尹宏基
Project ID: C22-M001-03450
Report No.: AA-22-06907_ONC
Date Reported: Nov 25, 2022

ACT Onco® + Report

PATIENT		
Identifier: 尹宏基		Patient ID: 49043278
Date of Birth: Sep 24, 1946		Gender: Male
Diagnosis: Adenocarcinoma		
ORDERING PHYSICIAN		
Name: 陳明晃醫師		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: S11144813A	Collection site: Duodenum	Type: FFPE tissue
Date received: Nov 14, 2022	Lab ID: AA-22-06907	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
CTNNB1 S45P	Imatinib	-
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.

ACT Onco® + Report

TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
CTNNB1	S45P	59.8%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr18	*SMAD4*	Homozygous deletion	0
Chr11	*ATM, CHEK1, MRE11*	Heterozygous deletion	1
Chr4	*FBXW7*	Heterozygous deletion	1
Chr9	*CDKN2A, PTCH1*	Heterozygous deletion	1
Chr5	*TERT*	Amplification	8

- 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 52% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is < 30%.

ACT Onco® + Report

THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 4		
CTNNB1 S45P	Imatinib	**sensitive**
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

ACT Onco® + Report

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

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

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

ACT Onco® + Report

VARIANT INTERPRETATION

CTNNB1 S45P

Biological Impact

The CTNNB1 gene encodes for the β-catenin, a transcriptional activator involves in the canonical Wnt signaling pathway[1][2]. β-catenin also regulates cyclin D1 and MYC expression, which play important roles in cancer development[3][4]. Mutations of CTNNB1 are common in a wide range of solid tumors, including liver, endometrial, colorectal, and lung cancer[5][6][7][8][9][10]. CTNNB1 mutations are more frequently found in hepatocellular carcinomas (HCCs) patients without hepatitis B virus (HBV) infection, which is mostly developed on the well-differentiated, noncirrhotic liver, and displayed cholestasis[11][12][13][14]. Of note, the majority of CTNNB1 alterations identified in cancers are missense mutations and all of which localize in the hotspot exon 3 at S33, S37, S45, T41, D32, and G34[15][16].

CTNNB1 S45P lies within a GSK3β phosphorylation site on the β-catenin protein (UniProtKB). CTNNB1 S45P is a gain-of-function mutation that increased β-catenin-dependent transcription[17]. This mutation has been identified in sporadic desmoid tumors and HCC[18][17].

Therapeutic and prognostic relevance

In a retrospective study, patients with desmoid fibromatosis harboring CTNNB1 activating mutations such as S45F/N/P or T41A demonstrated a greater progression arrest rate (PAR) at 6 months compared to patients with wild-type CTNNB1 when treated with imatinib, a multi-target inhibitor of c-KIT, PDGFR, and BCR-ABL[19].

Results from a Phase II study of temsirolimus-containing regiments in advanced endometrial cancer (EC) showed that CTNNB1 exon 3 mutations were associated with longer PFS on temsirolimus[20]. Besides, three patients with recurrent endometrial carcinoma harboring CTNNB1 mutations on exon 3 (one is D32V, another is S37Y, and the other is both H36Y and S37C) also responded well to everolimus and letrozole, based on the results of a Phase II study[21].

Low expression of CTNNB1 has been reported to associate with longer overall survival in low-grade endometrioid endometrial carcinoma (EEC)[22].

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[23]. 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[24][25][26][27][28]. 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[29]. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies[30][31][32][33]and a board range of tumors such as prostate cancer[34], head and neck squamous cell carcinoma (HNSCC)[35], pancreatic cancer[36], lung adenocarcinoma[37], breast cancer[38], and ovarian cancer[25].

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)[39].

In a phase II trial (TOPARP-A; NCT01682772), 3 out of 4 metastatic prostate cancer patients harboring only ATM

inactivating mutations responded to olaparib treatment[40]. Also, the phase II TOPARP-B trial (NCT01682772) demonstrated that olaparib treatment resulted in a RECIST 1.1 or PSA50 response rate of 10.5% (2/12) and a composite overall response rate of 36.8% (7/19) in prostate cancer patients harboring deleterious ATM mutations[41].In another randomized, double-blind phase II trial in Asian patients with metastatic gastric cancer has shown that addition of olaparib to paclitaxel significantly increased the OS in both the overall population and patients with low or undetectable ATM protein expression (NCT01063517)[42]. However, in the subsequent phase III trial (GOLD; NCT01924533), addition of olaparib to paclitaxel did not significantly improve OS in the overall or the ATM-negative population of Asian gastric cancer patients[43]. Besides, in a phase II trial (TBCRC 048; NCT03344965), 7 metastatic breast cancer patients harboring only ATM mutations were not responded to olaparib treatment (SD: n=2, PD: n=5)[44].In a phase II trial (TRITON2; NCT02952534), 49 mCRPC patients harboring ATM alteration had limited response to rucaparib treatment. The radiographic response rate was 10.5 % (n=2/19 evaluable patients), the prostate-specific antigen response rate was 4.1% (n=2/49), and the 6-month clinical benefit rate was 28.6% (n=12/42)[45].

In preclinical studies, cells with ATM alternation were sensitive to olaparib, niraparib, and talazoparib treatment in vitro and in vivo[46][47][48][49].

In addition, ATM has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in breast cancer (NCT04053322) and advanced solid tumors (NCT03297606), rucaparib efficacy in ovarian cancer (NCT01968213)[50]and prostate cancer (NCT02952534, NCT03533946)[45], niraparib efficacy in pancreatic cancer (NCT03553004, NCT03601923), prostate cancer (NCT02854436), melanoma (NCT03925350), metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma (NCT03840967), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in advanced or metastatic cancer (NCT02286687), HER2-negative solid tumors (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

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[51]. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer[52].

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer[53].

CDKN2A Heterozygous deletion

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53[54][55][56]. CDKN2A has been reported as a haploinsufficient tumor suppressor with one copy loss that may lead to weak protein expression and is insufficient to execute its original physiological functions[57]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[58][59].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[60][61]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[62][63][64]. However, there are clinical studies that demonstrated CDKN2A nuclear expression, CDKN2A/CDKN2B co-deletion, or CDKN2A inactivating mutation was not associated with clinical benefit from CDK4/6 inhibitors, such as palbociclib and ribociclib, in RB-positive patients[65][66][67]. However, CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

The phase II TAPUR trial demonstrated clinical benefits to palbociclib monotherapy in advanced NSCLC or head and neck cancer harboring a CDKN2A mutation or copy number loss. However, pancreatic and biliary cancer patients harboring a CDKN2A mutation or copy number loss did not demonstrate an objective response or stable disease when treated with palbociclib monotherapy for 16 weeks (DOI: 10.1200/JCO.2021.39.15_suppl.6043)[68][69].

Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for the treatment of ER+ and HER2- breast cancer[61][70][71].

In a Phase I trial, a KRAS wild-type squamous non-small cell lung cancer (NSCLC) patient with CDKN2A loss had a partial response when treated with CDK4/6 inhibitor abemaciclib[63]. Administration of combined palbociclib and MEK inhibitor PD-0325901 yield promising progression-free survival among patients with KRAS mutant non-small cell lung cancer (NSCLC) (AACR 2017, Abstract CT046). Moreover, MEK inhibitor in combination with CDK4/6 inhibitor demonstrates significant anti-KRAS-mutant NSCLC activity and radiosensitizing effect in preclinical models[72].

A retrospective analysis demonstrated that concurrent deletion of CDKN2A with EGFR mutation in patients with non-small cell lung cancer (NSCLC), predicts worse overall survival after EGFR-TKI treatment[73].

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[74]. 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[75][76]. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors[77], and CHEK1 mutations are extremely rare[74]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer[78], breast cancer[79], colorectal cancer[80], non-small cell lung (NSCLC) cancer[81], and nasopharyngeal cancer[82].

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)[39].

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)[50], 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[83].

FBXW7 Heterozygous deletion

Biological Impact

The F-box/WD repeat-containing protein 7 (FBXW7) gene encodes a protein that belongs to the SCF (SKP1-CUL1-F-box protein) E3 ligase complex. FBXW7 is recognized as a tumor suppressor which is involved in the negative regulation of oncogenes such as c-Myc[84][85], c-Jun[86], cyclin E[87], Notch family members[88][89], Aurora-A[90], mTOR[91], KLF5[92], and MCL-1[93]. Inactivating FBXW7 mutation or copy number loss may result in the accumulation of oncoproteins and therefore lead to malignant transformation[94]. FBXW7 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[92][93][95].

Therapeutic and prognostic relevance

Clinical efficacy of mTOR inhibitors was seen in patients harboring aberrations in the FBXW7 gene (one patient with refractory fibrolamellar hepatocellular carcinoma, and one patient with lung adenocarcinoma)[96][97]. Moreover, in vitro assay also suggested that loss or inactivation of FBXW7 may confer sensitivity to mTOR inhibitor[91].

Preclinical studies suggested that mutations or loss of FBXW7 were associated with regorafenib and oxaliplatin resistance in CRC cell lines and gefitinib resistance in lung cancer cells[98][99][100][101].

Retrospective studies have indicated that a relatively low expression level of FBXW7 is an independent prognostic marker of poor survival for patients with hepatocellular carcinoma, lung adenocarcinoma and squamous cell carcinoma[102][100].

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[103][104]. 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[103]. 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[103][104][105][106][107][108][109].

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[40]. Preclinically, loss of MRE11 also predicted sensitivity to PARP inhibitor talazoparib and ABT-888 in endometrial cancer[110]and microsatellite unstable colorectal cancer (CRC) cell lines[111]. MRE11 has been selected as an inclusion criterion for the trial examining olaparib in metastatic biliary tract cancer (NCT04042831), and talazoparib in HER2-negative breast cancer (NCT02401347) and prostate cancer (NCT03148795).

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[112].

PTCH1 Heterozygous deletion

Biological Impact

The PTCH1 (protein patched homolog 1) gene encodes a multi-pass transmembrane receptor for sonic hedgehog (shh), a tumor suppressor that acts to repress shh signaling in the absence of ligand[113]. Inactivation of PTCH1 results in hedgehog ligand-independent activation of SMO, causing a downstream activation of the pathway and lead to the neoplastic growth[114][115]. Recurrent PTCH1 mutations have been reported in sporadic basal cell carcinoma (BCCs) and medulloblastoma[116][117][118][119]. Germline PTCH1 mutations are associated with the nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome), predisposing patients to basal cell carcinoma and medulloblastoma[117]. PTCH1 is a haploinsufficient tumor suppressor gene with one copy loss may be sufficient to promote tumor development in mice[114][120].

Therapeutic and prognostic relevance

Vismodegib and sonidegib are small molecule inhibitors of SMO approved by the U.S. FDA for the treatment of patients with basal cell carcinoma[121][122][123][124].A heavily pretreated patient with metastatic medulloblastoma harboring loss-of-heterozygosity and somatic mutation of PTCH1 showed rapid regression of the tumor after treated with vismodegib[125]. Furthermore, a phase II study demonstrated that vismodegib treatment results in extended progression-free survival (PFS) in patients with loss-of-heterozygosity, SHH-driven medulloblastoma[126]. In the phase II MyPathway trial, three advanced solid tumors patients harboring PTCH1 loss-of-function mutations had partial responses to vismodegib treatment[127]. In a clinical study, two patients with Sonic Hedgehog (SHH) activated medulloblastoma harboring PTCH1 loss-of-function mutations demonstrated partial responses to sonidegib treatment[128].

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[129]. 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[130]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)[131][132][133][134]. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer[135], colorectal cancer (CRC)[133][136][8], and less frequently seen in other cancers such as lung adenocarcinoma[137], head and neck cancer[138][139], and cutaneous squamous cell carcinoma[140].

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[141]. 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[142].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)[143][144]. 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[145].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis[146][147][148][149][150][151][152][153]. 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[154].

ACT Onco® + Report

TERT Amplification

Biological Impact

The TERT gene encodes the catalytic subunit of telomerase, an enzyme that maintains telomere length and genomic integrity[155]. Upregulation of TERT promotes cancer development and progression via modulation of Wnt-catenin and nuclear factor kappa B signaling[156][157], and mitochondrial RNA processing[158]. Activating mutations in the TERT promoter have been identified in a number of cancer types including melanoma, hepatocellular carcinoma, urothelial carcinoma, medulloblastoma, and glioma whereas TERT gene amplification is implicated in lung cancer, cervical cancer, breast cancer, Merkel cell carcinoma, neuroblastoma and adrenocortical carcinoma[159][160][161][162][163].

Therapeutic and prognostic relevance

Imetelstat (GRN163L), a telomere inhibitor which has been shown to inhibit cell proliferation in various cancer cell lines and tumor xenografts is currently in clinical trials[155].

TERT gene amplification is an independent poor prognostic marker for disease-free survival in non-small cell lung cancer (NSCLC) and breast cancer[164][165][166].

ACT Onco® + Report

US FDA-APPROVED DRUG(S)

Abemaciclib (VERZENIO)

Abemaciclib is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. Abemaciclib is developed and marketed by Eli Lilly under the trade name VERZENIO.

- FDA Approval Summary of Abemaciclib (VERZENIO)

MONARCH E NCT03155997	**Breast cancer** (Approved on 2021/10/12)
	HR+/HER2-
	Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3[167] NCT02246621	**Breast cancer** (Approved on 2018/02/26)
	HR+/HER2-
	Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 2[71] NCT02107703	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1[168] NCT02102490	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib [ORR(%): 19.7 vs. 17.4]

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[169] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[170] 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[171] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[172] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[173] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

Imatinib (GLEEVEC)

Imatinib is an oral, small molecule inhibitor of tyrosine kinase enzymes, namely, the Abelson proto-oncogene (ABL), c-KIT, and platelet-derived growth factor receptor (PDGFR). Imatinib is developed and marketed by Novartis under the trade name GLEEVEC.

- FDA Approval Summary of Imatinib (GLEEVEC)

[174] NCT00022737	**Acute lymphocytic leukemia** (Approved on 2013/01/25)
	-
	Imatinib [EFS(%): 70]
	Gastrointestinal stromal tumor (Approved on 2012/01/31)
	KIT positive
	Imatinib [RFS(%): 42 (imatinib for 12)| 25 (imatinib for 36)]
	Gastrointestinal stromal tumor (Approved on 2009/02/10)
	KIT+
	Imatinib vs. Placebo [RFS(%): 21 vs. 28]
	Myelodysplastic myeloproliferative cancer (Approved on 2006/10/19)
	-
	Imatinib [MCyR(%): 39, CHR(%): 45]
[175]	**Acute lymphocytic leukemia** (Approved on 2006/10/19)
	Ph+
	Imatinib [MCyR(%): 35, CHR(%): 19]
	Dermatofibrosarcoma protuberans (Approved on 2006/10/19)
	-
	Imatinib [ORR(%): 83.0]
	Systemic mastocytosis (Approved on 2006/10/19)
	-
	Imatinib [CHR(%): 29]
	Chronic eosinophilic leukemia (Approved on 2006/10/19)
	-
	Imatinib [CHR(%): 61]
[176] NCT00471497	**Chronic myeloid leukemia** (Approved on 2003/05/20)
	Ph+
	Imatinib vs. Nilotinib [MMR(%): 22 vs. 44]
[177] NCT00333840	**Chronic myeloid leukemia** (Approved on 2003/04/18)
	-
	Imatinib vs. Interferon-α+ cytarabine [PFS(%): 81.2 vs. 60.6]
[178] NCT00009906	**Gastrointestinal stromal tumor** (Approved on 2002/02/01)
	-
	Imatinib [PFS(M): 18.9 (imatinib 400 mg)| 23.2 (imatinib 800 mg)]

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[179] 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[39] 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[180] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[181] 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[182] 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[183] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[184] 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[185] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

Palbociclib (IBRANCE)

Palbociclib is an oral, cyclin-dependent kinase (CDK) inhibitor specifically targeting CDK4 and CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Palbociclib is developed and marketed by Pfizer under the trade name IBRANCE.

- FDA Approval Summary of Palbociclib (IBRANCE)

PALOMA-2[186] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+/HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[187] NCT01942135	**Breast cancer** (Approved on 2016/02/19)
	ER+/HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

Ribociclib (KISQALI)

Ribociclib is a cyclin-dependent kinase (CDK) inhibitor specifically targeting cyclin D1/CDK4 and cyclin D3/CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Ribociclib is developed by Novartis and Astex Pharmaceuticals and marketed by Novartis under the trade name KISQALI.

- FDA Approval Summary of Ribociclib (KISQALI)

MONALEESA-2[70] NCT01958021	**Breast cancer** (Approved on 2017/03/13)
	HR+/HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

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[50] 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]

Sonidegib (ODOMZO)

Sonidegib is a Hedgehog signaling pathway inhibitor by blocking its key component, smoothened (smo). Sonidegib is developed and marketed by Novartis under the trade name ODOMZO.

- FDA Approval Summary of Sonidegib (ODOMZO)

BOLT[123] NCT01327053	**Basal cell carcinoma** (Approved on 2015/07/24)
	-
	Sonidegib [ORR(%): 58.0]

Talazoparib (TALZENNA)

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

- FDA Approval Summary of Talazoparib (TALZENNA)

EMBRACA[188] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	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)

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

Vismodegib (ERIVEDGE)

Vismodegib is a cyclopamine-competitive antagonist and acts as a first-in-class Hedgehog signaling pathway inhibitor by blocking its key component smoothened (smo). Vismodegib is developed by Genentech and marketed by Roche under the trade name ERIVEDGE.

- FDA Approval Summary of Vismodegib (ERIVEDGE)

ERIVANCE BCC[121] NCT00833417	**Basal cell carcinoma** (Approved on 2012/01/30)
	-
	Vismodegib [ORR (mBCC)(%): 30.3, ORR (laBCC)(%): 42.9]

D=day; W=week; M=month

ACT Onco® + Report

ONGOING CLINICAL TRIALS

Trials were searched by applying filters: study status, patient's diagnosis, intervention, location and/or biomarker(s). Please visit https://clinicaltrials.gov to search and view for a complete list of open available and updated matched trials.

No trial has been found.

SUPPLEMENTARY INFORMATION OF TESTING RESULTS

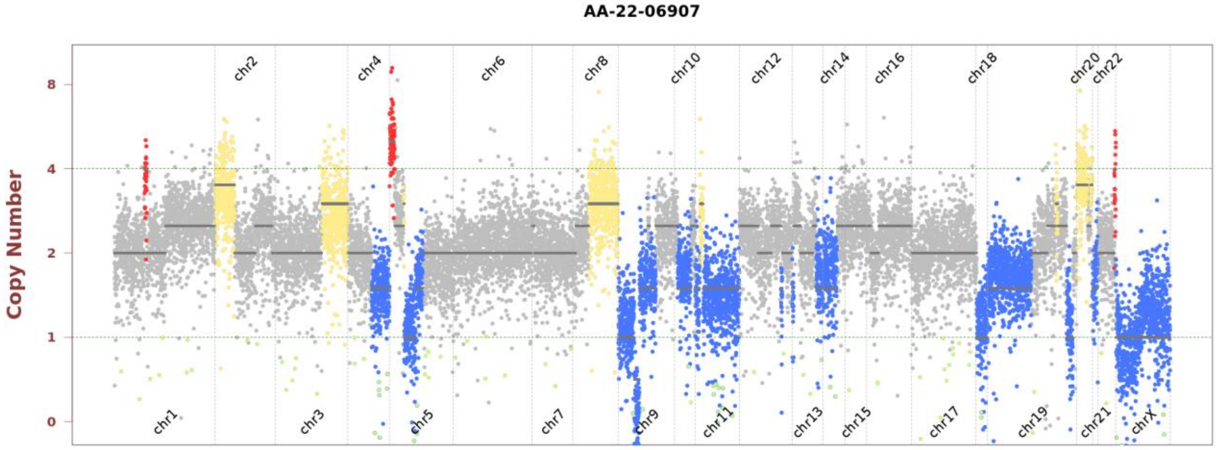
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
CTNNB1	S45P	3	c.133T>C	NM_001904	COSM5663	59.8%	1045

- 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.



Observed CN ≥ 3 but < 4
Observed CN ≥ 4
Observed CN < 2

ACT Onco® + Report

OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ADAMTS9	R967S	20	c.2901G>C	NM_182920	-	73.2%	1746
ADGRA2	Splice region	-	c.1447-6C>T	NM_032777	-	14.9%	316
ATM	H600D	11	c.1798C>G	NM_000051	-	81.5%	130
EPHA5	Y506C	6	c.1517A>G	NM_001281765	-	41.0%	507
ERBB2	R143Q	3	c.428G>A	NM_004448	COSM1382867	30.4%	832
FAT1	R548H	2	c.1643G>A	NM_005245	-	81.3%	171
IRS2	G1057V	1	c.3170G>T	NM_003749	-	50.0%	142
KMT2A	E1273*	7	c.3817G>T	NM_001197104	COSM9360034	44.6%	828
KMT2D	R4288Q	39	c.12863G>A	NM_003482	COSM2006804	47.8%	742
MUC16	I11646T	5	c.34937T>C	NM_024690	-	48.3%	687
NOTCH1	R2263Q	34	c.6788G>A	NM_017617	COSM3215831	36.5%	477
NOTCH1	V1260M	23	c.3778G>A	NM_017617	COSM6972741	55.0%	160
PRKDC	G2108S	48	c.6322G>A	NM_006904	-	40.6%	838
WT1	G181A	1	c.542G>C	NM_024426	-	10.3%	1045

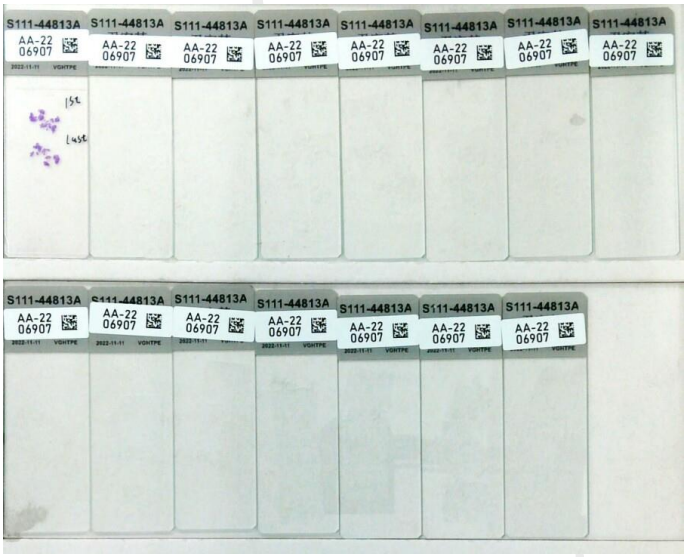
Note:

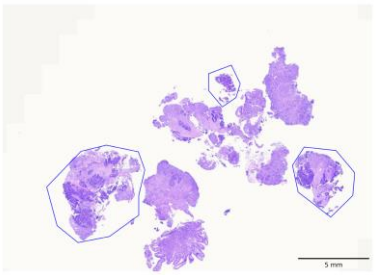
- This table enlists variants detected by the panel other than those with clinical relevance (reported in Testing Result section). The clinical impact of a genetic variant is determined according to ACT Genomics in-house clinical knowledge database. A negative result does not necessarily indicate absence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

ACT Onco® + Report

TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW





- Collection date: Nov 02, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11144813A
- Collection site: Duodenum
- Examined by: Dr. Yun-An Chen
    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 (%): 50%
    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: N/A
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 908x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 162

ACT Onco® + Report

LIMITATIONS

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

ACT Onco® + Report

RNA test

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

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

DATABASE USED

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

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

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

ACT Onco® + Report

GENE LIST

SNV & CNV

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

*Analysis of copy number alterations NOT available.

FUSION

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

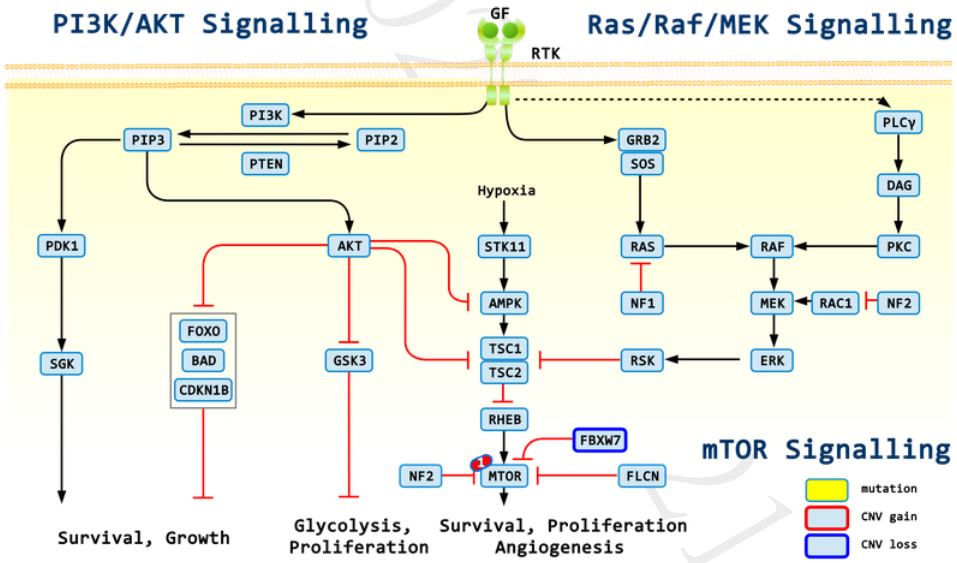
ACT Onco® + Report

APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

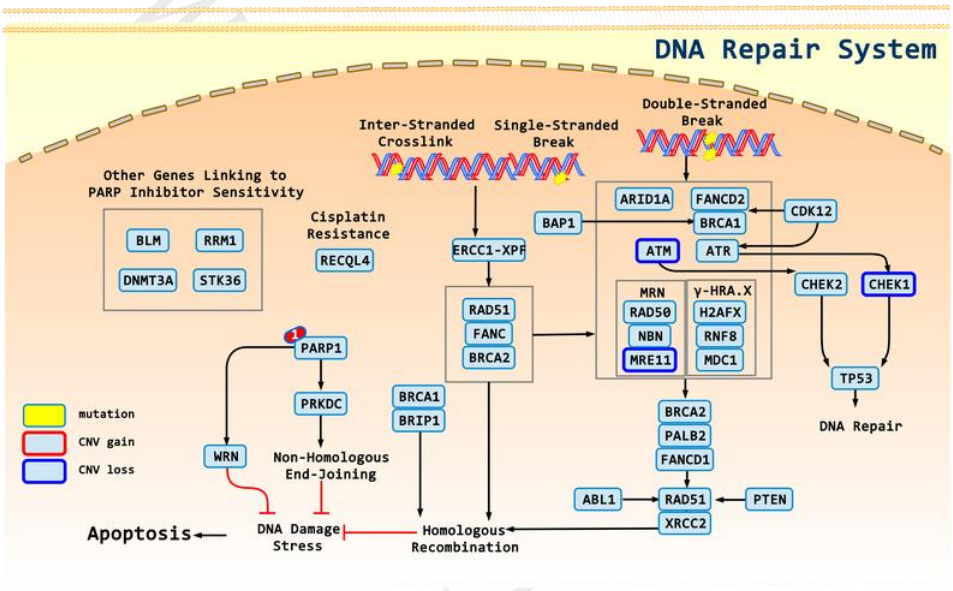
Gene	Therapies	Possible effect
CDKN2A	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
FBXW7	Everolimus, Temsirolimus	**sensitive**
ATM	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
MRE11	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
PTCH1	Sonidegib, Vismodegib	**sensitive**
FBXW7	Gefitinib, Regorafenib	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

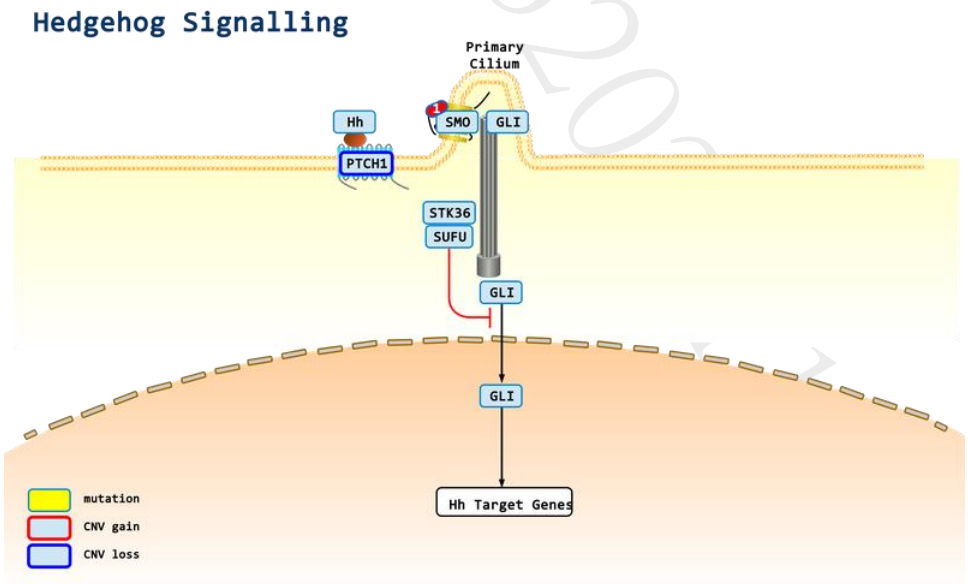


1: Everolimus, Temsirolimus

ACT Onco® + Report

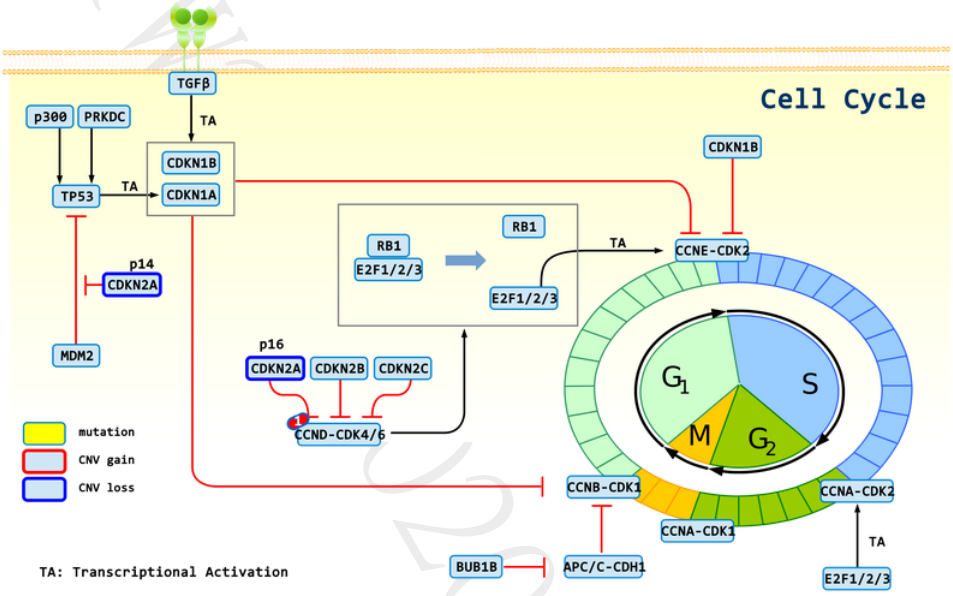


1: Olaparib, Niraparib, Rucaparib, Talazoparib



1: Sonidegib, Vismodegib

ACT Onco® + Report



1: Palbociclib, Ribociclib, Abemaciclib

ACT Onco® + Report

DISCLAIMER

法律聲明

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

醫療決策需由醫師決定

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

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

責任

本檢驗報告僅提供專業醫療參考，本公司及其員工不對任何由使用本報告之內容引起的直接、間接、特殊、連帶或衍生的損失或損害承擔責任。

ACT Onco® + Report

REFERENCE

1. PMID: 22682243; 2012, Cell;149(6):1192-205
Wnt/β-catenin signaling and disease.

2. PMID: 22617422; 2012, EMBO J;31(12):2714-36
The many faces and functions of β-catenin.

3. PMID: 10201372; 1999, Nature;398(6726):422-6
Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells.

4. PMID: 9727977; 1998, Science;281(5382):1509-12
Identification of c-MYC as a target of the APC pathway.

5. PMID: 23788652; 2013, Genome Res;23(9):1422-33
Whole-genome sequencing identifies recurrent mutations in hepatocellular carcinoma.

6. PMID: 22634756; 2012, Nat Genet;44(7):760-4
Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators.

7. PMID: 23636398; 2013, Nature;497(7447):67-73
Integrated genomic characterization of endometrial carcinoma.

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

9. PMID: 25079552; 2014, Nature;511(7511):543-50
Comprehensive molecular profiling of lung adenocarcinoma.

10. PMID: 22980975; 2012, Cell;150(6):1107-20
Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing.

11. PMID: 17187432; 2007, Hepatology;45(1):42-52
Transcriptome classification of HCC is related to gene alterations and to new therapeutic targets.

12. PMID: 17487939; 2007, J Pathol;212(3):345-52
Cholestasis is a marker for hepatocellular carcinomas displaying beta-catenin mutations.

13. PMID: 19101982; 2009, Hepatology;49(3):821-31
Unique phenotype of hepatocellular cancers with exon-3 mutations in beta-catenin gene.

14. PMID: 26171210; 2015, Mol Clin Oncol;3(4):936-940
β-catenin mutation is correlated with a favorable prognosis in patients with hepatocellular carcinoma.

15. PMID: 11957146; 2002, Hum Pathol;33(2):206-12
CTNNB1 mutations and beta-catenin expression in endometrial carcinomas.

16. PMID: 11955436; 2002, Cell;108(6):837-47
Control of beta-catenin phosphorylation/degradation by a dual-kinase mechanism.

17. PMID: 18282277; 2008, Mol Cancer;7():21
Correlation between beta-catenin mutations and expression of Wnt-signaling target genes in hepatocellular carcinoma.

18. PMID: 18832571; 2008, Am J Pathol;173(5):1518-27
Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors.

19. PMID: 26861905; 2016, Ann Surg Oncol;23(6):1924-7
Correlation of CTNNB1 Mutation Status with Progression Arrest Rate in RECIST Progressive Desmoid-Type Fibromatosis Treated with

Imatinib: Translational Research Results from a Phase 2 Study of the German Interdisciplinary Sarcoma Group (GISG-01).

20. PMID: 27016228; 2016, Gynecol Oncol;141(1):43-8
Tumor mutational analysis of GOG248, a phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer (EC): An NRG Oncology/Gynecologic Oncology Group study.

21. PMID: 25624430; 2015, J Clin Oncol;33(8):930-6
Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma.

22. PMID: 25214561; 2014, J Natl Cancer Inst;106(9):
Clinical significance of CTNNB1 mutation and Wnt pathway activation in endometrioid endometrial carcinoma.

23. PMID: 22079189; 2012, Trends Biochem Sci;37(1):15-22
The ATM protein kinase and cellular redox signaling: beyond the DNA damage response.

24. PMID: 1548942; 1992, Leukemia;6 Suppl 1():8-13
Cancer susceptibility in ataxia-telangiectasia.

25. PMID: 12810666; 2003, Cancer Res;63(12):3325-33
Contributions of ATM mutations to familial breast and ovarian cancer.

26. PMID: 1961222; 1991, N Engl J Med;325(26):1831-6
Incidence of cancer in 161 families affected by ataxia-telangiectasia.

27. 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.

28. PMID: 16400190; 2006, Carcinogenesis;27(4):848-55
Atm-haploinsufficiency enhances susceptibility to carcinogen-induced mammary tumors.

29. PMID: 29478780; 2018, Am J Hum Genet;102(3):401-414
Inherited DNA-Repair Defects in Colorectal Cancer.

30. PMID: 9488043; 1998, Oncogene;16(6):789-96
ATM is usually rearranged in T-cell prolymphocytic leukaemia.

31. PMID: 11429421; 2001, J Clin Pathol;54(7):512-6
Ataxia telangiectasia gene mutations in leukaemia and lymphoma.

32. 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.

33. 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.

34. PMID: 22981675; 2013, Eur Urol;63(5):920-6
Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity.

35. 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.

36. PMID: 23103869; 2012, Nature;491(7424):399-405
Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes.

37. PMID: 18948947; 2008, Nature;455(7216):1069-75
Somatic mutations affect key pathways in lung adenocarcinoma.

38. PMID: 30537493; 2019, Hum Pathol;86():85-92
Molecular characterization of metaplastic breast carcinoma via next-generation sequencing.

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

40. PMID: 26510020; 2015, N Engl J Med;373(18):1697-708
DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer.

41. PMID: 31806540; 2020, Lancet Oncol;21(1):162-174
Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial.

42. 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.

43. PMID: 29103871; 2017, Lancet Oncol;18(12):1637-1651
Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial.

44. PMID: 33119476; 2020, J Clin Oncol;38(36):4274-4282
TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes.

45. 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.

46. PMID: 20739657; 2010, Blood;116(22):4578-87
The PARP inhibitor olaparib induces significant killing of ATM-deficient lymphoid tumor cells in vitro and in vivo.

47. PMID: 31699977; 2019, Nat Commun;10(1):5065
AZD7648 is a potent and selective DNA-PK inhibitor that enhances radiation, chemotherapy and olaparib activity.

48. PMID: 34503215; 2021, Cancers (Basel);13(17):
Niraparib Suppresses Cholangiocarcinoma Tumor Growth by Inducing Oxidative and Replication Stress.

49. PMID: 23881923; 2013, Clin Cancer Res;19(18):5003-15
BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency.

50. 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.

51. 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.

52. 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.

53. 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.

54. PMID: 17055429; 2006, Cell;127(2):265-75
The regulation of INK4/ARF in cancer and aging.

55. PMID: 8521522; 1995, Cell;83(6):993-1000
Alternative reading frames of the INK4a tumor suppressor gene encode two unrelated proteins capable of inducing cell cycle arrest.

56. PMID: 9529249; 1998, Cell;92(6):725-34

ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways.

57. PMID: 16115911; 2005, Clin Cancer Res;11(16):5740-7
Comprehensive analysis of CDKN2A status in microdissected urothelial cell carcinoma reveals potential haploinsufficiency, a high frequency of homozygous co-deletion and associations with clinical phenotype.

58. PMID: 7550353; 1995, Nat Genet;11(2):210-2
Frequency of homozygous deletion at p16/CDKN2 in primary human tumours.

59. PMID: 24089445; 2013, Clin Cancer Res;19(19):5320-8
The cell-cycle regulator CDK4: an emerging therapeutic target in melanoma.

60. PMID: 27849562; 2017, Gut;66(7):1286-1296
Palbociclib (PD-0332991), a selective CDK4/6 inhibitor, restricts tumour growth in preclinical models of hepatocellular carcinoma.

61. PMID: 25524798; 2015, Lancet Oncol;16(1):25-35
The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.

62. PMID: 28283584; 2017, Oncologist;22(4):416-421
Clinical Benefit in Response to Palbociclib Treatment in Refractory Uterine Leiomyosarcomas with a Common CDKN2A Alteration.

63. PMID: 27217383; 2016, Cancer Discov;6(7):740-53
Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non-Small Cell Lung Cancer, and Other Solid Tumors.

64. PMID: 26715889; 2015, Curr Oncol;22(6):e498-501
Does CDKN2A loss predict palbociclib benefit?

65. PMID: 25501126; 2015, Clin Cancer Res;21(5):995-1001
CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment.

66. PMID: 27542767; 2016, Clin Cancer Res;22(23):5696-5705
A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas.

67. PMID: 24797823; 2014, Oncologist;19(6):616-22
Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel.

68. PMID: 35050752; 2020, JCO Precis Oncol;4():757-766
Palbociclib in Patients With Non-Small-Cell Lung Cancer With CDKN2A Alterations: Results From the Targeted Agent and Profiling Utilization Registry Study.

69. PMID: 35100714; 2019, JCO Precis Oncol;3():1-8
Palbociclib in Patients With Pancreatic and Biliary Cancer With CDKN2A Alterations: Results From the Targeted Agent and Profiling Utilization Registry Study.

70. PMID: 27717303; 2016, N Engl J Med;375(18):1738-1748
Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer.

71. PMID: 28580882; 2017, J Clin Oncol;35(25):2875-2884
MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy.

72. PMID: 26728409; 2016, Clin Cancer Res;22(1):122-33
Coadministration of Trametinib and Palbociclib Radiosensitizes KRAS-Mutant Non-Small Cell Lung Cancers In Vitro and In Vivo.

73. PMID: 31401335; 2019, Transl Oncol;12(11):1425-1431
Concomitant Genetic Alterations are Associated with Worse Clinical Outcome in EGFR Mutant NSCLC Patients Treated with Tyrosine Kinase Inhibitors.

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

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

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

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

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

79. 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.

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

81. 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.

82. 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.

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

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

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

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

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

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

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

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

91. PMID: 18787170; 2008, Science;321(5895):1499-502
FBXW7 targets mTOR for degradation and cooperates with PTEN in tumor suppression.

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

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

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

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

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

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

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

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

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

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

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

103. PMID: 19910469; 2010, J Biol Chem;285(2):1097-104
MRE11-RAD50-NBS1 complex dictates DNA repair independent of H2AX.

104. PMID: 20655309; 2010, FEBS Lett;584(17):3682-95
The MRN complex in double-strand break repair and telomere maintenance.

105. 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.

106. 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.

107. PMID: 11196167; 2001, Cancer Res;61(1):23-6
Alterations of the double-strand break repair gene MRE11 in cancer.

108. PMID: 11850399; 2002, EMBO Rep;3(3):248-54
Human MRE11 is inactivated in mismatch repair-deficient cancers.

109. PMID: 16959974; 2006, Science;314(5797):268-74
The consensus coding sequences of human breast and colorectal cancers.

110. PMID: 24927325; 2014, PLoS One;9(6):e100041
Effect of MRE11 loss on PARP-inhibitor sensitivity in endometrial cancer in vitro.

111. PMID: 21300766; 2011, Cancer Res;71(7):2632-42
MRE11 deficiency increases sensitivity to poly(ADP-ribose) polymerase inhibition in microsatellite unstable colorectal cancers.

112. 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.

113. PMID: 8906794; 1996, Nature;384(6605):176-9
Biochemical evidence that patched is the Hedgehog receptor.

114. PMID: 12016144; 2002, Carcinogenesis;23(5):727-33
Unbalanced overexpression of the mutant allele in murine Patched mutants.

115. PMID: 11130178; 2000, Cell Mol Life Sci;57(12):1720-31
Hedgehog signalling in cancer.

116. PMID: 8782823; 1996, Nat Genet;14(1):78-81
The role of the human homologue of Drosophila patched in sporadic basal cell carcinomas.

117. PMID: 8658145; 1996, Science;272(5268):1668-71
Human homolog of patched, a candidate gene for the basal cell nevus syndrome.

118. PMID: 9422511; 1998, Nature;391(6662):90-2
Activating Smoothened mutations in sporadic basal-cell carcinoma.

119. PMID: 22832583; 2012, Nature;488(7409):100-5
Dissecting the genomic complexity underlying medulloblastoma.

120. PMID: 10738305; 2000, Genes Chromosomes Cancer;28(1):77-81
Evidence that haploinsufficiency of Ptch leads to medulloblastoma in mice.

121. PMID: 22670903; 2012, N Engl J Med;366(23):2171-9
Efficacy and safety of vismodegib in advanced basal-cell carcinoma.

122. PMID: 28511673; 2017, BMC Cancer;17(1):332
Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study.

123. PMID: 25981810; 2015, Lancet Oncol;16(6):716-28
Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial.

124. PMID: 31545507; 2020, Br J Dermatol;182(6):1369-1378
Long-term efficacy and safety of sonidegib in patients with advanced basal cell carcinoma: 42-month analysis of the phase II randomized, double-blind BOLT study.

125. PMID: 19726761; 2009, N Engl J Med;361(12):1173-8
Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449.

126. PMID: 26169613; 2015, J Clin Oncol;33(24):2646-54
Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog-Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032.

127. PMID: 29320312; 2018, J Clin Oncol;36(6):536-542
Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study.

128. PMID: 34409296; 2021, Neurooncol Adv;3(1):vdab097
Clinical and molecular analysis of smoothened inhibitors in Sonic Hedgehog medulloblastoma.

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

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

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

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

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

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

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

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

137. 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.

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

139. 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.

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

141. 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.

142. 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.

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

144. 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.

145. 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.

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

147. 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.

148. 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.

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

150. PMID: 26947875; 2016, Transl Oncol;9(1):1-7

Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis.

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

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

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

154. 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.

155. PMID: 21332640; 2011, J Cell Mol Med;15(7):1433-42
Targeting telomerase-expressing cancer cells.

156. PMID: 19571879; 2009, Nature;460(7251):66-72
Telomerase modulates Wnt signalling by association with target gene chromatin.

157. PMID: 23159929; 2012, Nat Cell Biol;14(12):1270-81
Telomerase directly regulates NF-κB-dependent transcription.

158. PMID: 19701182; 2009, Nature;461(7261):230-5
An RNA-dependent RNA polymerase formed by TERT and the RMRP RNA.

159. PMID: 23348506; 2013, Science;339(6122):957-9
Highly recurrent TERT promoter mutations in human melanoma.

160. PMID: 23530248; 2013, Proc Natl Acad Sci U S A;110(15):6021-6
TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal.

161. PMID: 11103775; 2000, Cancer Res;60(22):6230-5
Frequent amplification of the telomerase reverse transcriptase gene in human tumors.

162. PMID: 12007187; 2002, Genes Chromosomes Cancer;34(3):269-75
Amplification of the telomerase reverse transcriptase (hTERT) gene in cervical carcinomas.

163. PMID: 25301727; 2014, Oncotarget;5(20):10048-57
TERT promoter mutations and gene amplification: promoting TERT expression in Merkel cell carcinoma.

164. PMID: 16641908; 2006, Br J Cancer;94(10):1452-9
Amplification of telomerase (hTERT) gene is a poor prognostic marker in non-small-cell lung cancer.

165. PMID: 27982019; 2017, Cancer Gene Ther;24(1):20-27
The associations of TERT-CLPTM1L variants and TERT mRNA expression with the prognosis of early stage non-small cell lung cancer.

166. PMID: 29100407; 2017, Oncotarget;8(44):77540-77551
TERT promoter status and gene copy number gains: effect on TERT expression and association with prognosis in breast cancer.

167. PMID: 28968163; 2017, J Clin Oncol;35(32):3638-3646
MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer.

168. PMID: 28533223; 2017, Clin Cancer Res;23(17):5218-5224
MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer.

169. 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.

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

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

172. 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.

173. 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.

174. PMID: 19805687; 2009, J Clin Oncol;27(31):5175-81
Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study.

175. PMID: 12200353; 2002, Blood;100(6):1965-71
A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias.

176. PMID: 21856226; 2011, Lancet Oncol;12(9):841-51
Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial.

177. PMID: 18256322; 2008, Blood;111(8):4022-8
Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study.

178. PMID: 28196207; 2017, JAMA Oncol;3(7):944-952
Correlation of Long-term Results of Imatinib in Advanced Gastrointestinal Stromal Tumors With Next-Generation Sequencing Results: Analysis of Phase 3 SWOG Intergroup Trial S0033.

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

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

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

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

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

184. 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.

185. 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.

186. PMID: 27959613; 2016, N Engl J Med;375(20):1925-1936
Palbociclib and Letrozole in Advanced Breast Cancer.

187. PMID: 26030518; 2015, N Engl J Med;373(3):209-19

Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer.

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

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