ACT Onco® + Report

PATIENT		
Name: 馮秋琴		Patient ID: 43924636
Date of Birth: Nov 09, 1978		Gender: Female
Diagnosis: NPC		
ORDERING PHYSICIAN		
Name: 楊慕華醫師		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: S11034455A	Collection site: Nasopharynx	Type: FFPE tissue
Date received: Sep 23, 2022	Lab ID: AA-22-05684	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
SMAD4 Homozygous deletion	-	Cetuximab

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.

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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
CYLD	S371*	18.4%
TP53	D281H	8.1%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr18	*SMAD4*	Homozygous deletion	0
Chr11	*CHEK1*	Heterozygous deletion	1
Chr3	*BAP1*	Heterozygous deletion	1
Chr5	*RAD50*	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 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 32% 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%.

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 4		
SMAD4 Homozygous deletion	Cetuximab	**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

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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

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
SMAD4 Homozygous deletion	Fluorouracil	**Resistant**	Clinical	Colorectal cancer

HORMONAL THERAPIES

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

OTHERS

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AG	Irinotecan-based regimens	Level 1B
Clinical Interpretation: Patients with the AG genotype and cancer who are treated with irinotecan-based regimens may have an increased risk of diarrhea and neutropenia as compared to patients with the GG genotype, or a decreased risk of diarrhea and neutropenia compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk of diarrhea and neutropenia.				

* Level of evidence was defined by PharmGKB (https://www.pharmgkb.org/page/clinAnnLevels)

Level 1A: Clinical annotations describe variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation.
Level 1B: Clinical annotations describe variant-drug combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label.
Level 2A: Variants in Level 2A clinical annotations are found in PharmGKB's Tier 1 Very Important Pharmacogenes (VIPs). These variants are in known pharmacogenes, implying causation of drug phenotype is more likely.

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

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VARIANT INTERPRETATION

CYLD S371*

Biological Impact

CYLD (cylindromatosis) gene encodes a deubiquitinase (DUB) which removes lysine-63-linked ubiquitin and functions as a negative regulator of NF-κB signaling[1][2]. Germline mutations of CYLD are often found in familial cylindromatosis and multiple familial trichoepithelioma which results in the formation of numerous benign skin adnexal tumors[3][4]. CYLD has been reported to regulate cell migration, angiogenesis, cell cycle progression and immune response[5][6][7]and loss of CYLD was associated with inhibition of apoptosis[8].

CYLD is mutated at low frequencies in various tumors and around 25% of CYLD alterations are truncating mutations (cBioPortal). S371* mutation results in a premature truncation of the CYLD protein at amino acid 371 (UniProtKB). This mutation is predicted to lead to a loss of CYLD function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

A study of breast cancer patients (n=244) indicated that lower expression of CYLD is correlated with poorer disease-free survival (DFS) and breast cancer-specific survival (BCSS)[9]. In addition, low expression of CYLD is associated with poor overall (OS) and progression free-survival (PFS) of multiple myeloma patients (n=327) and poor OS of oral squamous cell carcinoma patients (n=82)[10][11].

TP53 D281H

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[12]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[13].

D281H is a missense mutation located in the DNA-binding domain (DBD) of the p53 protein (UniProtKB). This mutation has not been characterized in the scientific literature and its effect on p53 protein function remains unknown.

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)[14].

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[15]. 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[16].

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[17][18][19]. 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)[20]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[21][22]. 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[23].

BAP1 Heterozygous deletion

Biological Impact

Breast cancer type 1 susceptibility protein (BRCA1)-associated protein (BAP1) encodes an enzyme with ubiquitin carboxyl hydrolase activity involved in the regulation of cell cycle, transcription, and double-strand DNA repair[24][25][26]. BAP1 acts as a tumor suppressor by forming a complex with BRCA1[27]. BAP1 is a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is related to renal cell carcinoma (RCC)[28]. Inactivating mutations of BAP1 were frequently observed in uveal melanoma with high metastatic risk, malignant mesothelioma and other carcinoma types, including a subtype of renal cell carcinoma and intrahepatic cholangiocarcinoma[25][29][30][31][32][33][34].

Therapeutic and prognostic relevance

In a Phase II trial (MiST1; NCT03654833), rucaparib demonstrated manageable toxicity and clinical activity in patients with relapsed malignant mesothelioma that were negative for BAP1 (n=23), BRCA1 (n=13), or both (n=10), resulting in a 12-week disease control rate (DCR) of 58% (15/26), a 24-week DCR of 23% (6/26), and an objective response rate of 11.5% (3/26)[35].The loss of BAP1 was shown to be associated with increased sensitivity to PARP inhibitor, olaparib, in renal cell carcinoma (RCC)[31]and mesothelioma cell lines[36]. However, no difference in sensitivity to the PARP inhibitor niraparib (MK4827) was observed between BAP1-mutant and wild-type mesothelioma cell[25]. BAP1 deficiency was also linked to a high tumor grade and was correlated with metastasis development in uveal melanoma[29].

An open-label, non-randomized, Phase II study (NCT03207347) has been initiated, aimed at investigating the use of niraparib in mesothelioma, uveal melanoma, renal cell carcinoma, and cholangiocarcinoma patients with tumors known to have mutations in BAP1 and other selected DNA double-strand break repair pathway genes. BAP1 loss of function mutation has been selected as an inclusion criteria for the trial examining olaparib in urothelial cancer (NCT03375307) and malignant mesothelioma (NCT04515836).

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[37]. 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[38][39]. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors[40], and CHEK1 mutations are extremely rare[37]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer[41], breast cancer[42], colorectal cancer[43], non-small cell lung (NSCLC) cancer[44], and nasopharyngeal cancer[45].

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)[46].

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)[47], 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].

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RAD50 Heterozygous deletion

Biological Impact

The RAD50 gene encodes a highly-conserved DNA double-strand break (DSB) repair factor. It forms MRN complex with NBS1 and MRE11 protein and is involved in sensing and early processing of DSB, cell cycle checkpoints, DNA recombination and maintenance of telomeres[49][50]. Mutations in the components of the MRN complex could increase susceptibility to familial breast cancer[51][52], gastric cancer[53], colorectal cancer[54], and urothelial cancer[55]. RAD50 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[56]. Besides, RAD50 deletion was also suggested as a marker of BRCAness, a phenotype shared between non-BRCA1/2-mutated ovarian cancers and BRCA1/2-mutated ovarian cancers[57].

Therapeutic and prognostic relevance

Preclinical data showed that knockdown of the RAD50 gene in ovarian cancer cell lines was significantly associated with better responses to two PARP inhibitors, olaparib and rucaparib[57]. RAD50 has been selected as an inclusion criterion for the trials examining talazoparib efficacy in HER2-negative breast cancer, olaparib efficacy in breast cancer, rucaparib efficacy in metastatic prostate cancer and niraparib efficacy in any malignancy (except prostate) (NCT02401347, NCT03207347, NCT03344965, NCT03413995).

SMAD4 Homozygous deletion

Biological Impact

The SMAD family member 4 (SMAD4) gene encodes a transcription factor that acts as a downstream effector in the TGF-β signaling pathway. Upon phosphorylated and activated by serine-threonine receptor kinase, Smad4 is the Co-Smad which recruits other activated R-Smad proteins to the Smad transcriptional complex and regulate TGF-β-targeted genes[58]. Smad4 has been identified as a haploinsufficient gene with one copy loss may lead to a weak protein expression and is insufficient to execute its original physiological function[59]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)[60][61][62][63]. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer[64], colorectal cancer (CRC)[62][65][66], and less frequently seen in other cancers such as lung adenocarcinoma[67], head and neck cancer[68][69], and cutaneous squamous cell carcinoma[70].

Therapeutic and prognostic relevance

In Chinese patients with metastatic colorectal cancer, SMAD4 or NF1 mutations are suggested as a potential biomarker for poor prognosis to cetuximab-based therapy[71]. Preclinical data demonstrated that depletion of SMAD4 by shRNA knockdown increased clonogenic survival and cetuximab resistance in HPV-negative head and neck squamous cell carcinoma cells[72].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)[73][74]. CRC patients with normal SMAD4 diploidy exhibited three-fold higher benefit of 5-FU/mitomycin-based adjuvant therapy when compared with those with SMAD4 deletion[75].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis[76][77][78][79][80][81][82][83]. In cervical cancer patients, weak cytoplasmic SMAD4 expression and absent nuclear SMAD4 expression were shown to be significantly associated with poor disease-free and overall 5-year survival[84].

US FDA-APPROVED DRUG(S)

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[85] 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[46] 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[86] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[87] 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[88] 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[89] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[90] 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[91] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

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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[47] 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)

EMBRACA[92] 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

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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.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

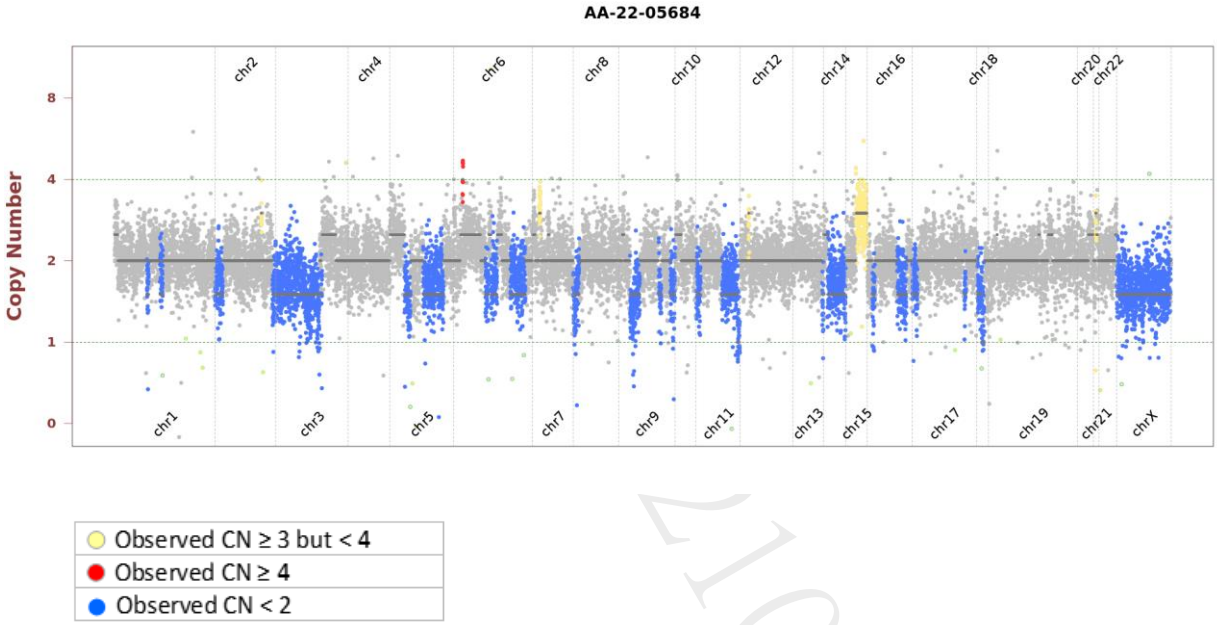
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
CYLD	S371*	9	c.1112C>A	NM_015247	COSM43402	18.4%	550
TP53	D281H	8	c.841G>C	NM_000546	COSM10943	8.1%	593

- 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.



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OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
APC	P19L	1	c.56C>T	NM_001127511	-	51.6%	624
CBL	D772E	15	c.2316T>G	NM_005188	COSM2106791	36.2%	2377
GRIN2A	I876T	14	c.2627T>C	NM_000833	-	49.7%	1486
INSR	K294R	3	c.881A>G	NM_000208	COSM2728577	49.6%	801
MSH6	G355S	4	c.1063G>A	NM_000179	COSM9102665	50.2%	1772
MUC4	A864S	2	c.2590G>T	NM_018406	-	42.2%	876
ZNF217	M727I	3	c.2181G>A	NM_006526	-	41.1%	625

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.

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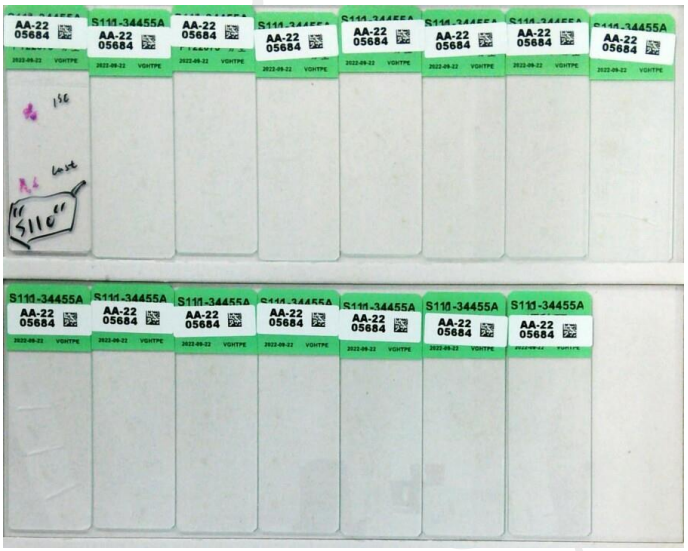
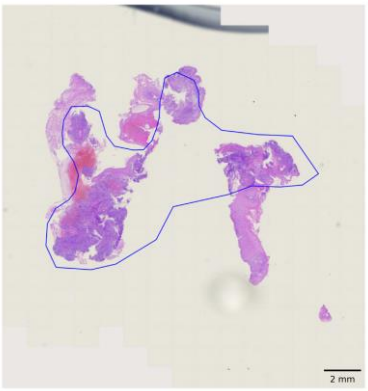
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: Oct 07, 2021
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11034455A
- Collection site: Nasopharynx
- Examined by: Dr. Chien-Ta Chiang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 20%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 65%
    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: 1064x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 98

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LIMITATIONS

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

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.

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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:
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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

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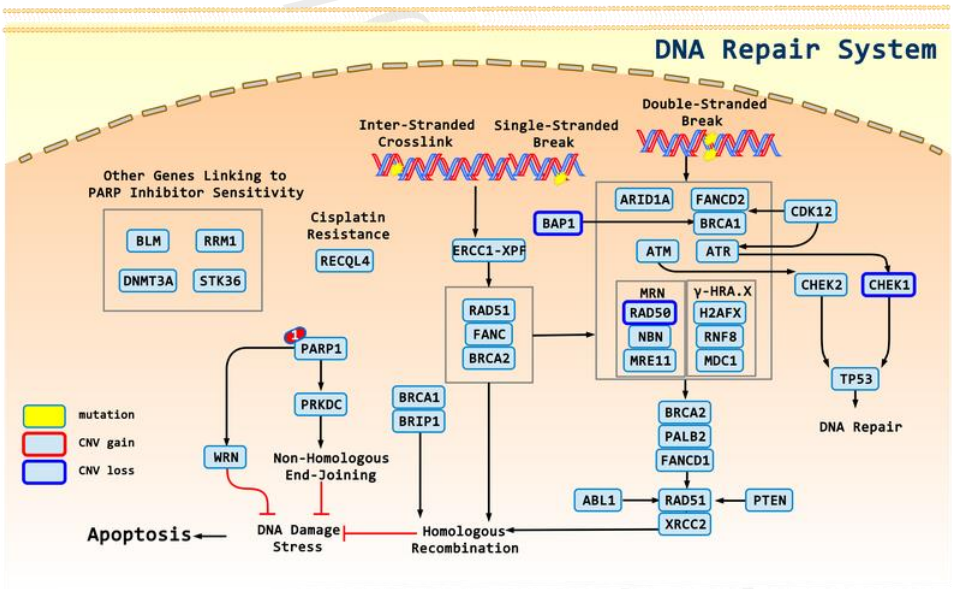
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
BAP1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RAD50	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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DISCLAIMER

法律聲明

本檢驗報告僅提供專業醫療參考，結果需經專業醫師解釋及判讀。基因突變資訊非必具備藥物或治療有效性指標，反之亦然。本檢驗報告提供之用藥指引不聲明或保證其臨床有效性，反之亦然。本基因檢測方法係由本公司研究開發，已經過有效性測試。
本檢驗報告非經本公司許可，不得私自變造、塗改，或以任何方式作為廣告及其他宣傳之用途。
本公司於提供檢驗報告後，即已完成本次契約義務，後續之報告解釋、判讀及用藥、治療，應自行尋求相關專業醫師協助，若需將報告移件其他醫師，本人應取得該醫師同意並填寫移件申請書，主動告知行動基因，行動基因僅能配合該醫師意願與時間提供醫師解說。

醫療決策需由醫師決定

任何治療與用藥需經由醫師在考慮病患所有健康狀況相關資訊包含健檢、其他檢測報告和病患意願後，依照該地區醫療照護標準由醫師獨立判斷。醫師不應僅依據單一報告結果(例如本檢測或本報告書內容)做決策。

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

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REFERENCE

1. PMID: 12917689; 2003, Nature;424(6950):793-6
CYLD is a deubiquitinating enzyme that negatively regulates NF-kappaB activation by TNFR family members.

2. PMID: 12917691; 2003, Nature;424(6950):801-5
The tumour suppressor CYLD negatively regulates NF-kappaB signalling by deubiquitination.

3. PMID: 26370355; 2015, Lancet Oncol;16(9):e460-e469
Inherited cylindromas: lessons from a rare tumour.

4. PMID: 16307661; 2005, Br J Dermatol;153(6):1213-5
Two novel CYLD gene mutations in Chinese families with trichoepithelioma and a literature review of 16 families with trichoepithelioma reported in China.

5. PMID: 18222923; 2008, J Biol Chem;283(14):8802-9
The tumor suppressor CYLD regulates microtubule dynamics and plays a role in cell migration.

6. PMID: 20194890; 2010, Blood;115(20):4130-7
CYLD regulates angiogenesis by mediating vascular endothelial cell migration.

7. PMID: 19373246; 2010, Cell Death Differ;17(1):25-34
CYLD: a tumor suppressor deubiquitinase regulating NF-kappaB activation and diverse biological processes.

8. PMID: 12917690; 2003, Nature;424(6950):797-801
Loss of the cylindromatosis tumour suppressor inhibits apoptosis by activating NF-kappaB.

9. PMID: 24398777; 2014, Breast Cancer Res Treat;143(3):447-57
Clinical significance of CYLD downregulation in breast cancer.

10. PMID: 27775078; 2017, Oncogene;36(15):2105-2115
Loss of CYLD expression unleashes Wnt signaling in multiple myeloma and is associated with aggressive disease.

11. PMID: 29235674; 2018, J Pathol;244(3):367-379
Loss of CYLD promotes cell invasion via ALK5 stabilization in oral squamous cell carcinoma.

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

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

14. 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.

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

16. 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.

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

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

ACT Onco® + Report

19. 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.

20. 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.

21. 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.

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

23. 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.

24. PMID: 20302916; 2010, Biochim Biophys Acta;1806(1):1-6
The potential role of ubiquitin c-terminal hydrolases in oncogenesis.

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

26. PMID: 19188440; 2009, Mol Cell Biol;29(8):2181-92
Association of C-terminal ubiquitin hydrolase BRCA1-associated protein 1 with cell cycle regulator host cell factor 1.

27. PMID: 18757409; 2008, Cancer Res;68(17):6953-62
BRCA1-associated protein-1 is a tumor suppressor that requires deubiquitinating activity and nuclear localization.

28. PMID: 26891804; 2016, Int J Oncol;48(4):1571-80
Genomic profiling of the genes on chromosome 3p in sporadic clear cell renal cell carcinoma.

29. PMID: 21051595; 2010, Science;330(6009):1410-3
Frequent mutation of BAP1 in metastasizing uveal melanomas.

30. PMID: 24128712; 2013, J Thorac Oncol;8(11):1430-3
Clinical characteristics of patients with malignant pleural mesothelioma harboring somatic BAP1 mutations.

31. PMID: 22683710; 2012, Nat Genet;44(7):751-9
BAP1 loss defines a new class of renal cell carcinoma.

32. PMID: 23333114; 2013, Lancet Oncol;14(2):159-167
Effects on survival of BAP1 and PBRM1 mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation.

33. PMID: 24185509; 2013, Nat Genet;45(12):1470-3
Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas.

34. PMID: 25889843; 2015, J Transl Med;13():122
BAP1 mutation is a frequent somatic event in peritoneal malignant mesothelioma.

35. PMID: 33515503; 2021, Lancet Respir Med;9(6):593-600
Rucaparib in patients with BAP1-deficient or BRCA1-deficient mesothelioma (MiST1): an open-label, single-arm, phase 2a clinical trial.

36. PMID: 28389374; 2017, J Thorac Oncol;12(8):1309-1319
A Novel BRCA1-Associated Protein-1 Isoform Affects Response of Mesothelioma Cells to Drugs Impairing BRCA1-Mediated DNA Repair.

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

38. PMID: 15261141; 2004, Cancer Cell;6(1):45-59

Chk1 is haploinsufficient for multiple functions critical to tumor suppression.

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

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

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

42. 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.

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

44. 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.

45. 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.

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

47. 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.

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

49. PMID: 9315668; 1997, Mol Cell Biol;17(10):6087-96
hMre11 and hRad50 nuclear foci are induced during the normal cellular response to DNA double-strand breaks.

50. PMID: 16467875; 2006, Cell Res;16(1):45-54
The role of NBS1 in DNA double strand break repair, telomere stability, and cell cycle checkpoint control.

51. PMID: 16385572; 2006, Int J Cancer;118(11):2911-6
Evaluation of RAD50 in familial breast cancer predisposition.

52. PMID: 24894818; 2014, Breast Cancer Res;16(3):R58
Rare key functional domain missense substitutions in MRE11A, RAD50, and NBN contribute to breast cancer susceptibility: results from a Breast Cancer Family Registry case-control mutation-screening study.

53. PMID: 18440592; 2008, Hum Pathol;39(6):925-32
Gastric cancer with high-level microsatellite instability: target gene mutations, clinicopathologic features, and long-term survival.

54. PMID: 11196187; 2001, Cancer Res;61(1):36-8
Frameshift mutations at coding mononucleotide repeats of the hRAD50 gene in gastrointestinal carcinomas with microsatellite instability.

55. PMID: 24934408; 2014, Cancer Discov;4(9):1014-21
Synthetic lethality in ATM-deficient RAD50-mutant tumors underlies outlier response to cancer therapy.

56. PMID: 16474176; 2006, Carcinogenesis;27(8):1593-9
RAD50 and NBS1 are breast cancer susceptibility genes associated with genomic instability.

57. PMID: 27016230; 2016, Gynecol Oncol;141(1):57-64
Copy number deletion of RAD50 as predictive marker of BRCAness and PARP inhibitor response in BRCA wild type ovarian cancer.

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58. PMID: 25935112; 2015, Trends Biochem Sci;40(6):296-308
Structural determinants of Smad function in TGF-β signaling.

59. PMID: 19014666; 2008, Pathogenetics;1(1):2
Smad4 haploinsufficiency: a matter of dosage.

60. PMID: 9545410; 1998, Am J Hum Genet;62(5):1129-36
A gene for familial juvenile polyposis maps to chromosome 18q21.1.

61. PMID: 8553070; 1996, Science;271(5247):350-3
DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1.

62. PMID: 8673134; 1996, Nat Genet;13(3):343-6
Evaluation of candidate tumour suppressor genes on chromosome 18 in colorectal cancers.

63. PMID: 18662538; 2008, Cell;134(2):215-30
TGFbeta in Cancer.

64. PMID: 9135016; 1997, Cancer Res;57(9):1731-4
Tumor-suppressive pathways in pancreatic carcinoma.

65. PMID: 23139211; 2013, Cancer Res;73(2):725-35
SMAD2, SMAD3 and SMAD4 mutations in colorectal cancer.

66. PMID: 22810696; 2012, Nature;487(7407):330-7
Comprehensive molecular characterization of human colon and rectal cancer.

67. PMID: 25890228; 2015, World J Surg Oncol;13():128
Clinical outcome and expression of mutant P53, P16, and Smad4 in lung adenocarcinoma: a prospective study.

68. PMID: 19841540; 2009, J Clin Invest;119(11):3208-11
Smad4: gatekeeper gene in head and neck squamous cell carcinoma.

69. PMID: 15867212; 2005, Clin Cancer Res;11(9):3191-7
Differences in Smad4 expression in human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck squamous cell carcinoma.

70. PMID: 25589618; 2015, Clin Cancer Res;21(6):1447-56
Genomic analysis of metastatic cutaneous squamous cell carcinoma.

71. 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.

72. PMID: 28522603; 2017, Clin Cancer Res;23(17):5162-5175
SMAD4 Loss Is Associated with Cetuximab Resistance and Induction of MAPK/JNK Activation in Head and Neck Cancer Cells.

73. PMID: 16144935; 2005, Clin Cancer Res;11(17):6311-6
SMAD4 levels and response to 5-fluorouracil in colorectal cancer.

74. PMID: 24384683; 2014, Br J Cancer;110(4):946-57
Loss of Smad4 in colorectal cancer induces resistance to 5-fluorouracil through activating Akt pathway.

75. PMID: 12237773; 2002, Br J Cancer;87(6):630-4
SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer.

76. PMID: 25749173; 2015, Transl Oncol;8(1):18-24
A Meta-Analysis of SMAD4 Immunohistochemistry as a Prognostic Marker in Colorectal Cancer.

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77. PMID: 19478385; 2009, Cell Oncol;31(3):169-78
Presence of a high amount of stroma and downregulation of SMAD4 predict for worse survival for stage I-II colon cancer patients.

78. PMID: 25681512; 2015, J Clin Pathol;68(5):341-5
Smad4 inactivation predicts for worse prognosis and response to fluorouracil-based treatment in colorectal cancer.

79. PMID: 26861460; 2016, Clin Cancer Res;22(12):3037-47
Reduced Expression of SMAD4 Is Associated with Poor Survival in Colon Cancer.

80. PMID: 26947875; 2016, Transl Oncol;9(1):1-7
Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis.

81. PMID: 25760429; 2015, Pancreas;44(4):660-4
SMAD4 expression predicts local spread and treatment failure in resected pancreatic cancer.

82. PMID: 22504380; 2012, Pancreas;41(4):541-6
SMAD4 genetic alterations predict a worse prognosis in patients with pancreatic ductal adenocarcinoma.

83. PMID: 19584151; 2009, Clin Cancer Res;15(14):4674-9
SMAD4 gene mutations are associated with poor prognosis in pancreatic cancer.

84. PMID: 18425078; 2008, Mod Pathol;21(7):866-75
Expression of Smad2 and Smad4 in cervical cancer: absent nuclear Smad4 expression correlates with poor survival.

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

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

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

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

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

90. 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.

91. 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.

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