

ACT Onco[®] + Report

PATIENT		
Name: 林芷萱		Patient ID: 45910369
Date of Birth: May 10, 2013		Gender: Female
Diagnosis: Ewing sarcoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11106535		Type: FFPE tissue
Collection site: Lung		
Date received: Mar 31, 2022	Lab ID: AA-22-01655	D/ID: NA

ABOUT ACT Onco[®]+

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
RB1 Homozygous deletion	-	Abemaciclib, Palbociclib, Ribociclib

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 criteria 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
PIK3C2G	Y1103fs	36.5%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr13	RB1	Homozygous deletion	0
Chr11	ATM, MRE11	Heterozygous deletion	1
Chr13	BRCA2	Heterozygous deletion	1
Chr15	RAD51	Heterozygous deletion	1
Chr17	NF1	Heterozygous deletion	1
Chr18	SMAD4	Heterozygous deletion	1
Chr19	STK11	Heterozygous deletion	1
Chr22	CHEK2, NF2	Heterozygous deletion	1
Chr7	KMT2C	Heterozygous deletion	1

- Fusions

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

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	< 1 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 48% 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		
RB1 Homozygous deletion	Abemaciclib, Palbociclib, Ribociclib	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
RB1 Homozygous deletion	Cisplatin	Sensitive	Clinical	Bladder carcinoma
	FAC T/FAC taxane/doxorubicin	Sensitive	Clinical	Breast cancer
PIK3C2G Y1103fs	Oxaliplatin	Resistant	Clinical	Colorectal cancer

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
RB1 Homozygous deletion	Tamoxifen	Resistant	Clinical	Breast cancer

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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

PIK3C2G Y1103fs

Biological Impact

The PIK3C2G gene encodes a protein contains a lipid kinase catalytic domain as well as a C-terminal C2 domain, a characteristic of the class II phosphoinositide 3-kinases (PI3Ks). C2 domains act as calcium-dependent phospholipid binding motifs that mediate translocation of proteins to membranes, and may also mediate protein-protein interactions^{[1][2]}. PIK3C2G plays roles in the regulation of protein trafficking signaling pathways and glycogen synthase^[3]. Inactivating mutations of PIK3C2G are found in melanomas^[4].

Y1103fs mutation results in a change in the amino acid sequence beginning at 1103, likely to cause premature truncation of the functional PIK3C2G protein (UniProtKB). This mutation is predicted to lead to a loss of PIK3C2G protein function, despite not being characterized in the literature.

Therapeutic and prognostic relevance

Low copy number of PIK3C2G has been reported to associate with shorter overall survival and recurrence-free survival in stage III colorectal cancer patients treated with oxaliplatin-based chemotherapy^[5].

ATM Heterozygous deletion

Biological Impact

The ataxia-telangiectasia mutated protein kinase (ATM) gene encodes a PI3K-related serine/threonine protein kinase involved in genomic integrity maintenance and plays central roles in DNA double-strand break (DSB) repair, which can be induced by ionizing radiation, chemotherapy drugs, or oxidative stress^[6]. ATM is a well-characterized tumor suppressor gene, hereditary mutations and haploinsufficiency of ATM result in markedly increased susceptibility to a variety of cancer types^{[7][8][9][10][11]}. Results from a case-cohort study of colorectal cancer and cancer-free control individuals suggested that germline pathogenic mutations in ATM and PALB2 should be added to established CRC risk genes as part of standard tumor genetic testing panels^[12]. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies^{[13][14][15][16]} and a board range of tumors such as prostate cancer^[17], head and neck squamous cell carcinoma (HNSCC)^[18], pancreatic cancer^[19], lung adenocarcinoma^[20], breast cancer^[21], and ovarian cancer^[8].

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^[22].

In addition, ATM has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer^[23] or prostate cancer^[24], niraparib efficacy in pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in advanced or metastatic cancer (NCT02286687), HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

Besides, another randomized, double-blind Phase II trial in patients with metastatic gastric cancer has shown that addition of olaparib to paclitaxel significantly increased the overall survival in both the overall population and patients with low or undetectable ATM protein expression^[25]. Also, a prospective study in muscle-invasive bladder cancer patients suggested that genomic alternations in the DNA repair genes ATMs, RB1 and FANCC could be recognized as biomarkers predictive of response to cisplatin-based neoadjuvant chemotherapy^[26]. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in

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patients with breast cancer^[27].

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer^[28].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair^[29]. 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^[30]. 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^[31]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers^[32].

Therapeutic and prognostic relevance

The U.S. FDA has approved olaparib in advanced ovarian cancer under several settings including (1) first-line maintenance treatment for patients with deleterious or suspected deleterious germline or somatic BRCA mutation who are in complete or partial response to first-line platinum-based chemotherapy^[33]; (2) in combination with bevacizumab as first-line maintenance treatment for patients with homologous recombination deficiency (HRD)-positive status^[34]; (3) maintenance treatment for patients with germline BRCA-mutated recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy^{[35][36]}; (4) treatment for patients with germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy^[37]. In addition, olaparib has also been approved in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in either neoadjuvant, adjuvant, or metastatic setting^[38] and germline BRCA-mutated metastatic pancreatic cancer^[39]. Of note, in May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate^[22].

Rucaparib has been approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and patients with BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more chemotherapies^{[23][40]}. In May 2020, the U.S. FDA also approved rucaparib to treat adult patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy (TRITON2, NCT02952534).

The U.S. FDA also approved niraparib for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy and patients who have been treated with three or more prior lines of chemotherapy and associated with HRD positive status^{[41][42][43]}. In addition, talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer^[44].

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CHEK2 Heterozygous deletion

Biological Impact

The checkpoint kinase 2 (CHEK2 or CHK2) gene encodes a serine/threonine protein kinase involved in transducing DNA damage signals that are required for both the intra-S phase and G2/M checkpoints^[45]. CHEK2 heterozygosity has been shown to cause haploinsufficient phenotypes that can contribute to tumorigenesis through inappropriate S phase entry, accumulation of DNA damage during replication, and failure to restrain mitotic entry^{[46][47]}. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers^{[48][49][50][51][52]}.

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^[22].

In addition, CHEK2 has been determined as an inclusion criterion for the trials evaluating rucaparib efficacy in ovarian cancer or prostate cancer (NCT03533946)^{[23][24]}, niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

In a phase 2 trial, two prostate cancer patients harboring CHEK2 homozygous deletion was enrolled. One of the two patients had a response to olaparib^[53].

KMT2C Heterozygous deletion

Biological Impact

Lysine methyltransferase 2C (KMT2C) gene encodes the histone methyltransferase MLL3, which methylates lysine residue four on the tail of histone H3 (H3K4)^[54] and regulates the gene expression during development and hematopoiesis^{[55][56][57]}. KMT2C is ubiquitously expressed, and its function is essential for normal embryonal development and cell proliferation^[58]. Genetic deletion of the region containing KMT2C is the most common chromosomal abnormality in acute myeloid leukemia^{[59][60]}, and KMT2C mutation has been reported in breast cancer, cutaneous squamous cell carcinoma, and leukemia^{[61][62][63][64][65]}. KMT2C was implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^[66]. Animal studies revealed that MLL3 haploinsufficiency enhances hematopoietic stem cells (HSCs) self-renewal capacity and induces extensive division of HSCs (AACR; Cancer Res 2018;78(13 Suppl): Abstract nr 4996).

Therapeutic and prognostic relevance

Preclinical studies of cell lines and xenograft models demonstrated that cells with reduced KMT2C expression and activity are deficient in homologous recombination-mediated double-strand break DNA repair and therefore, are more sensitive to olaparib, a PARP1/2 inhibitor^[67].

A meta-analysis indicated that low levels of KMT2C expression was associated with better overall survival in pancreatic ductal adenocarcinoma (PDAC) patients^[68]. However, another study of ER-positive breast cancer patients (n = 401) demonstrated that low KMT2C expression was associated with worse overall survival^[69].

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MRE11 Heterozygous deletion

Biological Impact

The MRE11 gene encodes a protein that forms the MRE11-RAD50-NBS (MRN) complex involved in sensing and repairing DNA double-strand breaks via homologous recombination and non-homologous end joining^{[70][71]}. MRE11 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 function^[70]. The carrier of MRE11 mutation may confer elevated risks for numerous types of cancers including breast cancer, ovarian cancer, endometrial cancer, colorectal cancer, and lymphoid cancer^{[70][71][72][73][74][75][76]}.

Therapeutic and prognostic relevance

In a Phase II clinical trial (n=50), one castration-resistant prostate cancer patient harboring an MRE11 inactivating mutation responded to olaparib^[53]. Preclinically, loss of MRE11 also predicted sensitivity to PARP inhibitor talazoparib and ABT-888 in endometrial cancer^[77] and microsatellite unstable colorectal cancer (CRC) cell lines^[78].

CRC patients with tumor deficient of MRE11 showed initially reduced disease-free survival (DFS) and overall survival (OS) but improved long-term DFS and OS compared with patients with an intact MRE11^[79].

NF1 Heterozygous deletion

Biological Impact

The neurofibromin 1 (NF1) gene encodes a GTPase activating protein (GAP) which is an important negative regulator of the Ras cellular proliferation pathways^{[80][81][82][83]}. Besides, NF1 also physically interacts with the N-terminal domain of focal adhesion kinase (FAK) and involves in the regulation of cell adhesion, growth, and other pathways^{[84][85]}. NF1 is considered a classical haploinsufficient tumor suppressor gene with loss of one allele through inherited or acquired mutation may lead to reduced protein expression and is insufficient to execute normal cellular functions contributing to tumor development^{[86][87][88][89][90]}. NF1 syndrome is a germline condition resulting in a predisposition to several types of cancer such as neurofibromas, melanoma, lung cancer, ovarian cancer, breast cancer, colorectal cancer, hematological malignancies^{[91][92][93]}. Meanwhile, sporadic NF1 mutations have been observed in multiple cancer types^[94], including myelodysplastic syndromes, melanomas, colon cancer^[95], glioblastomas^[96], lung cancer^[97], ovarian cancer, and breast cancer^[91].

Therapeutic and prognostic relevance

In April 2020, the U.S. FDA has approved selumetinib for pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN). A phase II trial (NCT02664935, NLMT) demonstrated that selumetinib in combination with docetaxel resulted in a confirmed ORR of 28.5% (4/14), durable clinical benefit (DCB) rate of 50% (7/14), and mPFS of 5.3 months in lung adenocarcinoma patients harboring NF1 loss^[98]. NF1 loss has been determined as an inclusion criterion for the trials evaluating selumetinib efficacies in lung cancer (NCT02664935) and NF1-associated tumors (NCT03326388).

NF1 depletion has been associated with drug resistance to RAF and EGFR inhibitors, tamoxifen, and retinoic acid^{[94][99]}. For example, loss of NF1 was identified in patients with lung adenocarcinomas or colorectal cancer who presented resistance to anti-EGFR treatment, including erlotinib, gefitinib, afatinib, and cetuximab, respectively^{[100][101][102]}. Loss of NF1 in patients with BRAF-mutated melanomas was also suggested conferring resistance to BRAF inhibitors^{[103][104][105][106]}.

Notably, preclinical studies further revealed that the addition of a MEK inhibitor could restore the sensitivity to erlotinib^[100]. Also, in a liquid biopsy-based ctDNA profiling study of HER2-positive metastatic gastric cancer, NF1 loss (either induced by mutation or deletion) was suggested as a novel mechanism contributes to trastuzumab resistance. The cell-based study also showed that the trastuzumab resistance could be overcome with a combination of HER2 and

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MEK/ERK inhibitors^[107]. A case study had reported that MEK inhibitor, trametinib, was effective in a treatment-refractory neurofibromatosis type I-associated glioblastoma^[108]. Various preclinical data had also supported the activity of MEK and mTOR inhibitors in NF1-deficient tumors^{[109][110][111][112][113][114]}. In an NGS-based study, patients harboring mutations in the mTOR pathway, including mTOR, TSC1, TSC2, NF1, PIK3CA, and PIK3CG responded to everolimus^[115].

NF2 Heterozygous deletion

Biological Impact

The neurofibromin (NF2) gene encodes the protein Merlin, a tumor suppressor that functions as a negative regulator of the PI3K/AKT/mTOR pathway^{[116][117][118]}. NF2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^[119]. Inactivation germline mutations in the NF2 are associated with the hereditary neurofibromatosis type 2, a disorder characterized by the growth of noncancerous tumors in the nervous system^{[116][120]}. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas^[121], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers^[122].

Therapeutic and prognostic relevance

Genomic alterations with activating effects on the mTOR signaling pathway have been identified to confer sensitivity to everolimus across multiple cancer types^{[123][124][125][115]}. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer and urothelial carcinoma^{[126][127]}, both harboring NF2 truncating mutations. Preclinical evidence has shown the efficacy of MEK1/2 inhibitor selumetinib in KRAS-mutant thyroid cancer model with NF2 loss^[128].

Analysis of afatinib-plus-cetuximab-resistant biopsy specimens revealed a loss-of-function alteration in genes that modulate mTOR signaling pathway, including NF2 and TSC1^[129].

RAD51 Heterozygous deletion

Biological Impact

The RAD51 gene encodes a recombinase that is crucial for homologous recombination (HR)-mediated repair of double-strand DNA breaks (DSBs) by forming complexes with known tumor suppressors including BRCA1, BRCA2, and PALB2^{[130][131][132]}. RAD51 has been characterized as a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^[133]. Overexpression of RAD51 has been observed in many cancer cells, including pancreatic cancer and breast cancer and its hyperexpression is implicated in drug resistance^{[134][135][136][137][138][139][140]}. Germline mutations in RAD51 are associated with increased susceptibility to breast cancer^{[141][142][143][144]}.

Therapeutic and prognostic relevance

RAD51 loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer^[145]; rucaparib efficacy in solid tumor (NCT04171700); talazoparib efficacy in lung cancer (NCT03377556); niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate cancer) (NCT03207347).

Preclinical studies showed that decreased RAD51 expression could sensitize cells to olaparib-induced tumor cell cytotoxicity^{[146][147]}.

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RB1 Homozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication^[148]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis^[149]. RB1 has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^{[150][151][152]}. Deletion or inactivating mutation of RB1 is found in a number of tumors, including lung, prostate, bladder, breast cancers and sarcomas. RB1 mutations are found in approximately half of all retinoblastoma cases^[153].

Therapeutic and prognostic relevance

A deleterious mutation in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response and better overall survival to cisplatin-based chemotherapy for muscle-invasive bladder cancer patients^[26]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytosine (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy^[154].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer^{[155][156]}.

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment^[157]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib^[158].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)^{[159][160]}. Analyses of repeat biopsy samples from patients with EGFR-mutant adenocarcinoma that had transformed to the SCLC subtype have revealed that 100% of these patients have loss of RB1 and may be the alteration that induces this non-small-cell to small-cell transformation^{[156][161]}.

SMAD4 Heterozygous 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^[162]. 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^[163]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)^{[164][165][166][167]}. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer^[168], colorectal cancer (CRC)^{[166][169][170]}, and less frequently seen in other cancers such as lung adenocarcinoma^[171], head and neck cancer^{[172][173]}, and cutaneous squamous cell carcinoma^[174].

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^[101]. 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^[175].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)^{[176][177]}. 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^[178].

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Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis^{[179][180][181][182][183][184][185][186]}. 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^[187].

STK11 Heterozygous deletion

Biological Impact

The serine/threonine kinase 11 (STK11, also known as LKB1) gene encodes the multifunctional serine/threonine kinase, a tumor suppressor that functions as an inhibitor for the mTOR signaling pathway^{[188][189]}. STK11 is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^{[190][191]}. In the mouse model, loss of STK11 promotes aggressive endometrial and squamous cell carcinomas^{[192][193]}. Mutations in STK11 have been found in lung, breast, cervical, testicular, and liver cancers, as well as malignant melanoma, pancreatic and biliary carcinoma^[194]. Germline mutations in STK11 are found in 30-70% of Peutz-Jeghers syndrome^[195].

Therapeutic and prognostic relevance

A clinical study in a pancreatic cancer patient with Peutz-Jeghers syndrome whose tumor harboring an STK11 D194E mutation coupled with the loss of heterozygosity of the other STK11 allele displayed partial response to the everolimus treatment^[196]. In another clinical case study, an adrenocorticotrophic pituitary carcinoma patient whose tumor bearing an STK11 inactivating mutation responded to a combination of everolimus and radiotherapy^[197].

Preclinical data suggested that lung cancer cell lines with STK11 inactivating mutations may confer increased sensitivity to the MEK-1 and MEK-2 inhibitor, trametinib^[198].

Inactivating mutations of STK11 was shown to be associated with resistance to immune checkpoint blockade in KRAS-mutant lung adenocarcinoma (LUAC) and NSCLC (DOI: 10.1200/JCO.2017.35.15_suppl.9016)^{[199][200][201]}. It was proposed that loss of STK11 negatively impacts the number and function of tumor-infiltrating T cells (TILs) and PD-L1 expression on tumor cells and therefore results in an ineffective response to PD-1-targeting antibodies^[202].

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US FDA-APPROVED DRUG(S)

Binimetinib (MEKTOVI)

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

- FDA Approval Summary of Binimetinib (MEKTOVI)

MEKTOVI ^[203] NCT01909453	Melanoma (Approved on 2018/06/27)
	BRAF V600E/K
	Encorafenib + binimetinib vs. Vemurafenib [PFS(M): 14.9 vs. 7.3]

Cobimetinib (COTELLIC)

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

- FDA Approval Summary of Cobimetinib (COTELLIC)

coBRIM ^[204] NCT01689519	Melanoma (Approved on 2015/11/10)
	BRAF V600E/K
	Cobimetinib + vemurafenib vs. Placebo + vemurafenib [PFS(M): 12.3 vs. 7.2]

Everolimus (AFINITOR)

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

- FDA Approval Summary of Everolimus (AFINITOR)

RADIANT-4 ^[205] NCT01524783	Lung or gastrointestinal neuroendocrine tumor (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2 ^[206] NCT00863655	Breast cancer (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
EXIST-2 NCT00790400	Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma (Approved on 2012/04/26)
	-
	Everolimus vs. Placebo [ORR(%): 41.8 vs. 0]
RADIANT-3 ^[207] NCT00510068	Pancreatic neuroendocrine tumor (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1 ^[208] NCT00789828	Subependymal giant cell astrocytoma (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]

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RECORD-1 ^[209] NCT00410124	Renal cell carcinoma (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

Niraparib (Zejula)

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

- FDA Approval Summary of Niraparib (Zejula)

PRIMA NCT02655016	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2020/04/29)
	-
	Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
QUADRA ^[43] NCT02354586	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2019/10/23)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Niraparib [ORR(%): 24.0, DOR(M): 8.3]
NOVA ^[42] 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)
	gBRCA
	Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound ^[22] NCT02987543	Prostate cancer (Approved on 2020/05/19)
	ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm, RAD54Lm
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1 ^[34] NCT02477644	Ovarian cancer (Approved on 2020/05/08)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO ^[39] NCT02184195	Pancreatic adenocarcinoma (Approved on 2019/12/27)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1 ^[33] NCT01844986	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2018/12/19)
	Germline or somatic BRCA-mutated (gBRCAm or sBRCAm)
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]

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OlympiAD ^[38] NCT02000622	Breast cancer (Approved on 2018/02/06)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21 ^[210] NCT01874353	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	gBRCA+
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19 ^[211] NCT00753545	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]
Study 42 ^[212] NCT01078662	Ovarian cancer (Approved on 2014/12/19)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

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+, sBRCA
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3 ^[23] NCT01968213	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2018/04/06)
	All HRD tBRCA
	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]
ARIEL2 ^[213] NCT01482715, NCT01891344	Ovarian cancer (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation
	Rucaparib [ORR(%): 54.0]

Selumetinib (KOSELUGO)

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

- FDA Approval Summary of Selumetinib (KOSELUGO)

SPRINT NCT01362803	Plexiform neurofibromas (Approved on 2020/04/10)
	Neurofibromatosis type 1
	Selumetinib [ORR(%): 66.0]

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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 ^[44] NCT01945775	Breast cancer (Approved on 2018/10/16)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

Temsirolimus (TORISEL)

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

- FDA Approval Summary of Temsirolimus (TORISEL)

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

Trametinib (MEKINIST)

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

- FDA Approval Summary of Trametinib (MEKINIST)

BRF117019 ^[215] NCT02034110	Anaplastic thyroid cancer (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928 ^[216] NCT01336634	Non-small cell lung cancer (Approved on 2017/06/22)
	BRAF V600E
	Trametinib + dabrafenib vs. Dabrafenib [ORR(%): 63.0 vs. 27.0, DOR(M): 12.6 vs. 9.9]
COMBI-d ^[217] NCT01584648	Melanoma (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC ^[218] NCT01245062	Melanoma (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

D=day; W=week; M=month

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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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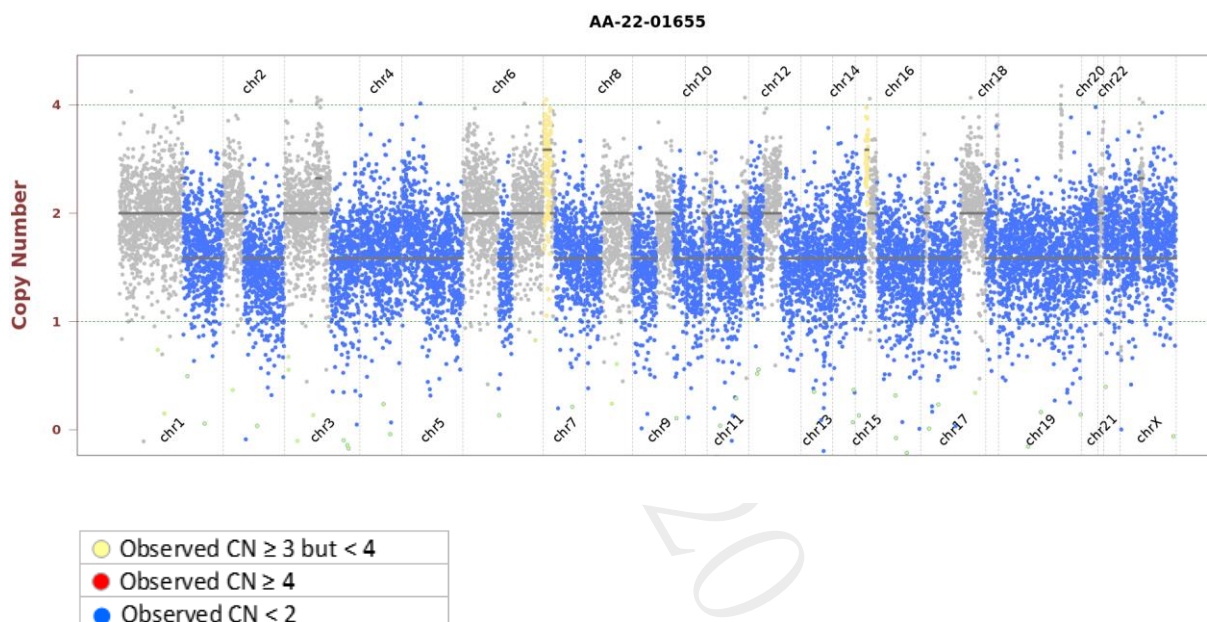
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
PIK3C2G	Y1103fs	24	c.3299_3306dup	NM_004570	COSM2003816	36.5%	1062

- 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
ADAMTSL1	D1494N	25	c.4480G>A	NM_001040272	-	36.7%	207
BRIP1	E454V	10	c.1361A>T	NM_032043	-	46.7%	1051
ERBB4	Splice region	-	c.3481+4T>G	NM_005235	-	68.9%	972
FLT3	M665I	16	c.1995G>T	NM_004119	-	7.3%	913
IRF4	H278Y	7	c.832C>T	NM_002460	-	45.3%	1381
KAT6A	P1799A	17	c.5395C>G	NM_006766	-	30.4%	876
KIT	R956Q	21	c.2867G>A	NM_000222	-	39.4%	2248
MUC16	A2401S	1	c.7201G>T	NM_024690	-	28.0%	1434
MUC16	D6322F	3	c.18964_18965delinsTT	NM_024690	-	69.6%	1265
MUC16	S1670R	1	c.5008A>C	NM_024690	-	20.8%	957
MUC6	D440del	11	c.1318_1320del	NM_005961	-	79.8%	99
TAF1	A19fs	1	c.29_53dup	NM_138923	-	26.0%	695
USH2A	Splice region	-	c.1645-8del	NM_206933	-	56.1%	1409

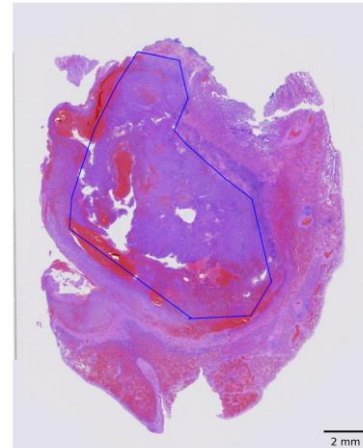
Note:

- 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: Feb 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11106535
- Collection site: Lung
- Examined by: Dr. Chien-Ta Chiang
 1. The percentage of viable tumor cells in total cells in the whole slide (%): 25%
 2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 60%
 3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
 4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
 5. Additional comment: NA
- Manual macrodissection: 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: 1276x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 100

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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 ≥ 25 , allele frequency $\geq 5\%$ and actionable variants with allele frequency $\geq 2\%$ were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at $100\times \geq 85\%$ with a mean coverage $\geq 500\times$.

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).

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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 $\geq 10\%$; (4) Fusions annotated in Quiver Gene Fusion Database.

DATABASE USED

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

Variant Analysis:

醫檢師張筑芻 博士
Chu-Yuan Chang Ph.D.
檢字第 020115 號



Sign Off

醫檢師張筑芻 博士
Chu-Yuan Chang Ph.D.
檢字第 020115 號



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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*	BTX	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*	SLC01B1*
SLC01B3*	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOC1*	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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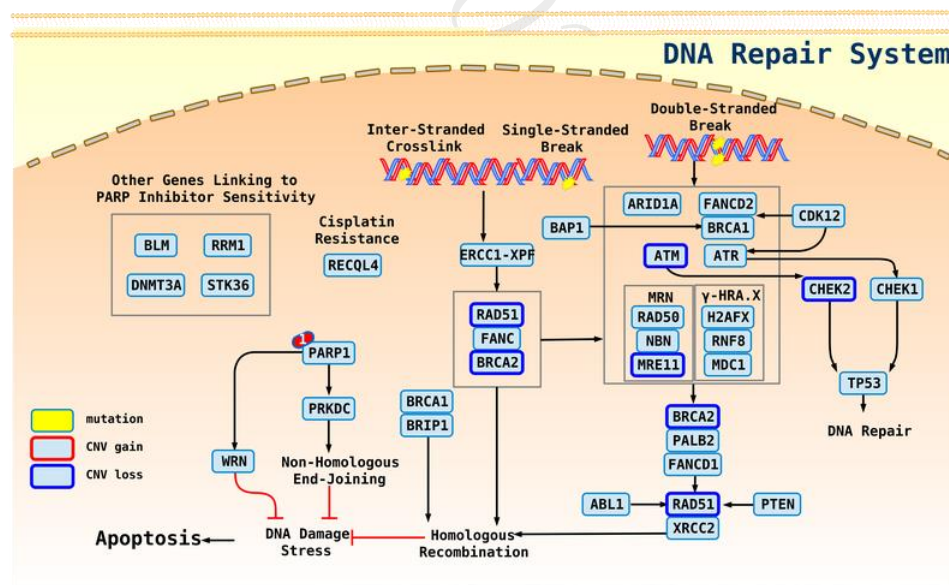
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

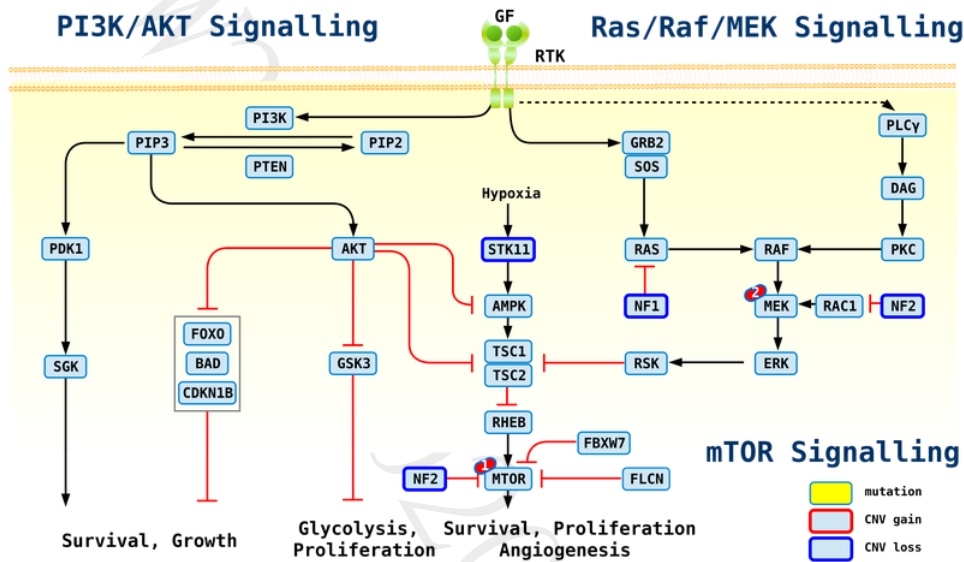
Gene	Therapies	Possible effect
NF1	Binimetinib, Cobimetinib, Trametinib, Selumetinib, Everolimus, Temsirolimus	sensitive
STK11	Binimetinib, Cobimetinib, Trametinib, Everolimus, Temsirolimus	sensitive
NF2	Everolimus, Temsirolimus	sensitive
ATM	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
CHEK2	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
KMT2C	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
MRE11	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
RAD51	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
NF1	Afatinib, Erlotinib, Gefitinib, Lapatinib, Vemurafenib, Cetuximab, Trastuzumab	resistant
SMAD4	Cetuximab	resistant

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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

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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。

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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: 22507127; 2012, Biochem J;443(3):587-601
Regulation and cellular functions of class II phosphoinositide 3-kinases.
2. PMID: 27644332; 2017, J Med Chem;60(1):47-65
Class II Phosphoinositide 3-Kinases as Novel Drug Targets.
3. PMID: 30691999; 2019, Trends Cell Biol;29(4):339-359
Class II PI3K Functions in Cell Biology and Disease.
4. PMID: 28522871; 2017, Sci Rep;7(1):2098
MUG-Mel2, a novel highly pigmented and well characterized NRAS mutated human melanoma cell line.
5. PMID: 25785104; 2015, Int J Clin Exp Med;8(1):1137-43
PIK3C2G copy number is associated with clinical outcomes of colorectal cancer patients treated with oxaliplatin.
6. PMID: 22079189; 2012, Trends Biochem Sci;37(1):15-22
The ATM protein kinase and cellular redox signaling: beyond the DNA damage response.
7. PMID: 1548942; 1992, Leukemia;6 Suppl 1(1):8-13
Cancer susceptibility in ataxia-telangiectasia.
8. PMID: 12810666; 2003, Cancer Res;63(12):3325-33
Contributions of ATM mutations to familial breast and ovarian cancer.
9. PMID: 1961222; 1991, N Engl J Med;325(26):1831-6
Incidence of cancer in 161 families affected by ataxia-telangiectasia.
10. PMID: 28779002; 2017, J Med Genet;54(11):732-741
Rare, protein-truncating variants in ATM, CHEK2 and PALB2, but not XRCC2, are associated with increased breast cancer risks.
11. PMID: 16400190; 2006, Carcinogenesis;27(4):848-55
Atm-haploinsufficiency enhances susceptibility to carcinogen-induced mammary tumors.
12. PMID: 29478780; 2018, Am J Hum Genet;102(3):401-414
Inherited DNA-Repair Defects in Colorectal Cancer.
13. PMID: 9488043; 1998, Oncogene;16(6):789-96
ATM is usually rearranged in T-cell prolymphocytic leukaemia.
14. PMID: 11429421; 2001, J Clin Pathol;54(7):512-6
Ataxia telangiectasia gene mutations in leukaemia and lymphoma.
15. PMID: 11756177; 2002, Blood;99(1):238-44
ATM gene inactivation in mantle cell lymphoma mainly occurs by truncating mutations and missense mutations involving the phosphatidylinositol-3 kinase domain and is associated with increasing numbers of chromosomal imbalances.
16. PMID: 21993670; 2012, Haematologica;97(1):47-55
ATM gene alterations in chronic lymphocytic leukemia patients induce a distinct gene expression profile and predict disease progression.
17. PMID: 22981675; 2013, Eur Urol;63(5):920-6
Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity.
18. PMID: 22410096; 2012, Oral Oncol;48(8):698-702
Correlation of Ataxia-Telangiectasia-Mutated (ATM) gene loss with outcome in head and neck squamous cell carcinoma.
19. PMID: 23103869; 2012, Nature;491(7424):399-405
Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes.

ACT Onco[®] + Report

20. PMID: 18948947; 2008, Nature;455(7216):1069-75
Somatic mutations affect key pathways in lung adenocarcinoma.
21. PMID: 30537493; 2019, Hum Pathol;86():85-92
Molecular characterization of metaplastic breast carcinoma via next-generation sequencing.
22. PMID: 32343890; 2020, N Engl J Med;382(22):2091-2102
Olaparib for Metastatic Castration-Resistant Prostate Cancer.
23. 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.
24. PMID: 32086346; 2020, Clin Cancer Res;26(11):2487-2496
Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: Analysis From the Phase II TRITON2 Study.
25. PMID: 26282658; 2015, J Clin Oncol;33(33):3858-65
Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer.
26. PMID: 26238431; 2015, Eur Urol;68(6):959-67
Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy in Muscle-invasive Bladder Cancer.
27. PMID: 22420423; 2012, Breast Cancer Res;14(2):R47
Low expression levels of ATM may substitute for CHEK2 /TP53 mutations predicting resistance towards anthracycline and mitomycin chemotherapy in breast cancer.
28. PMID: 23154512; 2012, Oncotarget;3(11):1348-55
Loss of expression of the double strand break repair protein ATM is associated with worse prognosis in colorectal cancer and loss of Ku70 expression is associated with CIN.
29. PMID: 11239455; 2001, Mol Cell;7(2):263-72
BRCA2 is required for homology-directed repair of chromosomal breaks.
30. PMID: 17597348; 2007, Ann Surg Oncol;14(9):2510-8
Heterogenic loss of the wild-type BRCA allele in human breast tumorigenesis.
31. PMID: 22193408; 2011, Nat Rev Cancer;12(1):68-78
BRCA1 and BRCA2: different roles in a common pathway of genome protection.
32. 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?
33. PMID: 30345884; 2018, N Engl J Med;379(26):2495-2505
Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.
34. PMID: 31851799; 2019, N Engl J Med;381(25):2416-2428
Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer.
35. PMID: 28884698; 2017, Lancet Oncol;18(9):e510
Correction to Lancet Oncol 2017; 18: 1274-84.
36. PMID: 22452356; 2012, N Engl J Med;366(15):1382-92
Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.
37. PMID: 26187614; 2015, Clin Cancer Res;21(19):4257-61
FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with

ACT Onco[®] + Report

Three or More Lines of Chemotherapy.

38. PMID: 28578601; 2017, N Engl J Med;377(6):523-533
Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation.
39. PMID: 31157963; 2019, N Engl J Med;381(4):317-327
Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer.
40. PMID: 28882436; 2017, Gynecol Oncol;147(2):267-275
Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2.
41. PMID: 31562799; 2019, N Engl J Med;381(25):2391-2402
Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.
42. PMID: 27717299; 2016, N Engl J Med;375(22):2154-2164
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer.
43. PMID: 30948273; 2019, Lancet Oncol;20(5):636-648
Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial.
44. PMID: 30110579; 2018, N Engl J Med;379(8):753-763
Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation.
45. PMID: 21088254; 2011, Clin Cancer Res;17(3):401-5
Tumor suppressor CHK2: regulator of DNA damage response and mediator of chromosomal stability.
46. PMID: 15261141; 2004, Cancer Cell;6(1):45-59
Chk1 is haploinsufficient for multiple functions critical to tumor suppression.
47. PMID: 15539958; 2005, Cell Cycle;4(1):131-9
Chk1 is essential for tumor cell viability following activation of the replication checkpoint.
48. PMID: 23296741; 2013, Fam Cancer;12(3):473-8
The risk of gastric cancer in carriers of CHEK2 mutations.
49. PMID: 24713400; 2014, Hered Cancer Clin Pract;12(1):10
A risk of breast cancer in women - carriers of constitutional CHEK2 gene mutations, originating from the North - Central Poland.
50. PMID: 25583358; 2015, Int J Cancer;137(3):548-52
CHEK2 mutations and the risk of papillary thyroid cancer.
51. PMID: 12052256; 2002, Breast Cancer Res;4(3):R4
Mutation analysis of the CHK2 gene in breast carcinoma and other cancers.
52. PMID: 15125777; 2004, Mol Cancer;3():14
CHK2 kinase expression is down-regulated due to promoter methylation in non-small cell lung cancer.
53. PMID: 26510020; 2015, N Engl J Med;373(18):1697-708
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer.
54. PMID: 25998713; 2015, Nat Rev Cancer;15(6):334-46
Hijacked in cancer: the KMT2 (MLL) family of methyltransferases.
55. PMID: 24081332; 2013, Mol Cell Biol;33(23):4745-54
The MLL3/MLL4 branches of the COMPASS family function as major histone H3K4 monomethylases at enhancers.
56. PMID: 23166019; 2012, Genes Dev;26(23):2604-20
Enhancer-associated H3K4 monomethylation by Trithorax-related, the Drosophila homolog of mammalian Mll3/Mll4.

ACT Onco[®] + Report

57. PMID: 27926873; 2016, Cell Rep;17(10):2715-2723
FOXA1 Directs H3K4 Monomethylation at Enhancers via Recruitment of the Methyltransferase MLL3.
58. PMID: 17021013; 2006, Proc Natl Acad Sci U S A;103(42):15392-7
Coactivator as a target gene specificity determinant for histone H3 lysine 4 methyltransferases.
59. PMID: 11891048; 2002, Gene;284(1-2):73-81
MLL3, a new human member of the TRX/MLL gene family, maps to 7q36, a chromosome region frequently deleted in myeloid leukaemia.
60. PMID: 22234698; 2012, Blood;119(10):e67-75
High-resolution genomic profiling of adult and pediatric core-binding factor acute myeloid leukemia reveals new recurrent genomic alterations.
61. PMID: 25537518; 2015, Oncotarget;6(4):2466-82
Genetic alterations of histone lysine methyltransferases and their significance in breast cancer.
62. PMID: 25303977; 2014, Clin Cancer Res;20(24):6582-92
Mutational landscape of aggressive cutaneous squamous cell carcinoma.
63. PMID: 25151357; 2014, Nat Genet;46(10):1097-102
Genetic landscape of esophageal squamous cell carcinoma.
64. PMID: 28801450; 2017, Blood;130(14):1644-1648
Genomic analysis of hairy cell leukemia identifies novel recurrent genetic alterations.
65. PMID: 25794446; 2015, Cancer Genet;208(5):178-91
The cancer COMPASS: navigating the functions of MLL complexes in cancer.
66. PMID: 24794707; 2014, Cancer Cell;25(5):652-65
MLL3 is a haploinsufficient 7q tumor suppressor in acute myeloid leukemia.
67. PMID: 30665945; 2019, EMBO Rep;20(3):
The lysine-specific methyltransferase KMT2C/MLL3 regulates DNA repair components in cancer.
68. PMID: 27280393; 2016, Cancer Res;76(16):4861-71
Reduced Expression of Histone Methyltransferases KMT2C and KMT2D Correlates with Improved Outcome in Pancreatic Ductal Adenocarcinoma.
69. PMID: 27986439; 2017, Clin Breast Cancer;17(3):e135-e142
Expression Levels of KMT2C and SLC20A1 Identified by Information-theoretical Analysis Are Powerful Prognostic Biomarkers in Estrogen Receptor-positive Breast Cancer.
70. PMID: 19910469; 2010, J Biol Chem;285(2):1097-104
MRE11-RAD50-NBS1 complex dictates DNA repair independent of H2AX.
71. PMID: 20655309; 2010, FEBS Lett;584(17):3682-95
The MRN complex in double-strand break repair and telomere maintenance.
72. 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.
73. PMID: 23755103; 2014, PLoS One;8(6):e63313
Sequencing of candidate chromosome instability genes in endometrial cancers reveals somatic mutations in ESCO1, CHTF18, and MRE11A.
74. PMID: 11196167; 2001, Cancer Res;61(1):23-6
Alterations of the double-strand break repair gene MRE11 in cancer.
75. PMID: 11850399; 2002, EMBO Rep;3(3):248-54
Human MRE11 is inactivated in mismatch repair-deficient cancers.

ACT Onco[®] + Report

76. PMID: 16959974; 2006, Science;314(5797):268-74
The consensus coding sequences of human breast and colorectal cancers.
77. PMID: 24927325; 2014, PLoS One;9(6):e100041
Effect of MRE11 loss on PARP-inhibitor sensitivity in endometrial cancer in vitro.
78. PMID: 21300766; 2011, Cancer Res;71(7):2632-42
MRE11 deficiency increases sensitivity to poly(ADP-ribose) polymerase inhibition in microsatellite unstable colorectal cancers.
79. PMID: 25310185; 2014, PLoS One;9(10):e108483
MRE11-deficiency associated with improved long-term disease free survival and overall survival in a subset of stage III colon cancer patients in randomized CALGB 89803 trial.
80. PMID: 8563751; 1996, Nat Genet;12(2):144-8
Loss of NF1 results in activation of the Ras signaling pathway and leads to aberrant growth in haematopoietic cells.
81. PMID: 1946382; 1991, Proc Natl Acad Sci U S A;88(21):9658-62
Identification of the neurofibromatosis type 1 gene product.
82. PMID: 2116237; 1990, Cell;62(3):599-608
The neurofibromatosis type 1 gene encodes a protein related to GAP.
83. PMID: 2121370; 1990, Cell;63(4):843-9
The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21.
84. PMID: 14502561; 2003, J Cell Physiol;197(2):214-24
NF1 modulates the effects of Ras oncogenes: evidence of other NF1 function besides its GAP activity.
85. PMID: 19479903; 2009, Mol Carcinog;48(11):1005-17
Neurofibromin physically interacts with the N-terminal domain of focal adhesion kinase.
86. PMID: 28680740; 2017, Adv Med Biol;118():83-122
Haploinsufficient tumor suppressor genes.
87. PMID: 10442636; 1999, Oncogene;18(31):4450-9
Haploinsufficiency for the neurofibromatosis 1 (NF1) tumor suppressor results in increased astrocyte proliferation.
88. PMID: 16288202; 2006, Oncogene;25(16):2297-303
Nf1 haploinsufficiency augments angiogenesis.
89. PMID: 18089636; 2008, Hum Mol Genet;17(7):936-48
Rac1 mediates the osteoclast gains-in-function induced by haploinsufficiency of Nf1.
90. PMID: 7920653; 1994, Nat Genet;7(3):353-61
Tumour predisposition in mice heterozygous for a targeted mutation in Nf1.
91. PMID: 25026295; 2014, Oncotarget;5(15):5873-92
The NF1 gene revisited - from bench to bedside.
92. PMID: 29892687; 2018, Gynecol Oncol Rep;23():41-44
Clonal lineage of high grade serous ovarian cancer in a patient with neurofibromatosis type 1.
93. PMID: 29926297; 2018, Breast Cancer Res Treat;171(3):719-735
Breast cancer in women with neurofibromatosis type 1 (NF1): a comprehensive case series with molecular insights into its aggressive phenotype.
94. PMID: 28637487; 2017, Hum Genomics;11(1):13
The NF1 somatic mutational landscape in sporadic human cancers.
95. PMID: 15840687; 2005, Gut;54(8):1129-35

ACT Onco[®] + Report

NF1 gene loss of heterozygosity and expression analysis in sporadic colon cancer.

96. PMID: 20129251; 2010, Cancer Cell;17(1):98-110
Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1.
97. PMID: 27158780; 2016, Nat Genet;48(6):607-16
Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas.
98. PMID: 32669708; 2020, Nature;583(7818):807-812
The National Lung Matrix Trial of personalized therapy in lung cancer.
99. PMID: 21482774; 2012, Proc Natl Acad Sci U S A;109(8):2730-5
Genome-wide functional screen identifies a compendium of genes affecting sensitivity to tamoxifen.
100. PMID: 24535670; 2014, Cancer Discov;4(5):606-19
Reduced NF1 expression confers resistance to EGFR inhibition in lung cancer.
101. 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.
102. PMID: 30858928; 2019, Oncotarget;10(14):1440-1457
CRISPR-induced RASGAP deficiencies in colorectal cancer organoids reveal that only loss of NF1 promotes resistance to EGFR inhibition.
103. PMID: 24576830; 2014, Cancer Res;74(8):2340-50
Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence.
104. PMID: 23171796; 2013, Cancer Discov;3(3):338-49
Elucidating distinct roles for NF1 in melanomagenesis.
105. PMID: 23288408; 2013, Cancer Discov;3(3):350-62
A genome-scale RNA interference screen implicates NF1 loss in resistance to RAF inhibition.
106. PMID: 24265153; 2014, Cancer Discov;4(1):94-109
The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma.
107. PMID: 30269082; 2019, Gut;68(7):1152-1161
Liquid biopsies to track trastuzumab resistance in metastatic HER2-positive gastric cancer.
108. PMID: 26936308; 2016, J Clin Pharm Ther;41(3):357-359
Prolonged disease control with MEK inhibitor in neurofibromatosis type I-associated glioblastoma.
109. PMID: 22573716; 2012, Cancer Res;72(13):3350-9
Sensitivity of glioblastomas to clinically available MEK inhibitors is defined by neurofibromin 1 deficiency.
110. PMID: 19727076; 2009, Nature;461(7262):411-4
Response and resistance to MEK inhibition in leukaemias initiated by hyperactive Ras.
111. PMID: 23858101; 2013, Mol Cancer Ther;12(9):1906-17
NF1 deletion generates multiple subtypes of soft-tissue sarcoma that respond to MEK inhibition.
112. PMID: 23221341; 2013, J Clin Invest;123(1):340-7
MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors.
113. PMID: 18483311; 2008, Mol Cancer Ther;7(5):1237-45
Effective in vivo targeting of the mammalian target of rapamycin pathway in malignant peripheral nerve sheath tumors.
114. PMID: 23209032; 2013, Clin Cancer Res;19(2):450-61
Prognostic significance of AKT/mTOR and MAPK pathways and antitumor effect of mTOR inhibitor in NF1-related and sporadic malignant

ACT Onco[®] + Report

peripheral nerve sheath tumors.

115. PMID: 26859683; 2016, Oncotarget;7(9):10547-56
Next-generation sequencing reveals somatic mutations that confer exceptional response to everolimus.
116. PMID: 25893302; 2016, Oncogene;35(5):537-48
Role of Merlin/NF2 inactivation in tumor biology.
117. PMID: 19451229; 2009, Mol Cell Biol;29(15):4235-49
Loss of the tumor suppressor gene NF2, encoding merlin, constitutively activates integrin-dependent mTORC1 signaling.
118. PMID: 19451225; 2009, Mol Cell Biol;29(15):4250-61
NF2/merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with meningioma and schwannoma growth.
119. PMID: 17655741; 2007, Brain Pathol;17(4):371-6
Role of NF2 haploinsufficiency in NF2-associated polyneuropathy.
120. PMID: 19545378; 2009, Orphanet J Rare Dis;4():16
Neurofibromatosis type 2 (NF2): a clinical and molecular review.
121. 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.
122. PMID: 24393766; 2014, Oncotarget;5(1):67-77
NF2/merlin in hereditary neurofibromatosis 2 versus cancer: biologic mechanisms and clinical associations.
123. PMID: 27091708; 2016, J Clin Oncol;34(18):2115-24
Molecular Alterations and Everolimus Efficacy in Human Epidermal Growth Factor Receptor 2-Overexpressing Metastatic Breast Cancers: Combined Exploratory Biomarker Analysis From BOLERO-1 and BOLERO-3.
124. PMID: 26503204; 2016, J Clin Oncol;34(5):419-26
Correlative Analysis of Genetic Alterations and Everolimus Benefit in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From BOLERO-2.
125. PMID: 24833916; 2014, Breast Cancer (Dove Med Press);6():43-57
Use of mTOR inhibitors in the treatment of breast cancer: an evaluation of factors that influence patient outcomes.
126. PMID: 22923433; 2012, Science;338(6104):221
Genome sequencing identifies a basis for everolimus sensitivity.
127. PMID: 25630452; 2015, Eur Urol;67(6):1195-1196
Exceptional Response on Addition of Everolimus to Taxane in Urothelial Carcinoma Bearing an NF2 Mutation.
128. PMID: 26359368; 2015, Cancer Discov;5(11):1178-93
NF2 Loss Promotes Oncogenic RAS-Induced Thyroid Cancers via YAP-Dependent Transactivation of RAS Proteins and Sensitizes Them to MEK Inhibition.
129. PMID: 24813888; 2014, Cell Rep;7(4):999-1008
Acquired resistance of EGFR-mutant lung adenocarcinomas to afatinib plus cetuximab is associated with activation of mTORC1.
130. PMID: 20930833; 2010, Nature;467(7316):667-8
DNA repair: A protein giant in its entirety.
131. PMID: 20729858; 2010, Nat Struct Mol Biol;17(10):1263-5
The breast cancer tumor suppressor BRCA2 promotes the specific targeting of RAD51 to single-stranded DNA.
132. PMID: 20729832; 2010, Nature;467(7316):678-83
Purified human BRCA2 stimulates RAD51-mediated recombination.

ACT Onco[®] + Report

133. PMID: 22305526; 2012, Am J Hum Genet;90(2):301-7
RAD51 haploinsufficiency causes congenital mirror movements in humans.
134. PMID: 18243065; 2008, DNA Repair (Amst);7(5):686-93
The consequences of Rad51 overexpression for normal and tumor cells.
135. PMID: 24811120; 2014, Oncotarget;5(10):3261-72
Rad51 supports triple negative breast cancer metastasis.
136. PMID: 26317153; 2015, Cell Cycle;14(19):3190-202
High levels of RAD51 perturb DNA replication elongation and cause unscheduled origin firing due to impaired CHK1 activation.
137. PMID: 21807066; 2011, Biochim Biophys Acta;1816(2):209-18
RAD51 as a potential biomarker and therapeutic target for pancreatic cancer.
138. PMID: 10851081; 2000, Oncogene;19(23):2791-5
DNA repair and recombination factor Rad51 is over-expressed in human pancreatic adenocarcinoma.
139. PMID: 24741789; 2014, Rev Med Chir Soc Med Nat Iasi;118(1):133-40
Rad51 overexpression and resistance to genotoxic agents. A study in the fission yeast Schizosaccharomyces pombe.
140. PMID: 18618591; 2009, Mol Carcinog;48(2):105-9
Rad51 overexpression rescues radiation resistance in BRCA2-defective cancer cells.
141. PMID: 10807537; 2000, J Hum Genet;45(3):133-7
Identification of Rad51 alteration in patients with bilateral breast cancer.
142. PMID: 26108708; 2015, Sci Rep;5():11588
RAD51 135G>C substitution increases breast cancer risk in an ethnic-specific manner: a meta-analysis on 21,236 cases and 19,407 controls.
143. PMID: 11248061; 2001, Proc Natl Acad Sci U S A;98(6):3232-6
A single nucleotide polymorphism in the RAD51 gene modifies cancer risk in BRCA2 but not BRCA1 carriers.
144. PMID: 17999359; 2007, Am J Hum Genet;81(6):1186-200
RAD51 135G-->C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies.
145. PMID: 30353044; 2018, Br J Cancer;119(11):1401-1409
Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes.
146. PMID: 24577941; 2014, Mol Cancer Ther;13(5):1170-80
The use of Olaparib (AZD2281) potentiates SN-38 cytotoxicity in colon cancer cells by indirect inhibition of Rad51-mediated repair of DNA double-strand breaks.
147. PMID: 28759753; 2017, Biomed Pharmacother;94():165-168
Inhibition of Rad51 sensitizes breast cancer cells with wild-type PTEN to olaparib.
148. PMID: 22293180; 2012, J Clin Invest;122(2):425-34
Understanding pRb: toward the necessary development of targeted treatments for retinoblastoma.
149. PMID: 6320372; 1984, Science;223(4640):1028-33
Retinoblastoma: clues to human oncogenesis.
150. PMID: 27308386; 2015, Mol Cell Oncol;2(1):e968069
Conditional haploinsufficiency of the retinoblastoma tumor suppressor gene.
151. PMID: 23687339; 2013, Cancer Res;73(14):4247-55
Rb1 haploinsufficiency promotes telomere attrition and radiation-induced genomic instability.
152. PMID: 28169375; 2017, Sci Rep;7():42056
The Rb1 tumour suppressor gene modifies telomeric chromatin architecture by regulating TERRA expression.

ACT Onco[®] + Report

153. PMID: 15884040; 2005, Hum Mutat;25(6):566-74
Sensitive multistep clinical molecular screening of 180 unrelated individuals with retinoblastoma detects 36 novel mutations in the RB1 gene.
154. PMID: 22811582; 2012, Clin Cancer Res;18(18):5110-22
RB-pathway disruption is associated with improved response to neoadjuvant chemotherapy in breast cancer.
155. PMID: 21358261; 2011, Cell Cycle;10(6):956-62
A non-functional retinoblastoma tumor suppressor (RB) pathway in premenopausal breast cancer is associated with resistance to tamoxifen.
156. PMID: 17160137; 2007, J Clin Invest;117(1):218-28
The retinoblastoma tumor suppressor modifies the therapeutic response of breast cancer.
157. PMID: 29236940; 2018, Ann Oncol;29(3):640-645
Polyclonal RB1 mutations and acquired resistance to CDK 4/6 inhibitors in patients with metastatic breast cancer.
158. PMID: 29483214; 2018, Mol Cancer Ther;17(5):897-907
Preclinical Activity of Abemaciclib Alone or in Combination with Antimitotic and Targeted Therapies in Breast Cancer.
159. PMID: 22941188; 2012, Nat Genet;44(10):1104-10
Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer.
160. PMID: 22941189; 2012, Nat Genet;44(10):1111-6
Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer.
161. PMID: 25846096; 2015, Lancet Oncol;16(4):e165-72
Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin.
162. PMID: 25935112; 2015, Trends Biochem Sci;40(6):296-308
Structural determinants of Smad function in TGF- β signaling.
163. PMID: 19014666; 2008, Pathogenetics;1(1):2
Smad4 haploinsufficiency: a matter of dosage.
164. PMID: 9545410; 1998, Am J Hum Genet;62(5):1129-36
A gene for familial juvenile polyposis maps to chromosome 18q21.1.
165. PMID: 8553070; 1996, Science;271(5247):350-3
DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1.
166. PMID: 8673134; 1996, Nat Genet;13(3):343-6
Evaluation of candidate tumour suppressor genes on chromosome 18 in colorectal cancers.
167. PMID: 18662538; 2008, Cell;134(2):215-30
TGFbeta in Cancer.
168. PMID: 9135016; 1997, Cancer Res;57(9):1731-4
Tumor-suppressive pathways in pancreatic carcinoma.
169. PMID: 23139211; 2013, Cancer Res;73(2):725-35
SMAD2, SMAD3 and SMAD4 mutations in colorectal cancer.
170. PMID: 22810696; 2012, Nature;487(7407):330-7
Comprehensive molecular characterization of human colon and rectal cancer.
171. 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.
172. PMID: 19841540; 2009, J Clin Invest;119(11):3208-11
Smad4: gatekeeper gene in head and neck squamous cell carcinoma.

ACT Onco[®] + Report

173. 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.
174. PMID: 25589618; 2015, Clin Cancer Res;21(6):1447-56
Genomic analysis of metastatic cutaneous squamous cell carcinoma.
175. 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.
176. PMID: 16144935; 2005, Clin Cancer Res;11(17):6311-6
SMAD4 levels and response to 5-fluorouracil in colorectal cancer.
177. 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.
178. 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.
179. PMID: 25749173; 2015, Transl Oncol;8(1):18-24
A Meta-Analysis of SMAD4 Immunohistochemistry as a Prognostic Marker in Colorectal Cancer.
180. 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.
181. 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.
182. PMID: 26861460; 2016, Clin Cancer Res;22(12):3037-47
Reduced Expression of SMAD4 Is Associated with Poor Survival in Colon Cancer.
183. PMID: 26947875; 2016, Transl Oncol;9(1):1-7
Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis.
184. PMID: 25760429; 2015, Pancreas;44(4):660-4
SMAD4 expression predicts local spread and treatment failure in resected pancreatic cancer.
185. PMID: 22504380; 2012, Pancreas;41(4):541-6
SMAD4 genetic alterations predict a worse prognosis in patients with pancreatic ductal adenocarcinoma.
186. PMID: 19584151; 2009, Clin Cancer Res;15(14):4674-9
SMAD4 gene mutations are associated with poor prognosis in pancreatic cancer.
187. 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.
188. PMID: 19029933; 2008, Oncogene;27(55):6908-19
LKB1; linking cell structure and tumor suppression.
189. PMID: 19584313; 2009, Physiol Rev;89(3):777-98
LKB1 and AMPK family signaling: the intimate link between cell polarity and energy metabolism.
190. PMID: 20142330; 2010, Dis Model Mech;3(3-4):181-93
Lkb1 inactivation is sufficient to drive endometrial cancers that are aggressive yet highly responsive to mTOR inhibitor monotherapy.
191. PMID: 17676035; 2007, Nature;448(7155):807-10
LKB1 modulates lung cancer differentiation and metastasis.
192. PMID: 18245476; 2008, Cancer Res;68(3):759-66

ACT Onco[®] + Report

Loss of Lkb1 provokes highly invasive endometrial adenocarcinomas.

193. PMID: 18172296; 2008, Cancer Res;68(1):55-63
LKB1 deficiency sensitizes mice to carcinogen-induced tumorigenesis.
194. PMID: 25244018; 2014, Int J Mol Sci;15(9):16698-718
Recent progress on liver kinase B1 (LKB1): expression, regulation, downstream signaling and cancer suppressive function.
195. PMID: 9425897; 1998, Nat Genet;18(1):38-43
Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase.
196. PMID: 21189378; 2011, J Clin Oncol;29(6):e150-3
mTOR inhibitor treatment of pancreatic cancer in a patient With Peutz-Jeghers syndrome.
197. PMID: 27615706; 2016, CNS Oncol;5(4):203-9
Widely metastatic atypical pituitary adenoma with mTOR pathway STK11(F298L) mutation treated with everolimus therapy.
198. PMID: 27821489; 2017, Cancer Res;77(1):153-163
A Transcriptional Signature Identifies LKB1 Functional Status as a Novel Determinant of MEK Sensitivity in Lung Adenocarcinoma.
199. PMID: 29764856; 2018, Clin Cancer Res;24(22):5710-5723
TP53, STK11, and EGFR Mutations Predict Tumor Immune Profile and the Response to Anti-PD-1 in Lung Adenocarcinoma.
200. PMID: 29773717; 2018, Cancer Discov;8(7):822-835
STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma.
201. PMID: 29337640; 2018, J Clin Oncol;36(7):633-641
Molecular Determinants of Response to Anti-Programmed Cell Death (PD)-1 and Anti-Programmed Death-Ligand 1 (PD-L1) Blockade in Patients With Non-Small-Cell Lung Cancer Profiled With Targeted Next-Generation Sequencing.
202. PMID: 26833127; 2016, Cancer Res;76(5):999-1008
STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment.
203. PMID: 29573941; 2018, Lancet Oncol;19(5):603-615
Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial.
204. PMID: 27480103; 2016, Lancet Oncol;17(9):1248-60
Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial.
205. PMID: 26703889; 2016, Lancet;387(10022):968-977
Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study.
206. PMID: 22149876; 2012, N Engl J Med;366(6):520-9
Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.
207. PMID: 21306238; 2011, N Engl J Med;364(6):514-23
Everolimus for advanced pancreatic neuroendocrine tumors.
208. PMID: 23158522; 2013, Lancet;381(9861):125-32
Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial.
209. PMID: 18653228; 2008, Lancet;372(9637):449-56
Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial.
210. PMID: 28754483; 2017, Lancet Oncol;18(9):1274-1284

ACT Onco[®] + Report

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.

211. 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.
212. PMID: 25366685; 2015, J Clin Oncol;33(3):244-50
Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation.
213. PMID: 27908594; 2017, Lancet Oncol;18(1):75-87
Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial.
214. PMID: 17538086; 2007, N Engl J Med;356(22):2271-81
Temsilolimus, interferon alfa, or both for advanced renal-cell carcinoma.
215. PMID: 29072975; 2018, J Clin Oncol;36(1):7-13
Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer.
216. PMID: 27080216; 2016, Lancet Oncol;17(5):642-50
Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial.
217. PMID: 25265492; 2014, N Engl J Med;371(20):1877-88
Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma.
218. PMID: 22663011; 2012, N Engl J Med;367(2):107-14
Improved survival with MEK inhibition in BRAF-mutated melanoma.