蔡鳳英
Project ID: C22-M001-03945
Report No.: AA-22-07950_ONC
Date Reported: Jan 10, 2023

ACT Onco® + Report

PATIENT		
Identifier: 蔡鳳英		Patient ID: 48318167
Date of Birth: May 13, 1966		Gender: Female
Diagnosis: GIST		
ORDERING PHYSICIAN		
Name: 顏厥全醫師		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: S11153713A	Collection site: Tissue, labeled subphrenic	Type: FFPE tissue
Date received: Dec 28, 2022	Lab ID: AA-22-07950	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
KIT A502_Y503dup (Exon 9 mutations)	Avapritinib, Cabozantinib, Imatinib, Regorafenib, Ripretinib, Sunitinib	-
KIT N822K	Avapritinib, Dasatinib, Midostaurin, Ponatinib, Regorafenib, Ripretinib	Imatinib

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.

ACTOnco®+ Report

TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
KIT	A502_Y503dup (Exon 9 mutations)	67.6%
KIT	N822K	48.9%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr1	*ARID1A, CDKN2C*	Heterozygous deletion	1
Chr11	*ATM, CHEK1, MRE11*	Heterozygous deletion	1
Chr13	*RB1*	Heterozygous deletion	1
Chr15	*RAD51*	Heterozygous deletion	1
Chr17	*FLCN*	Heterozygous deletion	1
Chr18	*SMAD4*	Heterozygous deletion	1
Chr19	*STK11*	Heterozygous deletion	1
Chr22	*CHEK2, NF2*	Heterozygous deletion	1
Chr9	*CDKN2A, PTCH1, TSC1*	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)	2.6 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 77% 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 3B		
KIT A502_Y503dup (Exon 9 mutations)	Avapritinib, Regorafenib, Ripretinib, Sunitinib	**sensitive**
KIT N822K	Avapritinib, Dasatinib, Ponatinib, Regorafenib, Ripretinib	**sensitive**
Level 4		
KIT A502_Y503dup (Exon 9 mutations)	Cabozantinib, Imatinib	**sensitive**
KIT N822K	Midostaurin	**sensitive**
KIT N822K	Imatinib	**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

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

HORMONAL THERAPIES

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

OTHERS

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

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

ACT Onco®+ Report

VARIANT INTERPRETATION

KIT A502_Y503dup (Exon 9 mutations), N822K

Biological Impact

KIT is a proto-oncogene that encodes a type 3 transmembrane receptor tyrosine kinase. Activation of KIT through dimerization and autophosphorylation upon binding by its ligand results in increased intracellular PI3K/AKT/mTOR, MAPK/ERK and JAK/STAT signaling pathways to promote cell proliferation and survival[1]. KIT activating mutations are frequently found in 80 - 90% of gastrointestinal stromal tumors (GISTs) which distributed over multiple exons with different frequencies (exons 11 (66.1%), exon 9 (13%), exon 13 (1.2%), and exon 17 (0.6%))[2][3].

KIT A502_Y503dup (also referred to as Y503_F504insAY) results in an insertion of 2 duplicate amino acids, alanine-502 through tyrosine-503, in the Ig-like C2-type domain 5 (exon 9) of the KIT protein (UniProtKB). A502_Y503dup confers a gain of function to the KIT protein, as demonstrated by constitutive phosphorylation of KIT and induces cell transforming in vitro[4][5].

KIT N822K is a gain-of-function mutation which located in the activation loop of the c-Kit protein. N822K results in ERK1/2 and STAT3 phosphorylation and cell transformation[6].

Therapeutic and prognostic relevance

The NCCN guidelines for cutaneous melanoma suggested KIT hotspots mutations which located in exon 11 and exon 13 (eg. W557, V559, L576P, K642E) have a high level of sensitivity to KIT inhibitors (imatinib, sunitinib, nilotinib)[7][8][9]. However, KIT exon 17 mutations (eg. D816H) and KIT amplification appeared to be resistant to KIT inhibitors in patients with melanoma.

The efficacies of several U.S. FDA-approved KIT-targeting tyrosine kinase inhibitors (TKIs) such as imatinib, sunitinib, regorafenib, and ripretinib are strongly dependent on the location of the activating KIT mutations[10][11][12][13][14][15][16][17][18][19]. Patients with GIST harboring KIT exon 9 mutations showed intermediate sensitivity to imatinib and had better relapse-free survival and overall survival (OS) compared with patients carrying KIT exon 11 mutations[11].

Ponatinib and dasatinib yielded a disease control rate and partial control rate of 67% and 32%, respectively, in GIST patients harboring KIT exon 11 mutations (DOI: 10.1200/jco.2015.33.15_suppl.10535, 10.1200/jco.2011.29.15_suppl.10006). Results from a Phase II trial involving melanoma showed 38.5% response rate to nilotinib in patients harboring KIT exon 11 mutations[20].

Both KIT and PDGFRA overexpression were associated with high tumor grade, high proliferation index, and poor outcome in patients with the serous type of ovarian carcinoma[21].

The newly developing agents such as avapritinib (BLU-285) and investigational AZD3229 all showed the potential to be better inhibitors for clinically relevant KIT/PDGFRA mutations in GIST[22].

KIT mutations have been determined as an inclusion criterion for the trials evaluating dasatinib, avapritinib, sunitinib, nilotinib, ponatinib, regorafenib, and ripretinib efficacies in melanoma, solid tumors, GIST, systemic mastocytosis (AdvSM), and relapsed or refractory myeloid malignancies (NCT00700882, NCT04771520, NCT03465722, NCT02693535, NCT02561988, NCT01028222, NCT01099514, NCT03171389, NCT02272998, NCT02501551, and NCT02571036).

In a clinical study, two patients with gastrointestinal stromal tumor harboring primary KIT A502_Y503dup mutation developed acquired mutations (KIT N822K and PDGFRA H687Y, respectively) after initial response to imatinib treatment[23]. Preclinical studies demonstrated that cells expressing KIT A502_Y503dup were resistant to imatinib[24][25].

In preclinical studies, transformed cells expressing KIT A502_Y503dup were sensitive to avapritinib, cabozantinib, regorafenib, ripretinib and sunitinib, as demonstrated by reduced cell viability in vitro and/or decreased tumor volume in PDX models[22][26][27][6].

KIT N822K was initially identified as a secondary mutation in patients with imatinib-resistant GIST[28]. In 2013, retrospective analysis has demonstrated that exon 17 mutations (including N822K mutations) were identified in 12 out of 38 patients who developed imatinib resistance. Besides, all the patients with these secondary mutations showed shorter progression-free survival after switching treatment to sunitinib[29][30][31].

In a phase II trial of regorafenib in GIST patients who failed imatinib and sunitinib treatment, a patient harboring KIT N822K mutant achieved protocol-defined clinical benefit and had a PFS for more than seven months[32]. Another phase II trial of regorafenib in GIST, which enrolled 18 patients with secondary mutations in exon 17 of the KIT gene, including eight patients with N822 mutant. In this trial, patients received regorafenib treatment had a longer median PFS compared to patients without regorafenib therapy in a historical cohort (22.1 vs. 5.5 months, respectively). The results demonstrated that GIST patients harboring KIT exon 17 mutations, including N822 mutant, could respond to regorafenib treatment with a disease control rate of 93.3%[33]. In a case report, a metastatic vulvar melanoma patient harboring KIT N822K mutation had a partial response for 11 months by avapritinib treatment[34].

The preclinical studies have shown that transformed cells expressing KIT N822K mutant were sensitive to avapritinib, ponatinib, dasatinib, regorafenib, ripretinib, midostaurin, and sunitinib, but resistant to imatinib treatment in vitro[35][36][37]. Furthermore, transformed cells co-expressing KIT W557_K558del and KIT N822K were sensitive to avapritinib, ponatinib, regorafenib, and ripretinib, but resistant to imatinib and sunitinib[38][22].

ARID1A Heterozygous deletion

Biological Impact

The AT-rich interactive domain 1A (ARID1A) gene encodes the BAF250A protein, a component of the SWI/SNF chromatin remodeling complex that plays a role in various cellular functions, including DNA repair, DNA synthesis, and transcription[39][40]. Haploinsufficiency of ARID1A is associated with tumor formation in some cancers[41]. Inactivation of ARID1A is commonly observed in ovarian, endometrial, uterine, and, gastric cancers[42][43][44][45][46].

Therapeutic and prognostic relevance

ARID1A is the most frequently mutated genes in ovarian clear cell carcinoma and several synthetic lethality hypothesis-based therapeutic targets in ARID1A mutated cancer are in development. For examples, 1) EZH2 inhibitor[47][48]; 2) AKT-inhibitors MK-2206 and perifosine, as well as PI3K-inhibitor buparlisib[49]; 3) multiple kinase inhibitor, dasatinib[50].

Some preclinical evidences suggested that reduced ARID1A expression confers resistance to several HER2/PI3K/mTOR signaling cascade inhibitors such as AZD8055 and trastuzumab, through activation of annexin A1 expression[51]. Loss or decreased expression of ARID1A has been reported to associate with resistance to platinum-based chemotherapies, shorter overall survival and lower complete response rate in ovarian cancer patients[52][53].

Low expression of ARID1A is a significant and independent prognostic factor for poor disease-free and overall survival in breast cancer patients[54][55]. Besides, loss of ARID1A expression was more frequently seen in mismatch repair (MMR)-deficient colorectal cancers, predominantly in tumor with MLH1 promoter hypermethylation[56]. Positive ARID1A expression could independently predict worse overall survival in stage IV CRC patients compared with negative ARID1A expression[57].

ARID1A mutation has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in metastatic biliary tract cancer (NCT04042831), and niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), or any malignancy, except prostate cancer (NCT03207347).

The preclinical study discovered that ARID1A deficiency sensitized some tumors to PARP inhibitor drugs, such as olaparib, rucaparib, talazoparib, and veliparib, which block DNA damage repair pathways[58].

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[59]. 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[60][61][62][63][64]. 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[65]. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies[66][67][68][69]and a board range of tumors such as prostate cancer[70], head and neck squamous cell carcinoma (HNSCC)[71], pancreatic cancer[72], lung adenocarcinoma[73], breast cancer[74], and ovarian cancer[61].

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)[75].

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[76]. 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[77].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)[78]. 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[79]. 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)[80].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)[81].

In preclinical studies, cells with ATM alternation were sensitive to olaparib, niraparib, and talazoparib treatment in vitro and in vivo[82][83][84][85].

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)[86]and prostate cancer (NCT02952534, NCT03533946)[81], 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.

ACT Onco® + Report

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[87]. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer[88].

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer[89].

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[90][91][92]. 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[93]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[94][95].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[96][97]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[98][99][100]. 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[101][102][103]. 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)[104][105].

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[97][106][107].

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[99]. 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[108].

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[109].

ACT Onco® + Report

CDKN2C Heterozygous deletion

Biological Impact

CDKN2C gene encodes for cyclin-dependent kinase inhibitor 2C (CDKN2C) or p18 or INK4C, a member of the INK4 family of cyclin-dependent kinase inhibitors. CDKN2C binds to CDK4 or CDK6 and inhibits the activation of cyclin-dependent kinases (CDK) to prevent cell cycle progression at the G1 phase[110]. CDKN2C has been implicated as a haploinsufficient tumor suppressor gene[111]with one copy loss may promote cell cycle progression and induce proliferation in a variety of cancers[112][113][114]. Loss of CDKN2C by gene deletion or inactivating mutation has been reported in multiple cancer types, including myeloma, lymphoma, glioblastoma, meningioma, testicular cancers, melanoma, hepatocellular carcinomas, thyroid, and parathyroid cancer[115][116][117][118][119][120][121][122][123].

Therapeutic and prognostic relevance

CDKN2C loss has been determined as an inclusion criterion for the trial evaluating abemaciclib and ribociclib efficacies in patients with glioblastoma and myeloma (NCT02981940, NCT04118036, NCT03834740, NCT02933736).

An in vitro study demonstrated that cells expressing CDKN2A/B/C triple deletions activates cyclin-dependent kinases (CDK) and improves the sensitivity to palbociclib in glioblastoma multiforme (GBM) tumor cells[124]. Deletion of CDKN2C was associated with poorer prognosis in myeloma, acute lymphoblastic leukemia, hepatocellular carcinomas, and diffuse large B cell lymphoma (DLBCL)[125][126][122][127].

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[128]. 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[129][130]. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors[131], and CHEK1 mutations are extremely rare[128]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer[132], breast cancer[133], colorectal cancer[134], non-small cell lung (NSCLC) cancer[135], and nasopharyngeal cancer[136].

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)[75].

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)[86], 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[137].

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[138]. 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[129][130]. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers[139][140][141][142][143].

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)[75].

In a phase II trial (TBCRC 048; NCT03344965), 7 metastatic breast cancer patients harboring only germline mutations in CHEK2 were not responded to olaparib treatment (SD: n=3, PD: n=4)[80]. Furthermore, in another phase II trial (TRITON2; NCT02952534), 12 mCRPC patients harboring CHEK2 alteration had limited response to rucaparib treatment. One patient with co-occurring ATM alteration had a radiographic partial response (n=1/9 evaluable patients). The prostate-specific antigen response rate was 16.7% (n=2/12), and the 6-month clinical benefit rate was 37.5% (n=3/8)[81].

In addition, CHEK2 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)[86], and prostate cancer (NCT02952534, NCT03533946)[81], niraparib efficacy in metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma (NCT03840967), melanoma (NCT03925350), pancreatic cancer (NCT03553004, NCT03601923), prostate cancer (NCT02854436), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in HER2-negative solid tumors (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

FLCN Heterozygous deletion

Biological Impact

The FLCN gene encodes the tumor suppressor, Folliculin, a GTPase activating protein (GAP) for RagC/D GTPase proteins involved in amino acid sensing and signaling to mTORC1[144]. FLCN has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[145][146]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[147][148]. Germline mutation of the FLCN gene causes the Birt-Hogg-Dubé syndrome, a rare disorder that is characterized by benign hamartomatous skin lesions and an increased risk of pneumothorax and renal tumors[149].

Therapeutic and prognostic relevance

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTC) patients who had PI3K/mTOR/AKT alterations, including TSC2, FLCN or NF1, showed impressive progression-free survival (PFS) of 15.2 months after receiving everolimus[150]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[151].

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[152][153]. 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[152]. 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[152][153][154][155][156][157][158].

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[76]. Preclinically, loss of MRE11 also predicted sensitivity to PARP inhibitor talazoparib and ABT-888 in endometrial cancer[159]and microsatellite unstable colorectal cancer (CRC) cell lines[160]. 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[161].

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[162][163][164]. 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[165]. 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[162][166]. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas[167], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers[168].

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[169][170][171][172]. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer and urothelial carcinoma[173][174], 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[175].

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[176].

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[177]. Inactivation of PTCH1 results in hedgehog ligand-independent activation of SMO, causing a downstream activation of the pathway and lead to the neoplastic growth[178][179]. Recurrent PTCH1 mutations have been reported in sporadic basal cell carcinoma (BCCs) and medulloblastoma[180][181][182][183].

Germline PTCH1 mutations are associated with the nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome), predisposing patients to basal cell carcinoma and medulloblastoma[181]. PTCH1 is a haploinsufficient tumor suppressor gene with one copy loss may be sufficient to promote tumor development in mice[178][184].

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[185][186][187][188].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[189]. 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[190]. In the phase II MyPathway trial, three advanced solid tumors patients harboring PTCH1 loss-of-function mutations had partial responses to vismodegib treatment[191]. In a clinical study, two patients with Sonic Hedgehog (SHH) activated medulloblastoma harboring PTCH1 loss-of-function mutations demonstrated partial responses to sonidegib treatment[192].

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[193][194][195]. 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[196]. Overexpression of RAD51 has been observed in many cancer cells, including pancreatic cancer and breast cancer and its hyperexpression is implicated in drug resistance[197][198][199][200][201][202][203]. Germline mutations in RAD51 are associated with increased susceptibility to breast cancer[204][205][206][207].

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[208]; 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[209][210].

RB1 Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[211]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[212]. 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[213][214][215]. 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[216].

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[87]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytoxan (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy[217].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[218][219].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[220]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[221].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[222][223]. 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[219][224].

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[225]. 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[226]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)[227][228][229][230]. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer[231], colorectal cancer (CRC)[229][232][233], and less frequently seen in other cancers such as lung adenocarcinoma[234], head and neck cancer[235][236], and cutaneous squamous cell carcinoma[237].

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[238]. 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[239].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)[240][241]. 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[242].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis[243][244][245][246][247][248][249][250]. 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[251].

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[252][253]. STK11 is a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[254][255]. In the mouse model, loss of STK11 promotes aggressive endometrial and squamous cell carcinomas[256][257]. Mutations in STK11 have been found in lung, breast, cervical, testicular, and liver cancers, as well as malignant melanoma, pancreatic and biliary carcinoma[258]. Germline mutations in STK11 are found in 30-70% of Peutz-Jeghers syndrome[259].

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[260]. In another clinical case study, an adrenocorticotropic pituitary carcinoma patient whose tumor bearing an STK11 inactivating mutation responded to a combination of everolimus and radiotherapy[261].

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[262].

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)[263][264][265]. 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[266].

TSC1 Heterozygous deletion

Biological Impact

The tuberous sclerosis complex 1 (TSC1) gene encodes a tumor suppressor, hamartin, a key negative regulator of the mammalian target of rapamycin (mTOR) pathway[267][268]. Mutations in TSC1/TSC2 tumor suppressor genes that result in inactivation of the complex are commonly found in patients with tuberous sclerosis[269][270][271], while LOH in TSC1/TSC2 has been identified in head and neck squamous cell carcinoma (HNSCC)[272]and endometrial cancer[273]. Loss of single TSC1 allele (haploinsufficiency) may provide a growth advantage to bladder epithelial cells, contributing to bladder cancer development[274]. Both TSC1 and TSC2 mutations cause the autosomal dominant genetic disorder tuberous sclerosis complex (TSC), in which individuals develop a variety of benign but often progressive neoplasms[275].

Therapeutic and prognostic relevance

Genomic alterations with activating effects of the mTOR signaling pathway (including deletion/inactivation of TSC1/TSC2) have been shown to confer sensitivity to everolimus across multiple neoplasms, such as bladder tumors[173], gastric, sarcoma, thyroid cancer, and HNSCC[172]. There were case reports demonstrated the efficacy of sirolimus in malignant uterine perivascular epithelioid cell tumors (PEComa) patients harboring mutations/deletions in TSC1 and TSC2 genes, and temsirolimus in PEComa patients with hyperactivated mTOR pathway. Genomic profiling analysis of GOG248, a Phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer showed that mutations in AKT1, TSC1 and TSC2 may predict clinical benefit from temsirolimus[276]. Recent studies indicate that there are mTORC1-independent signaling pathways downstream of hamartin-tuberin, which may represent new therapeutic targets[277].

Everolimus has been approval by the U.S. FDA for Tuberous Sclerosis Complex (TSC)-associated renal angiomyolipoma and Tuberous Sclerosis Complex (TSC)-associated subependymal giant cell astrocytoma (SEGA). This approval is based on the results from EXIST-1, EXIST-2, and Study 2485 trials (NCT00789828, NCT00790400, and NCT00411619).

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[278] 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[107] NCT02107703	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1[279] NCT02102490	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib [ORR(%): 19.7 vs. 17.4]

Avapritinib (AYVAKIT)

Avapritinib is a tyrosine kinase inhibitor that targets PDGFRA and PDGFRA D842 mutants as well asmultiple KIT exon 11, 11/17 and 17 mutants with half maximal inhibitory concentrations (IC50s) less than25 nM. Avapritinib is developed and and marketed by Blueprint Medicines Corporation under the trade name AYVAKIT.

- FDA Approval Summary of Avapritinib (AYVAKIT)

NAVIGATOR NCT02508532	**Gastrointestinal stromal tumor** (Approved on 2020/01/09)
	PDGFRA exon 18 mutation
	Avapritinib [ORR(%): 84.0]

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

Cabozantinib (COMETRIQ)

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

- FDA Approval Summary of Cabozantinib (COMETRIQ)

EXAM[281] NCT00704730	**Thyroid cancer** (Approved on 2012/11/29)
	-
	Cabozantinib vs. Placebo [PFS(M): 11.2 vs. 4]

Cabozantinib (CABOMETYX)

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

- FDA Approval Summary of Cabozantinib (CABOMETYX)

COSMIC-311 NCT03690388	**Differentiated thyroid cancer (dtc)** (Approved on 2021/09/17)
	-
	Cabozantinib vs. Placebo [PFS(M): 11 vs. 1.9, ORR(%): 18.0 vs. 0]
CHECKMATE-9ER NCT03141177	**Renal cell carcinoma** (Approved on 2021/01/22)
	-
	Nivolumab + cabozantinib vs. Sunitinib [ORR(%): 55.7 vs. 27.1, PFS(M): 16.6 vs. 8.3, OS(M): NR vs. NR]
CELESTIAL [282] NCT01908426	**Hepatocellular carcinoma** (Approved on 2019/01/14)
	-
	Cabozantinib vs. Placebo [OS(M): 10.2 vs. 8]
CABOSUN[283] NCT01835157	**Renal cell carcinoma** (Approved on 2017/12/09)
	-
	Cabozantinib vs. Sunitinib [PFS(M): 8.6 vs. 5.3]
METEOR[284] NCT01865747	**Renal cell carcinoma** (Approved on 2016/04/25)
	-
	Cabozantinib vs. Everolimus [PFS(M): 7.4 vs. 3.8]

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

Dasatinib (SPRYCEL)

Dasatinib is an oral Bcr-Abl tyrosine kinase inhibitor (inhibits the "Philadelphia chromosome") and Src family tyrosine kinase inhibitor. Dasatinib is produced by Bristol-Myers Squibb and sold under the trade name SPRYCEL.

- FDA Approval Summary of Dasatinib (SPRYCEL)

DASISION[286] NCT00481247	**Chronic myeloid leukemia** (Approved on 2010/10/28)
	-
	Dasatinib vs. Imatinib [ORR(%): 76.8 vs. 66.2]
[287] NCT00123474	**Chronic myeloid leukemia** (Approved on 2007/11/08)
	-
	Dasatinib [ORR(%): 63.0]
[288] NCT00123487	**Acute lymphocytic leukemia** (Approved on 2006/06/28)
	-
	Dasatinib [ORR(%): 38.0]

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[289] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[290] 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[291] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[292] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[293] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

ACT Onco® + Report

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)

[294] 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]
[295]	**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]
[296] NCT00471497	**Chronic myeloid leukemia** (Approved on 2003/05/20)
	Ph+
	Imatinib vs. Nilotinib [MMR(%): 22 vs. 44]
[297] NCT00333840	**Chronic myeloid leukemia** (Approved on 2003/04/18)
	-
	Imatinib vs. Interferon-α+ cytarabine [PFS(%): 81.2 vs. 60.6]
[298] NCT00009906	**Gastrointestinal stromal tumor** (Approved on 2002/02/01)
	-
	Imatinib [PFS(M): 18.9 (imatinib 400 mg)| 23.2 (imatinib 800 mg)]

Midostaurin (RYDAPT)

Midostaurin is a small molecule that inhibits multiple receptor tyrosine kinases including FLT3 (wild type, ITD and, TKD mutant), KIT (wild type and D816V), PDGFRα/β, and members of the serine/threonine kinase PKC (protein kinase C) family.Midostaurin is developed and marketed by Novartis under the trade name RYDAPT.

- FDA Approval Summary of Midostaurin (RYDAPT)

Study 1[299] NCT00651261	**Acute myeloid leukemia** (Approved on 2017/04/28)
	FLT3 mutation
	Cytarabine and daunorubicin vs. Placebo [OS(M): 74.7 vs. 25.6]
Study 2[300] NCT00782067	**Systemic mastocytosis** (Approved on 2017/04/28)
	-
	Midostaurin [ORR (aggressive systemic mastocytosis)(%): 75, ORR(systemic mastocytosis with an associated hematologic neoplasm)(%): 58, ORR (mast-cell leukemia)(%): 50]

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[301] 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[75] 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[302] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[303] 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[304] 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[305] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[306] 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[307] 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[308] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+/HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[309] NCT01942135	**Breast cancer** (Approved on 2016/02/19)
	ER+/HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

Ponatinib (ICLUSIG)

Ponatinib is an oral, small molecule, multi-kinase inhibitor designed to inhibit the activity of the tyrosine kinase ABL, including the T315I mutated ABL as well. Ponatinib is developed and marketed by ARIAD under the trade name ICLUSIG.

- FDA Approval Summary of Ponatinib (ICLUSIG)

PACE[310] NCT01207440	**Chronic phase chronic myeloid leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MCyR(%): 55]
PACE[310] NCT01207440	**Accelerated phase chronic myeloid leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MaHR(%): 57]
PACE[310] NCT01207440	**Blast phase chronic myeloid leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MaHR(%): 31]
PACE[310] NCT01207440	**Philadelphia-positive acute lymphoblastic leukemia** (Approved on 2014/03/12)
	-
	Ponatinib [MaHR(%): 41]

Regorafenib (STIVARGA)

Regorafenib is a multi-kinase inhibitor which targets angiogenic, stromal and oncogenic receptor tyrosine kinases (RTKs). Regorafenib is developed and marketed by Bayer HealthCare Pharmaceuticals under the trade name STIVARGA.

- FDA Approval Summary of Regorafenib (STIVARGA)

RESORCE[311] NCT01774344	**Hepatocellular carcinoma, Hepatocellular carcinoma** (Approved on 2017/04/27)
	-
	Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]
GRID[16] NCT01271712	**Gastrointestinal stromal tumor** (Approved on 2013/02/25)
	-
	Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]
CORRECT[312] NCT01103323	**Colorectal cancer** (Approved on 2012/09/27)
	-
	Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

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

Ripretinib (QINLOCK)

Ripretinib is a tyrosine kinase inhibitor that inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase, including wild type, primary, and secondary mutations. Ripretinib is developed and marketed by Decipera Pharmaceuticals under the trade name QINLOCK.

- FDA Approval Summary of Ripretinib (QINLOCK)

INVICTUS NCT03353753	**Gastrointestinal stromal tumor** (Approved on 2020/05/15)
	-
	Ripretinib vs. Placebo [PFS(M): 6.3 vs. 1]

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[86] 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[187] NCT01327053	**Basal cell carcinoma** (Approved on 2015/07/24)
	-
	Sonidegib [ORR(%): 58.0]

Sunitinib (SUTENT)

Sunitinib is an oral, small molecule, multi-kinase inhibitor that targets receptor tyrosine kinase including platelet-derived growth factor receptor-α, -β (PDGFR-α, -β), vascular endothelial growth factor receptors-1, -2, -3 (VEGFR-1, -2, -3), c-kit, Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET), thereby inhibiting angiogenesis. Sunitinib is developed and marketed by Pfizer under the trade name SUTENT.

- FDA Approval Summary of Sunitinib (SUTENT)

[313][314][315] NCT00428597	**Pancreatic cancer** (Approved on 2011/05/20)
	-
	Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]
[316][317] NCT00083889	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib vs. Ifn-α [PFS(W): 47.3 vs. 22]
[318][319][317] NCT00077974	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 34.0]
[319][317] NCT00054886	**Renal cell carcinoma** (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 36.5]

[320] NCT00075218	**Gastrointestinal stromal tumor** (Approved on 2006/01/26)
	-
	Sunitinib vs. Placebo [TTP(W): 27.3 vs. 6.4]

Talazoparib (TALZENNA)

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

- FDA Approval Summary of Talazoparib (TALZENNA)

EMBRACA[321] 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)

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

Trametinib (MEKINIST)

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

- FDA Approval Summary of Trametinib (MEKINIST)

BRF117019, NCI-MATCH, CTMT212X2101 NCT02034110, NCT02465060, NCT02124772	**Cancer** (Approved on 2022/06/22)
	BRAF V600E
	Dabrafenib + trametinib [ORR(adult patients)(%): 41.0, ORR(pediatric patients)(%): 25.0]
BRF117019[323] NCT02034110	**Anaplastic thyroid cancer** (Approved on 2018/05/04)
	BRAF V600E
	Dabrafenib + trametinib [ORR(%): 61.0]
BRF113928[324] 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]

ACT Onco® + Report

COMBI-d[325] NCT01584648	**Melanoma** (Approved on 2014/01/10)
	BRAF V600E/K
	Trametinib + dabrafenib vs. Dabrafenib + placebo [PFS(M): 9.3 vs. 8.8]
METRIC[326] NCT01245062	**Melanoma** (Approved on 2013/05/29)
	BRAF V600E/K
	Trametinib vs. Dacarbazine or paclitaxel [PFS(M): 4.8 vs. 1.5]

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[185] 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.

ACT Onco® + Report

SUPPLEMENTARY INFORMATION OF TESTING RESULTS

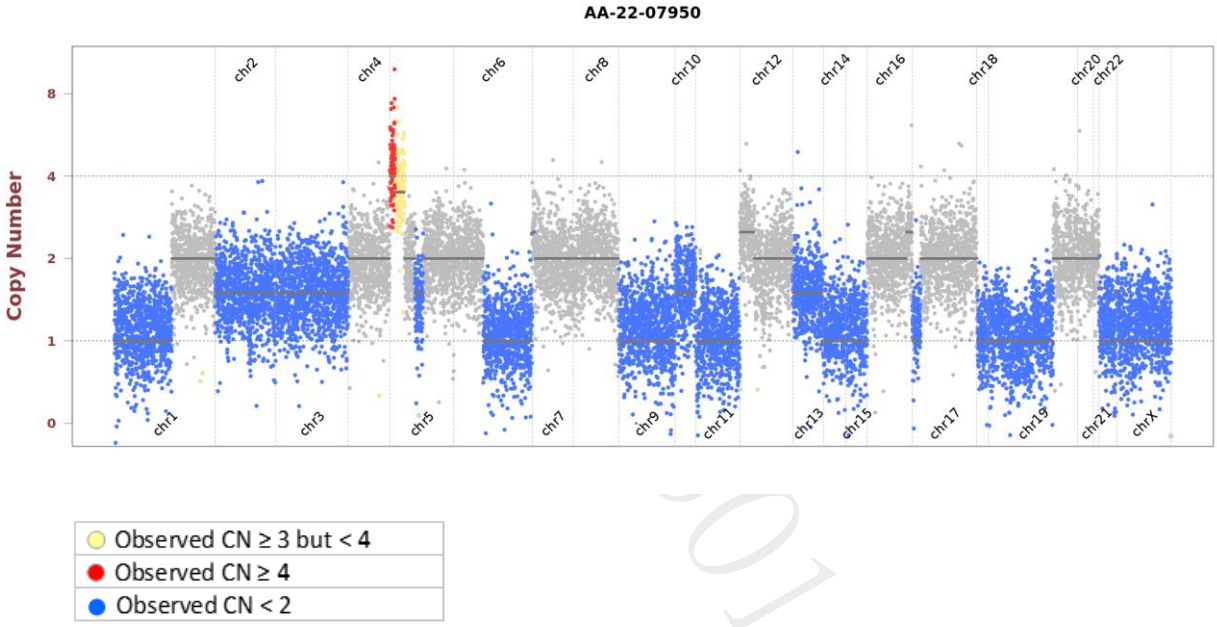
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
KIT	A502_Y503dup (Exon 9 mutations)	9	c.1504_1509dup	NM_000222	COSM1326	67.6%	1144
KIT	N822K	17	c.2466T>A	NM_000222	COSM1321	48.9%	708

- Copy Number Alterations

Observed copy number (CN) for each evaluated position is shown on the y-axis. Regions referred to as amplification or deletion are shown in color. Regions without significant changes are represented in gray.



ACT Onco® + Report

OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
AMER1	S111G	2	c.331A>G	NM_152424	-	82.0%	255
CDKN1B	P137L	1	c.410C>T	NM_004064	-	42.1%	958
ERCC5	E934K	13	c.2800G>A	NM_000123	-	95.2%	723
FANCG	R613W	14	c.1837C>T	NM_004629	COSM260835	87.5%	641
FGFR3	P778R	18	c.2333C>G	NM_000142	-	26.4%	515
MAX	R35H	3	c.104G>A	NM_002382	COSM330310	78.9%	1008
RAD50	Splice region	-	c.-204-5C>T	NM_005732	-	49.6%	1080
RXRA	Splice region	-	c.431-5C>T	NM_002957	-	88.4%	86
SETD2	P193L	3	c.578C>T	NM_014159	-	45.0%	620
SPEN	N2999K	11	c.8997C>G	NM_015001	-	9.0%	278

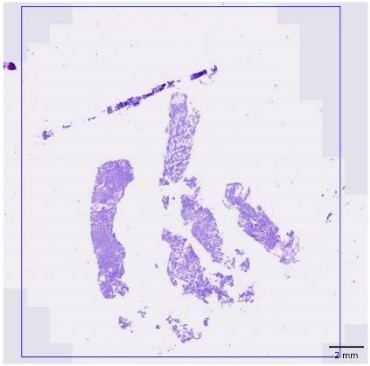
Note:

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

ACTOnco®+ Report

TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Dec 21, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11153713A
- Collection site: Tissue, labeled subphrenic
- Examined by: Dr. Yun-An Chen
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 90%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 90%
    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: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 617x
- Target Base Coverage at 100x: 93%

RNA test

- Average unique RNA Start Sites per control GSP2: 171

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:
醫檢師黃靖婷 博士
Ching-Ting Huang Ph.D.
檢字第 016511 號

CT Huang

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

Yehn

ACT Onco® + Report

GENE LIST

SNV & CNV

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

*Analysis of copy number alterations NOT available.

FUSION

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

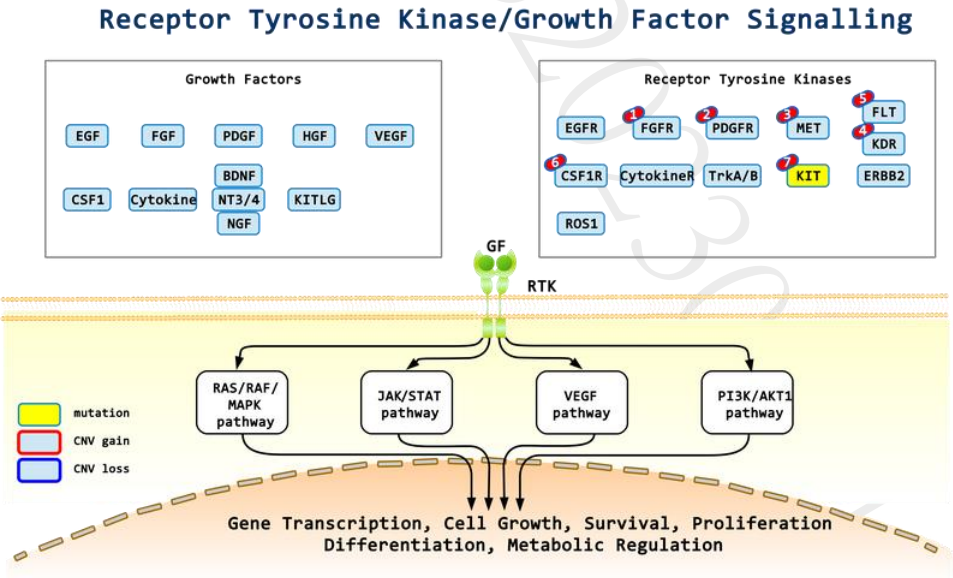
ACT Onco® + Report

APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

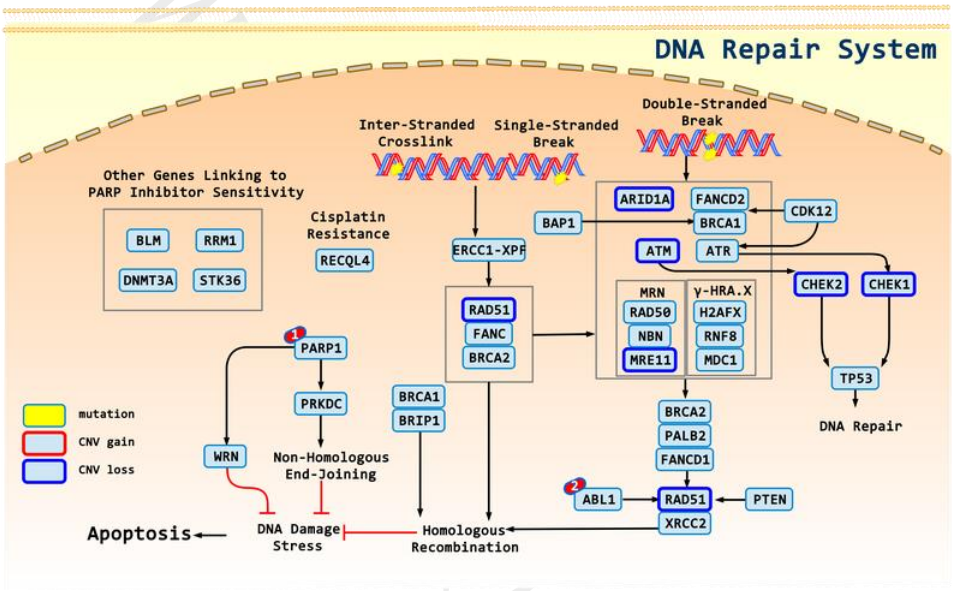
Gene	Therapies	Possible effect
CDKN2A	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
STK11	Binimetinib, Cobimetinib, Everolimus, Temsirolimus, Trametinib	**sensitive**
ARID1A	Dasatinib, Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
FLCN	Everolimus, Temsirolimus	**sensitive**
NF2	Everolimus, Temsirolimus	**sensitive**
TSC1	Everolimus, Temsirolimus	**sensitive**
ATM	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK1	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
CHEK2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
MRE11	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RAD51	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
PTCH1	Sonidegib, Vismodegib	**sensitive**
RB1	Abemaciclib, Palbociclib, Ribociclib	**resistant**
SMAD4	Cetuximab	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

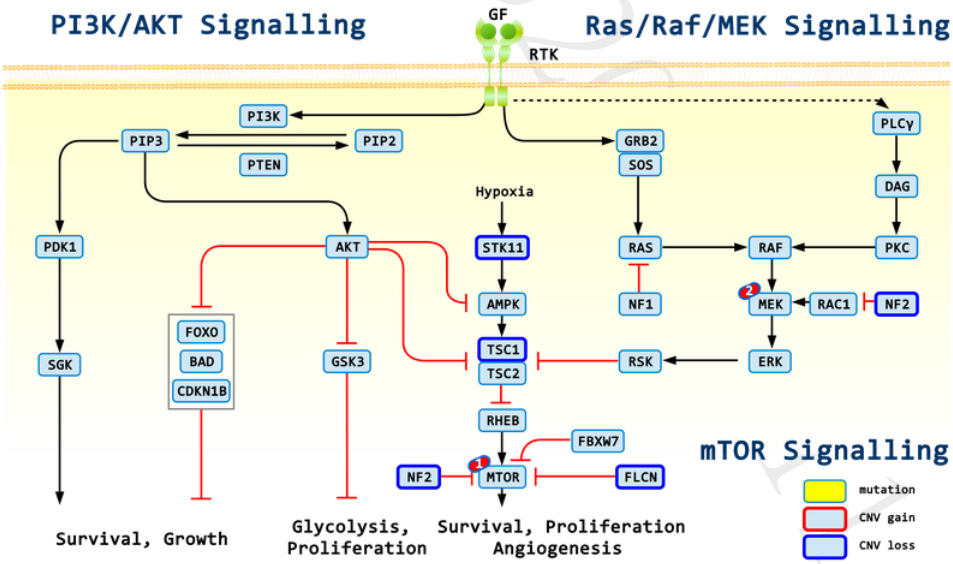


1: Ponatinib; 2: Imatinib, Sunitinib, Regorafenib, Dasatinib, Avapritinib, Ripretinib, Ponatinib, Midostaurin; 3: Cabozantinib; 4: Sunitinib, Cabozantinib, Ponatinib; 5: Sunitinib, Ponatinib, Midostaurin; 6: Sunitinib; 7: Imatinib, Sunitinib, Avapritinib, Regorafenib, Ripretinib, Ponatinib, Dasatinib, Midostaurin

ACT Onco® + Report

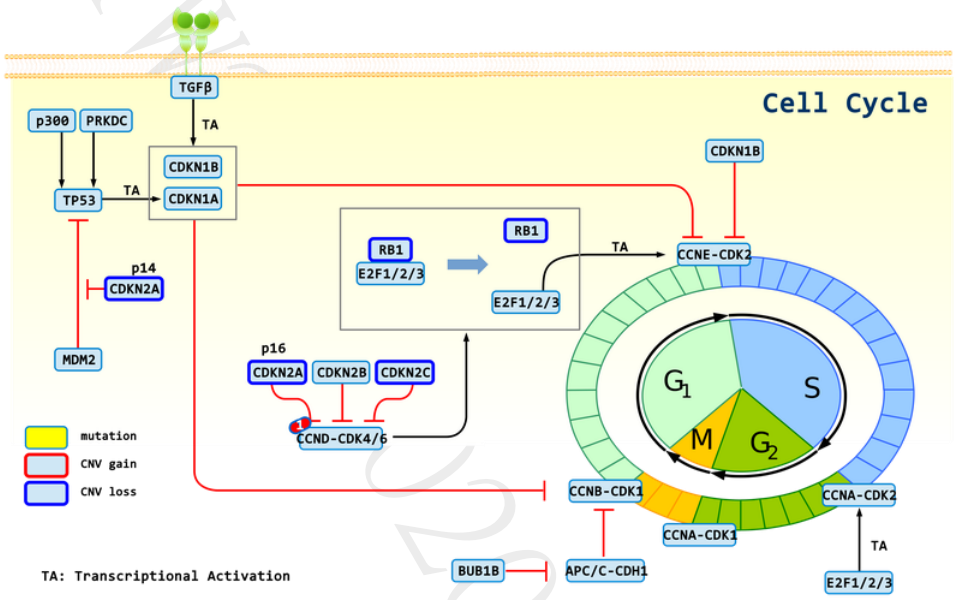


1: Olaparib, Niraparib, Rucaparib, Talazoparib; 2: Ponatinib

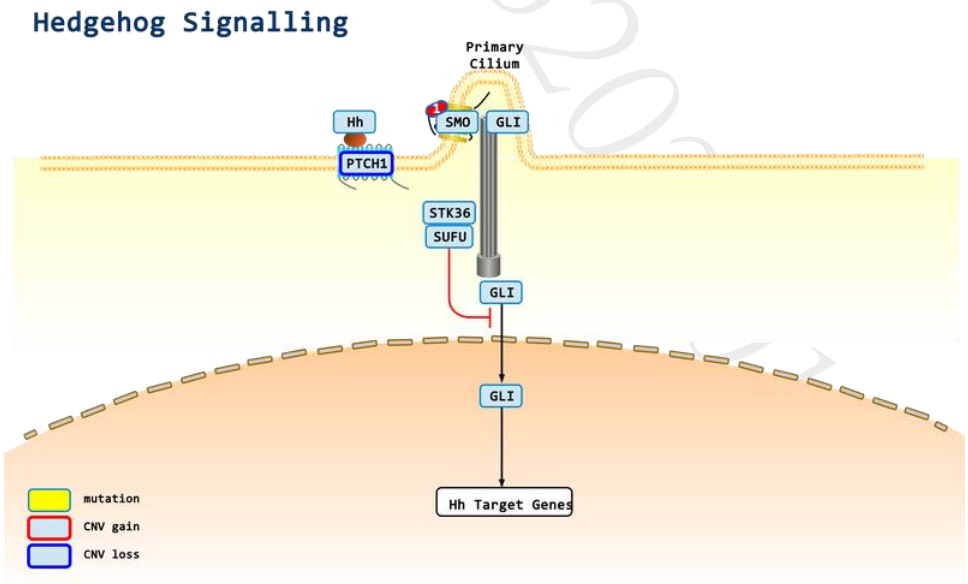


1: Everolimus, Temsirolimus; 2: Trametinib, Binimetinib, Cobimetinib

ACT Onco® + Report



1: Abemaciclib, Palbociclib, Ribociclib



1: Sonidegib, Vismodegib

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: 17546049; 2007, Oncogene;26(54):7560-8
KIT oncogenic signaling mechanisms in imatinib-resistant gastrointestinal stromal tumor: PI3-kinase/AKT is a crucial survival pathway.

2. PMID: 15365079; 2004, J Clin Oncol;22(18):3813-25
Biology of gastrointestinal stromal tumors.

3. PMID: 22089421; 2011, Nat Rev Cancer;11(12):865-78
Gastrointestinal stromal tumours: origin and molecular oncology.

4. PMID: 15790786; 2005, Blood;106(2):721-4
Activation mutations of human c-KIT resistant to imatinib mesylate are sensitive to the tyrosine kinase inhibitor PKC412.

5. PMID: 19865100; 2010, J Invest Dermatol;130(3):804-15
Pediatric mastocytosis is a clonal disease associated with D816V and other activating c-KIT mutations.

6. PMID: 24205792; 2014, Cancer Sci;105(1):117-25
Flumatinib, a selective inhibitor of BCR-ABL/PDGFR/KIT, effectively overcomes drug resistance of certain KIT mutants.

7. PMID: 21690468; 2011, J Clin Oncol;29(21):2904-9
Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification.

8. PMID: 21642685; 2011, JAMA;305(22):2327-34
KIT as a therapeutic target in metastatic melanoma.

9. PMID: 23775962; 2013, J Clin Oncol;31(26):3182-90
Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin.

10. PMID: 12181401; 2002, N Engl J Med;347(7):472-80
Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors.

11. PMID: 18955458; 2008, J Clin Oncol;26(33):5352-9
Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor.

12. PMID: 19164557; 2009, Proc Natl Acad Sci U S A;106(5):1542-7
KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients.

13. PMID: 18235121; 2008, J Clin Oncol;26(4):620-5
Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT.

14. PMID: 16098458; 2005, Eur J Cancer;41(12):1751-7
Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg.

15. PMID: 15451219; 2004, Lancet;364(9440):1127-34
Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial.

16. PMID: 23177515; 2013, Lancet;381(9863):295-302
Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial.

17. PMID: 25641662; 2015, Cancer;121(9):1405-13
Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib.

18. PMID: 19282169; 2009, Eur J Cancer;45(11):1959-68
Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure.

19. PMID: 32511981; 2020, Lancet Oncol;21(7):923-934
Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial.

20. PMID: 28327988; 2017, Ann Oncol;28(6):1380-1387
Efficacy and safety of nilotinib in patients with KIT-mutated metastatic or inoperable melanoma: final results from the global, single-arm, phase II TEAM trial.

21. PMID: 15583695; 2004, Br J Cancer;91(12):2048-55
Genetic alterations and protein expression of KIT and PDGFRA in serous ovarian carcinoma.

22. PMID: 32350132; 2020, Sci Transl Med;12(541):
Discovery and pharmacological characterization of AZD3229, a potent KIT/PDGFRα inhibitor for treatment of gastrointestinal stromal tumors.

23. PMID: 18488160; 2008, Med Oncol;25(2):207-13
Molecular analysis of secondary kinase mutations in imatinib-resistant gastrointestinal stromal tumors.

24. PMID: 27777285; 2016, Mol Cancer Ther;15(12):2845-2852
Cabozantinib Is Active against Human Gastrointestinal Stromal Tumor Xenografts Carrying Different KIT Mutations.

25. PMID: 2910034; 1989, Am J Dis Child;143(1):105-7
Failure of electrocardiographic monitoring to detect cardiac arrest in patients with pacemakers.

26. PMID: 30274985; 2019, Clin Cancer Res;25(2):609-618
Robust Activity of Avapritinib, Potent and Highly Selective Inhibitor of Mutated KIT, in Patient-derived Xenograft Models of Gastrointestinal Stromal Tumors.

27. PMID: 29100343; 2017, Oncotarget;8(44):76712-76721
Establishment and characterization of patient-derived xenograft models of gastrointestinal stromal tumor resistant to standard tyrosine kinase inhibitors.

28. PMID: 19390946; 2009, Int J Clin Oncol;14(2):143-9
Sunitinib-resistant gastrointestinal stromal tumors harbor cis-mutations in the activation loop of the KIT gene.

29. PMID: 23456621; 2013, Med Oncol;30(2):522
Secondary mutations of c-KIT contribute to acquired resistance to imatinib and decrease efficacy of sunitinib in Chinese patients with gastrointestinal stromal tumors.

30. PMID: 26316776; 2015, Onco Targets Ther;8():1997-2003
Inactivity of imatinib in gastrointestinal stromal tumors (GISTs) harboring a KIT activation-loop domain mutation (exon 17 mutation pN822K).

31. PMID: 16954519; 2006, J Clin Oncol;24(29):4764-74
Molecular correlates of imatinib resistance in gastrointestinal stromal tumors.

32. PMID: 22614970; 2012, J Clin Oncol;30(19):2401-7
Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial.

33. PMID: 28487491; 2017, Oncotarget;8(27):44121-44130
A phase II trial of regorafenib in patients with metastatic and/or a unresectable gastrointestinal stromal tumor harboring secondary mutations of exon 17.

34. PMID: 32821296; 2020, Ther Adv Med Oncol;12():1758835920946158
Successful treatment with avapritinib in patient with mucosal metastatic melanoma.

35. PMID: 21482694; 2011, Mol Cancer Ther;10(6):1028-35
Potent activity of ponatinib (AP24534) in models of FLT3-driven acute myeloid leukemia and other hematologic malignancies.

36. PMID: 31182436; 2019, Clin Cancer Res;25(16):5038-5048

Functional Properties of KIT Mutations Are Associated with Differential Clinical Outcomes and Response to Targeted Therapeutics in CBF Acute Myeloid Leukemia.

37. PMID: 31085175; 2019, Cancer Cell;35(5):738-751.e9
Ripretinib (DCC-2618) Is a Switch Control Kinase Inhibitor of a Broad Spectrum of Oncogenic and Drug-Resistant KIT and PDGFRA Variants.

38. PMID: 25239608; 2014, Clin Cancer Res;20(22):5745-5755
Ponatinib inhibits polyclonal drug-resistant KIT oncoproteins and shows therapeutic potential in heavily pretreated gastrointestinal stromal tumor (GIST) patients.

39. PMID: 10757798; 2000, Mol Cell Biol;20(9):3137-46
The human SWI-SNF complex protein p270 is an ARID family member with non-sequence-specific DNA binding activity.

40. PMID: 25387058; 2015, Annu Rev Pathol;10():145-71
SWI/SNF chromatin remodeling and human malignancies.

41. PMID: 23208470; 2013, Cancer Discov;3(1):35-43
ARID1A mutations in cancer: another epigenetic tumor suppressor?

42. PMID: 20826764; 2010, Science;330(6001):228-31
Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma.

43. PMID: 20942669; 2010, N Engl J Med;363(16):1532-43
ARID1A mutations in endometriosis-associated ovarian carcinomas.

44. PMID: 21590771; 2011, J Pathol;224(3):328-33
Loss of BAF250a (ARID1A) is frequent in high-grade endometrial carcinomas.

45. PMID: 21412130; 2011, Am J Surg Pathol;35(5):625-32
Mutation and loss of expression of ARID1A in uterine low-grade endometrioid carcinoma.

46. PMID: 22037554; 2011, Nat Genet;43(12):1219-23
Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer.

47. PMID: 26125128; 2015, Expert Opin Ther Targets;19(11):1419-22
Potential therapeutic targets in ARID1A-mutated cancers.

48. PMID: 29093822; 2017, Gynecol Oncol Res Pract;4():17
EZH2 inhibition in ARID1A mutated clear cell and endometrioid ovarian and endometrioid endometrial cancers.

49. PMID: 24979463; 2014, Oncotarget;5(14):5295-303
Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition.

50. PMID: 27364904; 2016, Mol Cancer Ther;15(7):1472-84
Synthetic Lethal Targeting of ARID1A-Mutant Ovarian Clear Cell Tumors with Dasatinib.

51. PMID: 27172896; 2016, Clin Cancer Res;22(21):5238-5248
Loss of ARID1A Activates ANXA1, which Serves as a Predictive Biomarker for Trastuzumab Resistance.

52. PMID: 22101352; 2012, Mod Pathol;25(2):282-8
Loss of ARID1A expression is related to shorter progression-free survival and chemoresistance in ovarian clear cell carcinoma.

53. PMID: 24459582; 2014, J Gynecol Oncol;25(1):58-63
Decreased ARID1A expression is correlated with chemoresistance in epithelial ovarian cancer.

54. PMID: 26770240; 2015, J Breast Cancer;18(4):339-46
Loss of Tumor Suppressor ARID1A Protein Expression Correlates with Poor Prognosis in Patients with Primary Breast Cancer.

55. PMID: 21889920; 2012, Cancer Epidemiol;36(3):288-93
Frequent low expression of chromatin remodeling gene ARID1A in breast cancer and its clinical significance.

ACT Onco® + Report

56. PMID: 25311944; 2014, Hum Pathol;45(12):2430-6
Immunohistochemical detection of ARID1A in colorectal carcinoma: loss of staining is associated with sporadic microsatellite unstable tumors with medullary histology and high TNM stage.

57. PMID: 25561809; 2014, World J Gastroenterol;20(48):18404-12
Clinicopathologic and prognostic relevance of ARID1A protein loss in colorectal cancer.

58. PMID: 26069190; 2015, Cancer Discov;5(7):752-67
ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors.

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

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

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

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

63. 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.

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

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

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

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

68. 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.

69. 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.

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

71. 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.

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

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

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

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

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

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

82. 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.

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

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

85. 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.

86. 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.

87. 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.

88. 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.

89. 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.

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

91. 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.

92. 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.

93. 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.

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

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

96. 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.

97. 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.

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

99. 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.

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

101. 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.

102. 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.

103. 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.

104. 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.

105. 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.

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

107. 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.

108. 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.

109. 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.

110. PMID: 11124804; 2000, Genes Dev;14(24):3115-25
Structural basis of inhibition of CDK-cyclin complexes by INK4 inhibitors.

111. PMID: 12556487; 2003, Mol Cell Biol;23(4):1269-77
Haploinsufficiency of p18(INK4c) sensitizes mice to carcinogen-induced tumorigenesis.

112. PMID: 22997239; 2012, J Natl Cancer Inst;104(21):1673-9
Dual suppression of the cyclin-dependent kinase inhibitors CDKN2C and CDKN1A in human melanoma.

113. PMID: 19411068; 2009, Cancer Cell;15(5):389-401
CDK inhibitor p18(INK4c) is a downstream target of GATA3 and restrains mammary luminal progenitor cell proliferation and tumorigenesis.

114. PMID: 17409423; 2007, Cancer Res;67(7):3162-70
p18Ink4c collaborates with Men1 to constrain lung stem cell expansion and suppress non-small-cell lung cancers.

115. PMID: 25576899; 2015, Hum Mol Genet;24(8):2318-29
Characterization of the mutational landscape of anaplastic thyroid cancer via whole-exome sequencing.

116. PMID: 16960149; 2007, Blood;109(1):271-80
Homozygous deletions localize novel tumor suppressor genes in B-cell lymphomas.

117. PMID: 23616356; 2013, J Pathol;230(3):249-60
Complete genomic landscape of a recurring sporadic parathyroid carcinoma.

118. PMID: 22133722; 2011, Sci Transl Med;3(111):111ra121
Personalized oncology through integrative high-throughput sequencing: a pilot study.

119. PMID: 18829482; 2008, Clin Cancer Res;14(19):6033-41
Deletions of CDKN2C in multiple myeloma: biological and clinical implications.

120. PMID: 18381405; 2008, Cancer Res;68(8):2564-9
Identification of p18 INK4c as a tumor suppressor gene in glioblastoma multiforme.

121. PMID: 11485924; 2001, Am J Pathol;159(2):661-9
Alterations of the tumor suppressor genes CDKN2A (p16(INK4a)), p14(ARF), CDKN2B (p15(INK4b)), and CDKN2C (p18(INK4c)) in atypical and anaplastic meningiomas.

122. PMID: 15349907; 2004, Hepatology;40(3):677-86
Reduced expression of cell cycle regulator p18(INK4C) in human hepatocellular carcinoma.

123. PMID: 10652429; 2000, Int J Cancer;85(3):370-5
Cell cycle regulators in testicular cancer: loss of p18INK4C marks progression from carcinoma in situ to invasive germ cell tumours.

124. PMID: 22711607; 2012, Neuro Oncol;14(7):870-81
p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells.

125. PMID: 21994415; 2011, Clin Cancer Res;17(24):7776-84
Mapping of chromosome 1p deletions in myeloma identifies FAM46C at 1p12 and CDKN2C at 1p32.3 as being genes in regions associated with adverse survival.

126. PMID: 20303590; 2010, Leuk Res;34(11):1476-82
Prognostic classification of patients with acute lymphoblastic leukemia by using gene copy number profiles identified from array-based comparative genomic hybridization data.

127. PMID: 19455257; 2007, Cancer Inform;3():399-420
Germinal center B cell-like (GCB) and activated B cell-like (ABC) type of diffuse large B cell lymphoma (DLBCL): analysis of molecular predictors, signatures, cell cycle state and patient survival.

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

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

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

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

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

133. 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.

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

135. 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.

136. 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.

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

138. PMID: 21088254; 2011, Clin Cancer Res;17(3):401-5
Tumor suppressor CHK2: regulator of DNA damage response and mediator of chromosomal stability.

139. PMID: 23296741; 2013, Fam Cancer;12(3):473-8
The risk of gastric cancer in carriers of CHEK2 mutations.

140. 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.

141. PMID: 25583358; 2015, Int J Cancer;137(3):548-52
CHEK2 mutations and the risk of papillary thyroid cancer.

142. PMID: 12052256; 2002, Breast Cancer Res;4(3):R4
Mutation analysis of the CHK2 gene in breast carcinoma and other cancers.

143. PMID: 15125777; 2004, Mol Cancer;3():14
CHK2 kinase expression is down-regulated due to promoter methylation in non-small cell lung cancer.

144. PMID: 24095279; 2013, Mol Cell;52(4):495-505
The folliculin tumor suppressor is a GAP for the RagC/D GTPases that signal amino acid levels to mTORC1.

145. PMID: 26342594; 2016, Fam Cancer;15(1):127-32
Birt-Hogg-Dubé syndrome: novel FLCN frameshift deletion in daughter and father with renal cell carcinomas.

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

147. PMID: 19850877; 2009, Proc Natl Acad Sci U S A;106(44):18722-7
Homozygous loss of BHD causes early embryonic lethality and kidney tumor development with activation of mTORC1 and mTORC2.

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

ACT Onco® + Report

149. PMID: 15956655; 2005, J Natl Cancer Inst;97(12):931-5
High frequency of somatic frameshift BHD gene mutations in Birt-Hogg-Dubé-associated renal tumors.

150. PMID: 29301825; 2018, Clin Cancer Res;24(7):1546-1553
Genomic Correlates of Response to Everolimus in Aggressive Radioiodine-refractory Thyroid Cancer: A Phase II Study.

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

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

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

154. 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.

155. 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.

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

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

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

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

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

161. 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.

162. PMID: 25893302; 2016, Oncogene;35(5):537-48
Role of Merlin/NF2 inactivation in tumor biology.

163. 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.

164. 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.

165. PMID: 17655741; 2007, Brain Pathol;17(4):371-6
Role of NF2 haploinsufficiency in NF2-associated polyneuropathy.

166. PMID: 19545378; 2009, Orphanet J Rare Dis;4():16
Neurofibromatosis type 2 (NF2): a clinical and molecular review.

167. 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.

168. PMID: 24393766; 2014, Oncotarget;5(1):67-77
NF2/merlin in hereditary neurofibromatosis 2 versus cancer: biologic mechanisms and clinical associations.

169. 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.

170. 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.

171. 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.

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

173. PMID: 22923433; 2012, Science;338(6104):221
Genome sequencing identifies a basis for everolimus sensitivity.

174. PMID: 25630452; 2015, Eur Urol;67(6):1195-1196
Exceptional Response on Addition of Everolimus to Taxane in Urothelial Carcinoma Bearing an NF2 Mutation.

175. 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.

176. 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.

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

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

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

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

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

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

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

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

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

186. 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.

187. 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.

188. 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.

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

190. 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.

191. 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.

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

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

194. 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.

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

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

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

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

199. 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.

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

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

202. 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.

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

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

205. 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.

206. 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.

207. 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.

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

209. 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.

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

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

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

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

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

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

216. 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.

217. PMID: 22811582; 2012, Clin Cancer Res;18(18):5110-22
RB-pathway disruption is associated with improved response to neoadjuvant chemotherapy in breast cancer.

218. 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.

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

220. 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.

221. 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.

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

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

224. 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.

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

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

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

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

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

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

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

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

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

234. 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.

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

236. 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.

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

238. 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.

239. 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.

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

241. 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.

242. 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.

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

244. 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.

245. 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.

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

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

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

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

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

251. 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.

252. PMID: 19029933; 2008, Oncogene;27(55):6908-19
LKB1; linking cell structure and tumor suppression.

253. PMID: 19584313; 2009, Physiol Rev;89(3):777-98
LKB1 and AMPK family signaling: the intimate link between cell polarity and energy metabolism.

254. 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.

255. PMID: 17676035; 2007, Nature;448(7155):807-10
LKB1 modulates lung cancer differentiation and metastasis.

256. PMID: 18245476; 2008, Cancer Res;68(3):759-66
Loss of Lkb1 provokes highly invasive endometrial adenocarcinomas.

257. PMID: 18172296; 2008, Cancer Res;68(1):55-63
LKB1 deficiency sensitizes mice to carcinogen-induced tumorigenesis.

258. 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.

259. PMID: 9425897; 1998, Nat Genet;18(1):38-43
Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase.

260. PMID: 21189378; 2011, J Clin Oncol;29(6):e150-3
mTOR inhibitor treatment of pancreatic cancer in a patient With Peutz-Jeghers syndrome.

261. PMID: 27615706; 2016, CNS Oncol;5(4):203-9
Widely metastatic atypical pituitary adenoma with mTOR pathway STK11(F298L) mutation treated with everolimus therapy.

262. 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.

263. 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.

264. PMID: 29773717; 2018, Cancer Discov;8(7):822-835

STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma.

265. 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.

266. 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.

267. PMID: 21157483; 2011, Nat Rev Mol Cell Biol;12(1):21-35
mTOR: from growth signal integration to cancer, diabetes and ageing.

268. PMID: 12271141; 2002, Proc Natl Acad Sci U S A;99(21):13571-6
Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling.

269. PMID: 9242607; 1997, Science;277(5327):805-8
Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34.

270. PMID: 8269512; 1993, Cell;75(7):1305-15
Identification and characterization of the tuberous sclerosis gene on chromosome 16.

271. PMID: 1303246; 1992, Nat Genet;2(1):37-41
Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease.

272. PMID: 18538015; 2008, BMC Cancer;8():163
Involvement of TSC genes and differential expression of other members of the mTOR signaling pathway in oral squamous cell carcinoma.

273. PMID: 28339086; 2017, Int J Oncol;50(5):1778-1784
Identification of novel mutations in endometrial cancer patients by whole-exome sequencing.

274. PMID: 20610279; 2010, Urol Oncol;28(4):409-28
Bladder cancer or bladder cancers? Genetically distinct malignant conditions of the urothelium.

275. PMID: 17005952; 2006, N Engl J Med;355(13):1345-56
The tuberous sclerosis complex.

276. 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.

277. PMID: 26412398; 2015, Sci Rep;5():14534
PAK2 is an effector of TSC1/2 signaling independent of mTOR and a potential therapeutic target for Tuberous Sclerosis Complex.

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

279. 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.

280. 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.

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

282. PMID: 29972759; 2018, N Engl J Med;379(1):54-63

Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma.

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

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

285. 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.

286. PMID: 20525995; 2010, N Engl J Med;362(24):2260-70
Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.

287. PMID: 18541900; 2008, J Clin Oncol;26(19):3204-12
Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia.

288. PMID: 17496201; 2007, Blood;110(7):2309-15
Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study.

289. 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.

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

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

292. 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.

293. 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.

294. 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.

295. 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.

296. 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.

297. 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.

298. 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.

ACT Onco® + Report

299. PMID: 28644114 ; 2017, N Engl J Med;377(5):454-464
Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation.

300. PMID: 27355533; 2016, N Engl J Med;374(26):2530-41
Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis.

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

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

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

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

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

306. 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.

307. 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.

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

309. PMID: 26030518; 2015, N Engl J Med;373(3):209-19
Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer.

310. PMID: 24180494; 2013, N Engl J Med;369(19):1783-96
A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias.

311. PMID: 27932229; 2017, Lancet;389(10064):56-66
Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial.

312. PMID: 23177514; 2013, Lancet;381(9863):303-12
Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial.

313. PMID: 27924459; 2016, Target Oncol;11(6):815-824
Patient-Reported Outcomes and Quality of Life with Sunitinib Versus Placebo for Pancreatic Neuroendocrine Tumors: Results From an International Phase III Trial.

314. PMID: 27836885; 2017, Ann Oncol;28(2):339-343
Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study.

315. PMID: 21306237; 2011, N Engl J Med;364(6):501-13
Sunitinib malate for the treatment of pancreatic neuroendocrine tumors.

316. PMID: 17227905; 2007, Oncologist;12(1):107-13
Food and Drug Administration drug approval summary: Sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma.

ACT Onco® + Report

317. PMID: 27238653; 2016, Eur Urol;70(6):1006-1015
Early Tumour Shrinkage: A Tool for the Detection of Early Clinical Activity in Metastatic Renal Cell Carcinoma.

318. PMID: 16757724; 2006, JAMA;295(21):2516-24
Sunitinib in patients with metastatic renal cell carcinoma.

319. PMID: 25577718; 2015, Eur Urol;67(5):952-8
Depth of remission is a prognostic factor for survival in patients with metastatic renal cell carcinoma.

320. PMID: 17046465; 2006, Lancet;368(9544):1329-38
Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial.

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

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

323. 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.

324. 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.

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

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