
	BRCA mutation
	Olaparib + abiraterone + prednisone vs. Placebo + abiraterone + prednisone [rPFS(M): not reached vs. 8]
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[48] 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[49] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[50] 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[51] 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[52] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[53] 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[54] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

ACT Onco® + Report

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[55] 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]

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)

TALAPRO-2 NCT03395197	**Prostate cancer** (Approved on 2023/06/20)
	HRR genes mutation
	Talazoparib + enzalutamide vs. Placebo + enzalutamide [rPFS(M): Not reached vs. 13.8]
EMBRACA[56] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

D=day; W=week; M=month

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

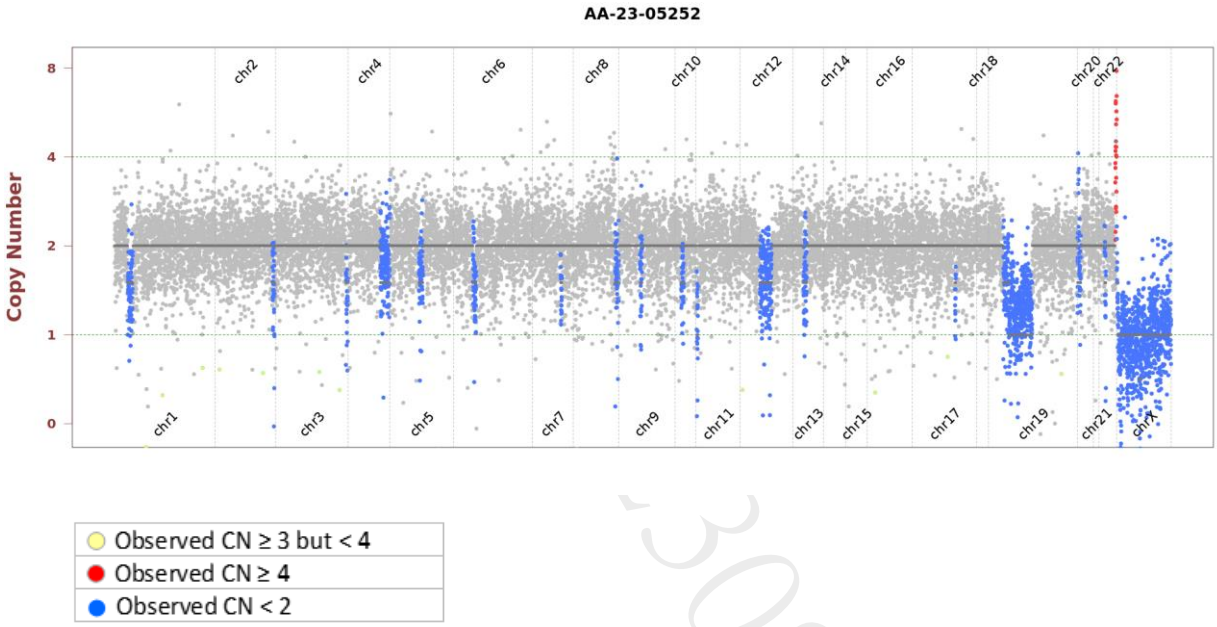
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
Not Detected							

- 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
ADAMTSL1	R1322G	22	c.3964A>G	NM_001040272	-	47.7%	1279
ADAMTSL1	G915D	19	c.2744G>A	NM_001040272	-	49.7%	2578
AKT1	R121W	5	c.361C>T	NM_005163	-	55.4%	596
CCNB3	R397H	5	c.1190G>A	NM_033031	COSM1122623	97.4%	584
ERCC4	Q849E	11	c.2545C>G	NM_005236	-	52.1%	1337
ESR2	L413V	8	c.1237C>G	NM_001437	COSM7637015	47.0%	912
KMT2C	C385F	8	c.1154G>T	NM_170606	COSM9180259	7.0%	3996
LIG3	R942Q	20	c.2825G>A	NM_013975	-	49.2%	1975
MUC16	G13811C	64	c.41431G>T	NM_024690	-	51.0%	2455
NEFH	S787R	4	c.2361C>G	NM_021076	-	53.4%	436
POLD1	R166W	5	c.496C>T	NM_001256849	-	46.7%	910
RET	L481V	7	c.1441C>G	NM_020975	-	50.0%	1096
STK11	R147C	3	c.439C>T	NM_000455	-	60.3%	237

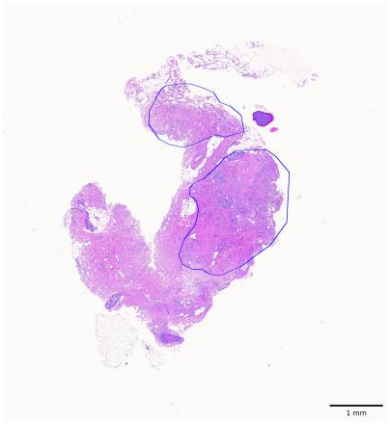
Note:

- 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: Jul 31, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11237349A
- Collection site: Skin
- Examined by: Dr. Chien-Ta Chiang
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 10%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 30%
  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: 1123x
- Target Base Coverage at 100x: 97%

RNA test

- Average unique RNA Start Sites per control GSP2: 83

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.

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

Yun Yu Chen

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

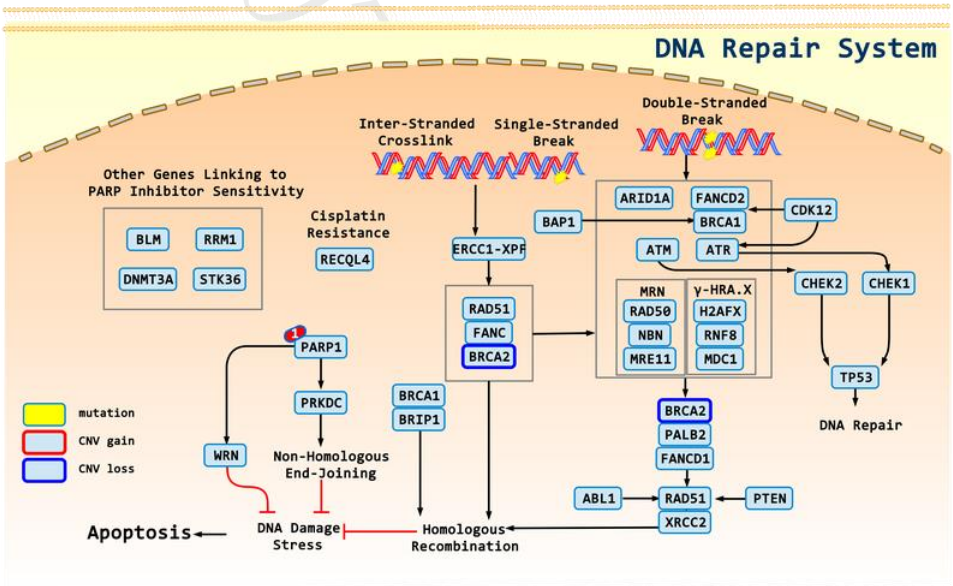
詹益飛
Project ID: C23-M001-02461
Report No.: AA-23-05252_ONC
Date Reported: Aug 23, 2023

APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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: 18778756; 2009, Biochim Biophys Acta;1795(1):37-52
The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer.

2. PMID: 22327623; 2012, Nat Med;18(3):378-81
RET, ROS1 and ALK fusions in lung cancer.

3. PMID: 21253578; 2011, PLoS One;6(1):e15640
Survey of tyrosine kinase signaling reveals ROS kinase fusions in human cholangiocarcinoma.

4. PMID: 22163003; 2011, PLoS One;6(12):e28250
Chromosome 3 anomalies investigated by genome wide SNP analysis of benign, low malignant potential and low grade ovarian serous tumours.

5. PMID: 23400546; 2013, Cancer;119(9):1627-35
Identification of ROS1 rearrangement in gastric adenocarcinoma.

6. PMID: 23637631; 2013, PLoS Genet;9(4):e1003464
Breakpoint analysis of transcriptional and genomic profiles uncovers novel gene fusions spanning multiple human cancer types.

7. PMID: 22215748; 2012, J Clin Oncol;30(8):863-70
ROS1 rearrangements define a unique molecular class of lung cancers.

8. PMID: 24218589; 2013, Proc Natl Acad Sci U S A;110(48):19519-24
Foretinib is a potent inhibitor of oncogenic ROS1 fusion proteins.

9. PMID: 24154728; 2013, Proc Natl Acad Sci U S A;110(48):19513-8
Mouse model of intrahepatic cholangiocarcinoma validates FIG-ROS as a potent fusion oncogene and therapeutic target.

10. PMID: 22661537; 2012, Clin Cancer Res;18(16):4449-57
Analysis of receptor tyrosine kinase ROS1-positive tumors in non-small cell lung cancer: identification of a FIG-ROS1 fusion.

11. PMID: 25231053; 2014, Genes Chromosomes Cancer;53(12):1033-40
Screening for the FIG-ROS1 fusion in biliary tract carcinomas by nested PCR.

12. PMID: 26648752; 2015, Cancer Growth Metastasis;8():51-60
Synergistic Effects of Crizotinib and Temozolomide in Experimental FIG-ROS1 Fusion-Positive Glioblastoma.

13. PMID: 28183697; 2017, Cancer Discov;7(4):400-409
Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1).

14. PMID: 32652753; 2020, Oncologist;25(11):e1720-e1724
Successful Treatment of Patients with Refractory High-Grade Serous Ovarian Cancer with GOPC-ROS1 Fusion Using Crizotinib: A Case Report.

15. PMID: 31669155; 2019, Lancet Oncol;20(12):1691-1701
Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial.

16. PMID: 30217491; 2019, J Thorac Oncol;14(2):e21-e24
Lengthy Progression-Free Survival and Intracranial Activity of Cabozantinib in Patients with Crizotinib and Ceritinib-Resistant ROS1-Positive Non-Small Cell Lung Cancer.

17. PMID: 27836716; 2016, Lancet Oncol;17(12):1683-1696
Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial.

18. PMID: 29805770; 2018, Oncotarget;9(34):23729-23737

Safety and pharmacokinetics of DS-6051b in Japanese patients with non-small cell lung cancer harboring ROS1 fusions: a phase I study.

19. PMID: 27094798; 2016, J Thorac Oncol;11(7):1140-52
Efficacy of Pemetrexed-Based Chemotherapy in Patients with ROS1 Fusion-Positive Lung Adenocarcinoma Compared with in Patients Harboring Other Driver Mutations in East Asian Populations.

20. PMID: 29935846; 2018, J Thorac Oncol;13(7):e114-e116
GOPC-ROS1 Rearrangement as an Acquired Resistance Mechanism to Osimertinib and Responding to Crizotinib Combined Treatments in Lung Adenocarcinoma.

21. PMID: 35395680; 2022, Neuro Oncol;24(10):1776-1789
Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG).

22. PMID: 35172482; 2017, JCO Precis Oncol;1():1-7
Acral Lentiginous Melanoma Harboring a ROS1 Gene Fusion With Clinical Response to Entrectinib.

23. PMID: 27780853; 2016, Clin Cancer Res;22(22):5527-5538
The Potent ALK Inhibitor Brigatinib (AP26113) Overcomes Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in Preclinical Models.

24. PMID: 30171048; 2018, Clin Cancer Res;24(24):6471-6482
Rare but Recurrent ROS1 Fusions Resulting From Chromosome 6q22 Microdeletions are Targetable Oncogenes in Glioma.

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

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

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

28. 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?

29. PMID: 32695780; 2020, Front Cell Dev Biol;8():514
The Diverse Roles of the Mucin Gene Cluster Located on Chromosome 11p15.5 in Colorectal Cancer.

30. PMID: 21851820; 2011, Exp Cell Res;317(17):2408-19
MUC6 mucin expression inhibits tumor cell invasion.

31. PMID: 35574418; 2022, Front Oncol;12():756117
Tumor Suppressive Role of MUC6 in Wilms Tumor via Autophagy-Dependent β-Catenin Degradation.

32. PMID: 33494186; 2021, Diagnostics (Basel);11(2):
The Evaluation of 17 Gastrointestinal Tumor Markers Reveals Prognosis Value for MUC6, CK17, and CD10 in Gallbladder-Cancer Patients.

33. PMID: 35353213; 2022, Histochem Cell Biol;157(6):671-684
MUC6 expression is a preferable prognostic marker for invasive mucinous adenocarcinoma of the lung.

34. PMID: 27298226; 2016, Virchows Arch;469(3):255-65
MUC1, MUC2, MUC5AC, and MUC6 in colorectal cancer: expression profiles and clinical significance.

35. PMID: 24002501; 2013, J Clin Oncol;31(29):3639-46
Cabozantinib in progressive medullary thyroid cancer.

36. PMID: 29972759; 2018, N Engl J Med;379(1):54-63
Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma.

ACT Onco® + Report

37. PMID: 28199818; 2017, J Clin Oncol;35(6):591-597
Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial.

38. PMID: 26406150; 2015, N Engl J Med;373(19):1814-23
Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma.

39. PMID: 28126333; 2017, Lancet;389(10072):917-929
First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study.

40. PMID: 24670165; 2014, N Engl J Med;370(13):1189-97
Ceritinib in ALK-rearranged non-small-cell lung cancer.

41. PMID: 25264305; 2014, N Engl J Med;371(21):1963-71
Crizotinib in ROS1-rearranged non-small-cell lung cancer.

42. PMID: 25470694; 2014, N Engl J Med;371(23):2167-77
First-line crizotinib versus chemotherapy in ALK-positive lung cancer.

43. PMID: 23724913; 2013, N Engl J Med;368(25):2385-94
Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.

44. PMID: 31838007; 2020, Lancet Oncol;21(2):271-282
Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials.

45. PMID: 31838015; 2020, Lancet Oncol;21(2):261-270
Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials.

46. PMID: 29074098; 2017, Lancet Oncol;18(12):1590-1599
Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial.

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

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

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

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

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

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

53. 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.

54. 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.

55. PMID: 28916367; 2017, Lancet;390(10106):1949-1961

ACT Onco® + Report

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial.

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