林靜宇
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ACT Onco® + Report

PATIENT		
Identifier: 林靜宇		Patient ID: 21012464
Date of Birth: May 03, 1968		Gender: Male
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: C11207402	Collection site: Pleural effusion	Type: FFPE tissue
Date received: Mar 02, 2023	Lab ID: AA-23-01242	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	
EGFR L747_T751del (Exon 19 deletion)	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-	-

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
EGFR C797S	Brigatinib	Osimertinib
EGFR E709G	Afatinib	Erlotinib, Gefitinib
EGFR L747_T751del (Exon 19 deletion)	-	Cetuximab

Note:

- The above summary tables present genomic variants and biomarkers based on the three-tiered approach proposed by US FDA for reporting tumor profiling NGS testing. "Variants/biomarkers with evidence of clinical significance" refers to mutations that are widely recognized as standard-of-care biomarkers (FDA level 2/AMP tier 1). "Variants/biomarkers with potential clinical significance" refers to mutations that are not included in the standard of care but are informational for clinicians, which are commonly biomarkers used as inclusion criterial for clinical trials (FDA level 3/AMP tier 2).
- The therapeutic agents and possible effects to a given drug are based on mapping the variants/biomarkers with ACT Genomics clinical knowledge database. The mapping results only provide information for reference, but not medical recommendation.
- Please refer to corresponding sections for more detailed information about genomic alteration and clinical relevance listed above.

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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
CTNNB1	S37C	28.1%
EGFR	L747_T751del (Exon 19 deletion)	68.0%
EGFR	E709G	65.8%
EGFR	C797S	28.2%
TP53	R273C	78.0%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr22	*CHEK2, NF2*	Heterozygous deletion	1
Chr5	*RAD50*	Heterozygous deletion	1
Chr9	*CDKN2A*	Heterozygous deletion	1
Chr7	*CARD11*	Amplification	6

- 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)	3.8 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:
- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 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%.

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 1		
EGFR L747_T751del (Exon 19 deletion)	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	**sensitive**
Level 4		
EGFR C797S	Brigatinib	**sensitive**
EGFR E709G	Afatinib	**sensitive**
EGFR C797S	Osimertinib	**resistant**
EGFR E709G	Erlotinib, Gefitinib	**resistant**
EGFR L747_T751del (Exon 19 deletion)	Cetuximab	**resistant**

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

No genomic alterations detected to confer sensitivity or lack of benefit to immune checkpoint therapies.

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
EGFR aberration	Likely associated with WORSE response to ICIs

Note: Tumor non-genomic factors, such as patient germline genetics, PDL1 expression, tumor microenvironment, epigenetic alterations or other factors not provided by this test may affect ICI response.

CHEMOTHERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
TP53 R273C	Platinum- and taxane-based regimens	**Less sensitive**	Clinical	Ovarian cancer

HORMONAL THERAPIES

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

OTHERS

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

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

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VARIANT INTERPRETATION

CTNNB1 S37C

Biological Impact

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

CTNNB1 S37C lies within the ubiquitination recognition motif of the β-catenin protein. Mutation at the S37 residue abolish the phosphorylation of β-catenin by GSK3β and may lead to deregulated accumulation of β-catenin[16][17]. S37C and S37F mutations have been observed in ovarian cancer and were demonstrated as an oncogenic mutation with elevated nuclear accumulation of β-catenin protein[18].

Therapeutic and prognostic relevance

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

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

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

EGFR C797S, E709G, L747_T751del (Exon 19 deletion)

Biological Impact

The EGFR gene encodes for the Epidermal Growth Factor Receptor, a receptor tyrosine kinase which binds to its ligands, including Epidermal Growth Factor (EGF) and Transforming Growth Factor-alpha (TGF-alpha), activates downstream signaling pathways, including the canonical oncogenic MAPK and PI3K/AKT/mTOR signaling cascades[23]. Increased EGFR activity by mutations and/or amplification of the EGFR gene has been described in a wide range of cancers, such as lung, brain, colorectal and head and neck cancer[24]. Mutations in the kinase domain of EGFR are commonly observed in non-small cell lung cancer (NSCLC), resulting in a constitutively activated form of the receptor[25]. On the other hand, in the brain and colorectal cancers, the most prevalent EGFR alteration is copy number amplification that results in receptor overexpression[26].

EGFR C797S lies within the ATP-binding pocket in the protein kinase domain of the EGFR protein and is known to be oncogenic[27].

E709G is an uncommon mutation located in the cytoplasmic domain of the EGFR protein (UniProtKB). Of note, most E709X present as complex mutations which frequently coexist with other EGFR mutation, such as L858R, G719C, or exon 19 del[28][29][30]. Preclinical studies have demonstrated that E709A, E709G and E709K are oncogenic mutations that are able to transform cells[31][32].

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EGFR L747_T751del (exon 19 deletion) lies within the tyrosine kinase domain of EGFR, resulting in a deletion of 5 amino acids from residues 747 to 751 (UniProtKB). This mutation was demonstrated as an activating mutation with an increased EGFR kinase activity in vitro[33].

EGFR exon 19 deletions are in-frame deletions of 9–24 nucleotides in exon 19 centred around codons 746–750 of the kinase domain of EGFR. The two most common EGFR alterations, L858R mutation and exon 19 deletions can result in constitutive activation of signal transduction pathways, leading to cell proliferation or anti-apoptosis without ligand binding[34].

Therapeutic and prognostic relevance

There is accumulated clinical evidence suggested that patients with MDM2/MDM4 amplification or EGFR aberrations exhibited poor clinical outcome and demonstrated a significantly increased rate of tumor growth (hyper-progression) after receiving immune checkpoint (PD-1/PD-L1) inhibitors therapies[35] (Annals of Oncology (2017) 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376).

EGFR C797S is one of the most commonly acquired aberrations associated with resistance to the third-generation EGFR inhibitor, osimertinib[27][36][37][38]. The combination treatment of first and third generation EGFR TKIs yielded clinical response in patients with concomitant T790M and C797S mutation detected in trans[39][40].

Besides, preclinical studies indicated that ALK inhibitor, brigatinib-based combination regimens could inhibit the cell growth of EGFRm (activating mutations)/T790M/C797S (triple-mutant, TM) expressing cells (Abstract #916, 2018 AACR)[41]. A patient with non-small cell lung carcinoma harboring triple EGFR mutations of L858R, T790M, and cis-797S showed response to combination therapy containing osimertinib, bevacizumab, and brigatinib[42].

A trial study of clinical activity of afatinib in patients with non-small-cell lung cancer reported that two patients with K739_1744dup6 or L858R plus E709G/V have 100% tumor shrinkage after afatinib treatment[43]. Clinical studies demonstrated that two NSCLC patients harboring E709G plus L858R and one patient co-harboring E709G and exon 19 deletion achieved partial responses (PR) to erlotinib and gefitinib treatment, respectively. However, two patients co-harboring E709G and L858R showed different responses to gefitnib treatment, one had PR with PFS of 18.4 months and overall survival (OS) of 75.3 months, and the other had progressive disease with PFS of 2.4 months and OS of 6.8 months[29][44]. Preclinical study have shown that E709G mutant is more resistant to gefitinib treatment than wild-type EGFR protein[31]. Another preclinical study demonstrated that cells harboring EGFR E709A/G alone or compound mutations are sensitive to afatinib but resistant to gefitinib or erlotinib[45].

In two case reports, two lung adenocarcinoma patients harboring EGFR L747_T751del mutation had partial responses to erlotinib treatment, but were found to have acquired EGFR T790M or MET amplification upon disease progressions[46][47].

In a preclinical study, transformed cells expressing EGFR L747_T751del were sensitive to afatinib, erlotinib and gefitinib treatment that reduced cell viability, but resistant to cetuximab in vitro[45].

The first- and second-generation EGFR-TKIs, including dacomitinib, erlotinib, gefitinib, and afatinib, have been approved by the U.S. FDA as first-line treatments for non-small cell lung cancer patients with EGFR exon 19 deletion or L858R mutation. Osimertinib, a third-generation EGFR-TKI, has also been approved by the U.S. FDA. It indicated for adjuvant treatment or first-line treatment of metastatic NSCLC patients with EGFR exon 19 deletion or L858R mutation.

A phase III trial (NCT01774721) show that dacomitinib significantly improved PFS over gefitinib in first-line treatment of patients with EGFR-mutation-positive NSCLC[48]. Another phase III trial (NCT00949650) demonstrated that median PFS among lung cancer patients with exon 19 deletion or L858R EGFR mutation (n=308) was 13.6 months for afatinib and 6.9 months for chemotherapy[49]. Results from a double-blind, phase 3 trial further showed that osimertinib significantly demonstrated longer PFS than standard EGFR-TKIs (18.9 months vs. 10.2 months) in previously untreated EGFR mutation–positive (exon 19 deletion or L858R) advanced NSCLC[50].

TP53 R273C

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[51]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[52].

R273C is a hotspot mutation occurred at the DNA-binding domain (DBD) of the p53 protein[53]. This is a gain-of-function mutation that has been shown to cause aberrant activation of gene expression, increased cell proliferation, migration and increase the HER2 promoter activity and mRNA expression in vitro[54][55][56].

Therapeutic and prognostic relevance

Despite having a high mutation rate in cancers, there are currently no approved targeted therapies for TP53 mutations. A phase II trial demonstrated that Wee1 inhibitor (AZD1775) in combination with carboplatin was well tolerated and showed promising anti-tumor activity in TP53-mutated ovarian cancer refractory or resistant (< 3 months) to standard first-line therapy (NCT01164995)[57].

In a retrospective study (n=19), advanced sarcoma patients with TP53 loss-of-function mutations displayed improved progression-free survival (208 days versus 136 days) relative to patients with wild-type TP53 when treated with pazopanib[58]. Results from another Phase I trial of advanced solid tumors (n=78) demonstrated that TP53 hotspot mutations are associated with better clinical response to the combination of pazopanib and vorinostat[59].

Advanced solid tumor and colorectal cancer patients harboring a TP53 mutation have been shown to be more sensitive to bevacizumab when compared with patients harboring wild-type TP53[60][61][62]. In a pilot trial (n=21), TP53-negative breast cancer patients demonstrated increased survival following treatment with bevacizumab in combination with chemotherapy agents, Adriamycin (doxorubicin) and Taxotere (docetaxel)[63]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[64][65]. In a retrospective study of NSCLC, TP53 mutations were associated with high expression of VEGF-A, the primary target of bevacizumab, offering a mechanistic explanation for why patients exhibit improved outcomes after bevacizumab treatment when their tumors harbor mutant TP53 versus wild-type TP53[66].

TP53 oncomorphic mutations, including P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L, and R282W have been shown to predict resistance to platinum- and taxane-based chemotherapy in advanced serous ovarian carcinoma patients[67].

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CARD11 Amplification

Biological Impact

CARD11 (caspase recruitment domain 11) gene encodes a cytoplasmic scaffold protein of the CARD11/BCL10/MALT1 (CBM) complex which plays essential roles in regulating apoptosis and NF-κB activation in response to upstream stimuli[68][69]. CARD11 gain-of-function mutations are frequently detected in human diffuse large B-cell lymphoma (DLBCL)[70]and cutaneous squamous cell carcinoma[71]. Moreover, CARD11 gene amplification has been observed in a significant proportion of DLBCL[72]. Biochemical assays revealed that enforced expression of CARD11/BCL10/MALT1 is essential for transformation of B-cell and survival of DLBCL cell[73].

Therapeutic and prognostic relevance

Retrospective studies have shown that high CARD11 expression or CARD11 gene amplification was associated with poor survival in diffuse large B cell lymphoma (DLBCL)[74][72].

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[75][76][77]. 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[78]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[79][80].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[81][82]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[83][84][85]. 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[86][87][88]. 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)[89][90].

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[82][91][92].

In a Phase I trial, a KRAS wild-type squamous NSCLC patient with CDKN2A loss had a partial response when treated with CDK4/6 inhibitor abemaciclib[84]. Administration of combined palbociclib and MEK inhibitor PD-0325901 yield promising progression-free survival among patients with KRAS mutant 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[93].

A retrospective analysis demonstrated that concurrent deletion of CDKN2A with EGFR mutation in patients with NSCLC, predicts worse overall survival after EGFR-TKI treatment[94].

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[95]. 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[96][97]. CHEK2 aberrations are associated with glioblastoma, breast, ovarian, prostate, colorectal, gastric, thyroid, and lung cancers[98][99][100][101][102].

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)[103].

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)[104]. 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)[105].

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)[106], and prostate cancer (NCT02952534, NCT03533946)[105], 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.

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[107][108][109]. 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[110]. 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[107][111]. Somatic mutations or deletion of NF2 are frequently observed in human cancers, including 20-50% of pleural mesotheliomas[112], 6% papillary renal cell carcinoma, 5% pancreas cancer, and 4% melanoma (cbioPortal; June 2015), and less frequently in other cancers[113].

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[114][115][116][117]. There are at least two case studies indicating the clinical efficacy of everolimus in bladder cancer and urothelial carcinoma[118][119], 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[120].

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[121].

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RAD50 Heterozygous deletion

Biological Impact

The RAD50 gene encodes a highly-conserved DNA double-strand break (DSB) repair factor. It forms MRN complex with NBS1 and MRE11 protein and is involved in sensing and early processing of DSB, cell cycle checkpoints, DNA recombination and maintenance of telomeres[122][123]. Mutations in the components of the MRN complex could increase susceptibility to familial breast cancer[124][125], gastric cancer[126], colorectal cancer[127], and urothelial cancer[128]. RAD50 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[129]. Besides, RAD50 deletion was also suggested as a marker of BRCAness, a phenotype shared between non-BRCA1/2-mutated ovarian cancers and BRCA1/2-mutated ovarian cancers[130].

Therapeutic and prognostic relevance

Preclinical data showed that knockdown of the RAD50 gene in ovarian cancer cell lines was significantly associated with better responses to two PARP inhibitors, olaparib and rucaparib[130]. RAD50 has been selected as an inclusion criterion for the trials examining talazoparib efficacy in HER2-negative breast cancer, olaparib efficacy in breast cancer, rucaparib efficacy in metastatic prostate cancer and niraparib efficacy in any malignancy (except prostate) (NCT02401347, NCT03207347, NCT03344965, NCT03413995).

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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[131] 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[92] NCT02107703	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1[132] NCT02102490	**Breast cancer** (Approved on 2017/09/28)
	HR+/HER2-
	Abemaciclib [ORR(%): 19.7 vs. 17.4]

Afatinib (GILOTRIF)

Afatinib acts as an irreversible covalent inhibitor of the ErbB family of receptor tyrosine kinases, including epidermal growth factor receptor (EGFR) and erbB-2 (HER2). Afatinib is developed and marketed by Boehringer Ingelheim under the trade name GILOTRIF (United States) and GIOTRIF (Europe).

- FDA Approval Summary of Afatinib (GILOTRIF)

LUX-Lung 8[133] NCT01523587	**Non-small cell lung carcinoma** (Approved on 2016/04/15)
	EGFR ex19del or L858R
	Afatinib vs. Erlotinib [PFS(M): 2.4 vs. 1.9]
LUX-Lung 3[134] NCT00949650	**Non-small cell lung carcinoma** (Approved on 2013/07/13)
	EGFR ex19del or L858R
	Afatinib vs. Pemetrexed + cisplatin [PFS(M): 11.1 vs. 6.9]

Brigatinib (ALUNBRIG)

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

- FDA Approval Summary of Brigatinib (ALUNBRIG)

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

Dacomitinib (VIZIMPRO)

Dacomitinib is an oral kinase inhibitor that targets EGFR. Dacomitinib is developed and marketed by Pfizer under the trade name VIZIMPRO.

- FDA Approval Summary of Dacomitinib (VIZIMPRO)

ARCHER 1050[48] NCT01774721	**Non-small cell lung carcinoma** (Approved on 2018/09/27)
	EGFR ex19del or L858R
	Dacomitinib vs. Gefitinib [PFS(M): 14.7 vs. 9.2]

Erlotinib (TARCEVA)

Erlotinib is a small molecule, reversible inhibitor of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase. Erlotinib is developed by OSI Pharmaceuticals, Genentech and Roche, and marketed by Astellas Pharm Global Development under the trade name TARCEVA.

- FDA Approval Summary of Erlotinib (TARCEVA)

RELAY NCT02411448	**Non-small cell lung carcinoma** (Approved on 2020/05/29)
	EGFR ex19del or L858R
	Erlotinib + ramucirumab vs. Erlotinib + placebo [PFS(M): 19.4 vs. 12.4]
EURTAC[135] NCT00446225	**Non-small cell lung carcinoma** (Approved on 2013/05/14)
	EGFR ex19del or L858R
	Erlotinib vs. Cisplatin + gemcitabine or cisplatin + docetaxel or carboplatin + gemcitabine or carboplatin + docetaxel [PFS(M): 10.4 vs. 5.2]
PA.3[136] NCT00026338	**Pancreatic cancer** (Approved on 2005/11/02)
	-
	Gemcitabine vs. Placebo [OS(M): 6.4 vs. 6]

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[137] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[138] 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[139] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[140] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[141] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

Gefitinib (IRESSA)

Gefitinib is a small molecule inhibitor of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase. Gefitinib is developed and marketed by AstraZeneca under the trade name IRESSA.

- FDA Approval Summary of Gefitinib (IRESSA)

IFUM[142] NCT01203917	**Non-small cell lung carcinoma** (Approved on 2015/07/13)
	EGFR ex19del or L858R
	Gefitinib [ORR(%): 50.0]

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[143] 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[103] 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[144] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[145] 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[146] 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[147] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[148] 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[149] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

Osimertinib (TAGRISSO)

Osimertinib is a third-generation tyrosine kinase inhibitor (TKI) for patients with tumors harboring EGFR T790M mutation. Osimertinib is developed and marketed by AstraZeneca under the trade name TAGRISSO.

- FDA Approval Summary of Osimertinib (TAGRISSO)

ADAURA NCT02511106	**Non-small cell lung carcinoma** (Approved on 2020/12/18)
	EGFR ex19del or L858R
	Osimertinib vs. Placebo + adjuvant chemotherapy [DFS(M): NR vs. 19.6]
FLAURA[50] NCT02296125	**Non-small cell lung carcinoma** (Approved on 2018/04/18)
	EGFR ex19del or L858R
	Osimertinib vs. Gefitinib or erlotinib [PFS(M): 18.9 vs. 10.2]
AURA3[150] NCT02151981	**Non-small cell lung carcinoma** (Approved on 2017/03/30)
	EGFR T790M
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA[151] NCT01802632	**Non-small cell lung carcinoma** (Approved on 2015/11/13)
	EGFR T790M
	Osimertinib [ORR(%): 59.0]

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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[152] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+/HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[153] NCT01942135	**Breast cancer** (Approved on 2016/02/19)
	ER+/HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

Ribociclib (KISQALI)

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

- FDA Approval Summary of Ribociclib (KISQALI)

MONALEESA-2[91] NCT01958021	**Breast cancer** (Approved on 2017/03/13)
	HR+/HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

Rucaparib (RUBRACA)

Rucaparib is an inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1, -2 and -3 (PARP-1, -2, -3). Rucaparib is developed and marketed by Clovis Oncology under the trade name RUBRACA.

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[106] 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]

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Talazoparib (TALZENNA)

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

- FDA Approval Summary of Talazoparib (TALZENNA)

EMBRACA[154] 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)

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

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

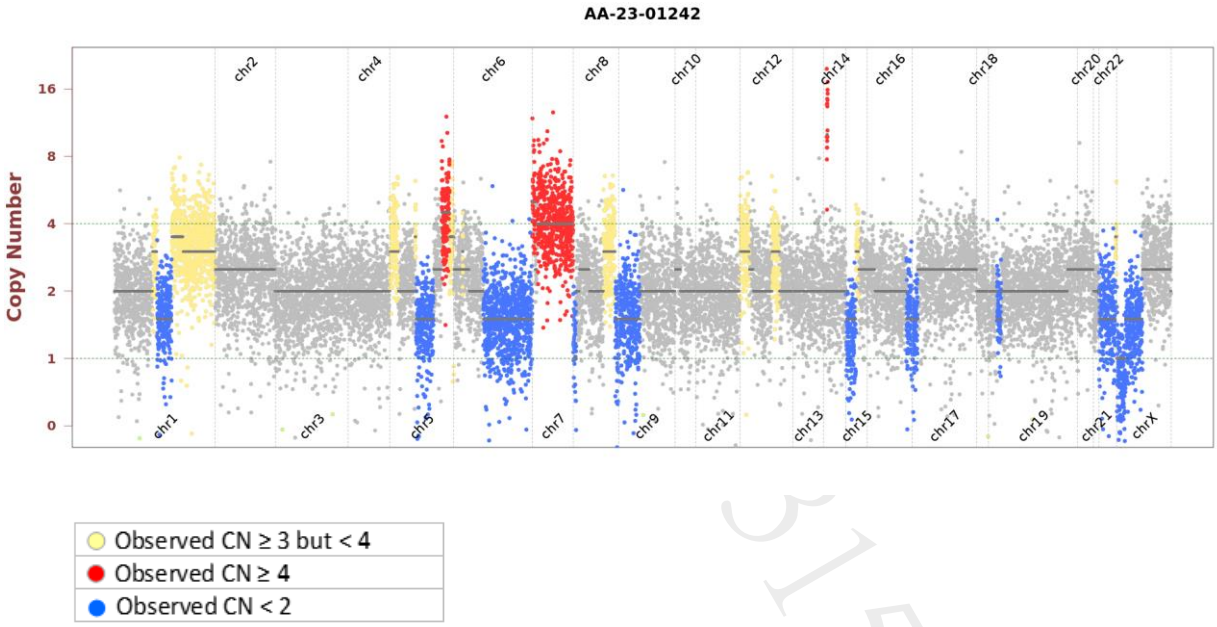
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
CTNNB1	S37C	3	c.110C>G	NM_001904	COSM5679	28.1%	1031
EGFR	C797S	20	c.2390G>C	NM_005228	COSM5945664	28.2%	904
EGFR	E709G	18	c.2126A>G	NM_005228	COSM13009	65.8%	3958
EGFR	L747_T751del (Exon 19 deletion)	19	c.2240_2254del	NM_005228	COSM12369	68.0%	2527
TP53	R273C	8	c.817C>T	NM_000546	COSM10659	78.0%	391

- Copy Number Alterations

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



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OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ADAMTS16	K301M	5	c.902A>T	NM_139056	-	18.0%	1123
ADGRA2	Splice region	-	c.1833+7G>A	NM_032777	-	57.0%	114
ADGRA2	L474W	10	c.1421T>G	NM_032777	-	54.3%	245
AR	R101H	1	c.302G>A	NM_000044	-	99.7%	1591
BRCA1	G275D	10	c.824G>A	NM_007294	COSM133666	52.0%	3269
CEBPA	M354L	1	c.1060A>C	NM_001285829	-	43.7%	348
HSP90AB1	K552M	10	c.1655A>T	NM_001271969	COSM7665758	24.5%	1435
IDH1	P149L	5	c.446C>T	NM_005896	-	28.1%	1852
LRP1B	Splice region	-	c.7762+4A>G	NM_018557	-	69.7%	1372
MET	Splice region	-	c.2419-4C>T	NM_001127500	-	11.8%	1699
MUC16	Q14313*	79	c.42937C>T	NM_024690	-	28.2%	522
NOTCH3	G974E	18	c.2921G>A	NM_000435	-	65.5%	296
NOTCH4	G185A	4	c.554G>C	NM_004557	-	14.8%	1107
NOTCH4	G228S	4	c.682G>A	NM_004557	COSM3348635	96.1%	751
PTPRD	H1394L	33	c.4181A>T	NM_002839	-	12.0%	568
SYNE1	Splice region	-	c.24642+3A>G	NM_182961	-	89.3%	103

Note:

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

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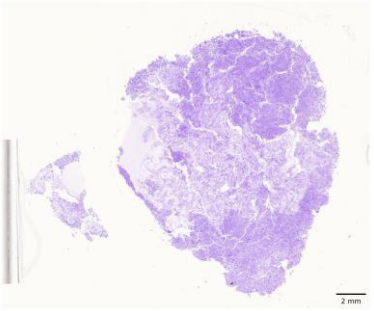
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Feb 23, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: C11207402
- Collection site: Pleural effusion
- Examined by: N/A
- Manual macrodissection: N/A

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 875x
- Target Base Coverage at 100x: 93%

RNA test

- Average unique RNA Start Sites per control GSP2: 205

LIMITATIONS

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

RNA test

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

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.

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DATABASE USED

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

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

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

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GENE LIST

SNV & CNV

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

*Analysis of copy number alterations NOT available.

FUSION

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

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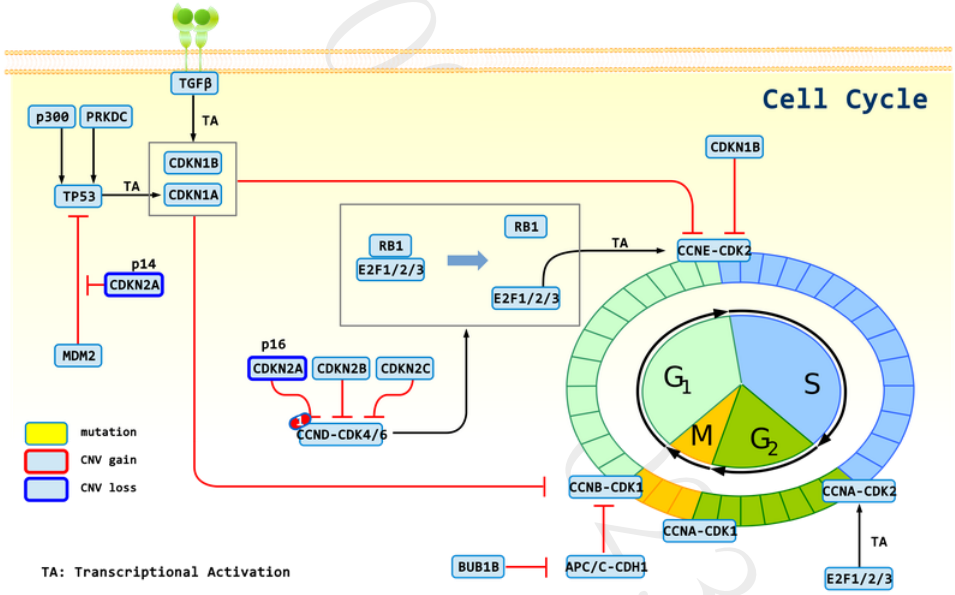
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
CDKN2A	Abemaciclib, Palbociclib, Ribociclib	**sensitive**
NF2	Everolimus, Temsirolimus	**sensitive**
CHEK2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RAD50	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Abemaciclib, Palbociclib, Ribociclib

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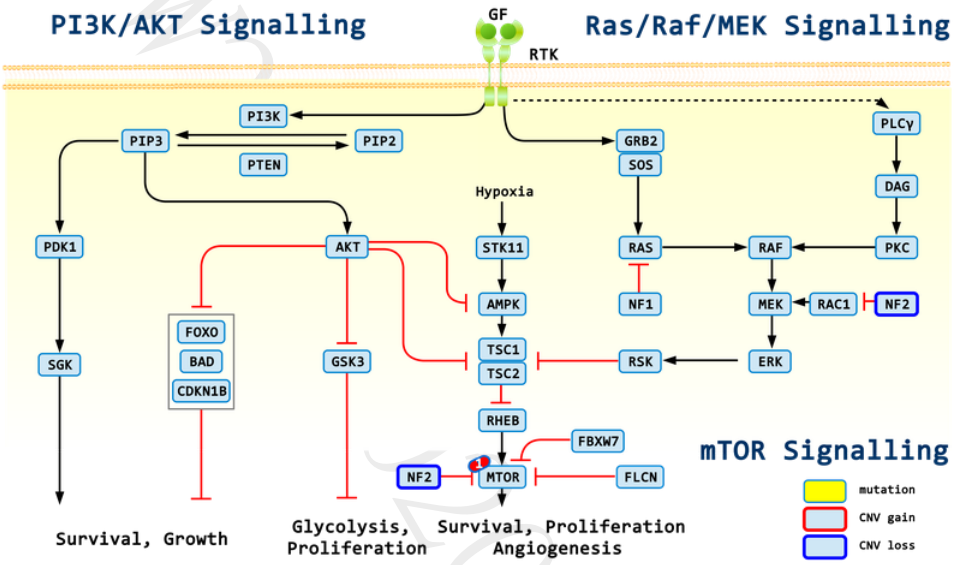
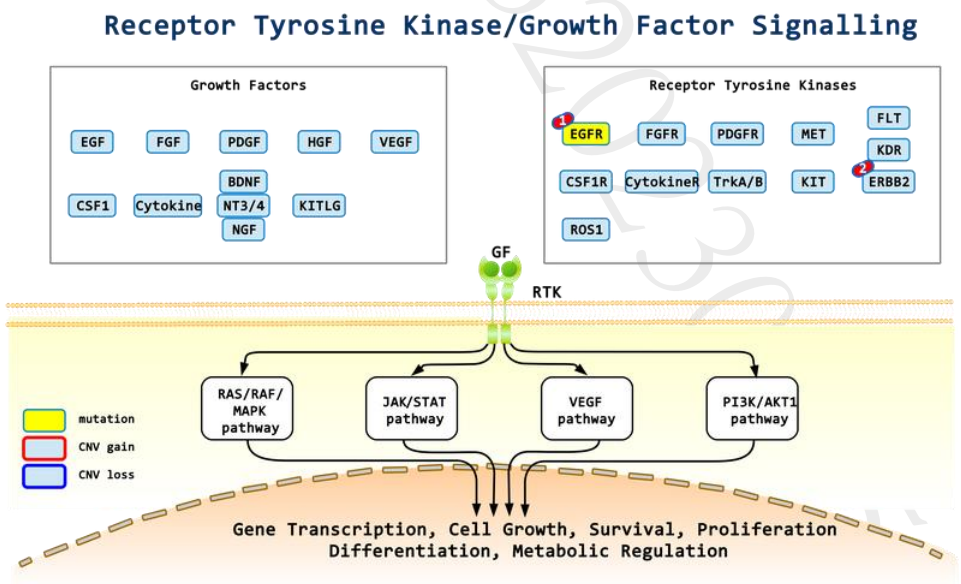


1: Everolimus, Temsirolimus



1: Gefitinib, Afatinib, Erlotinib, Osimertinib, Dacomitinib, Brigatinib; 2: Afatinib

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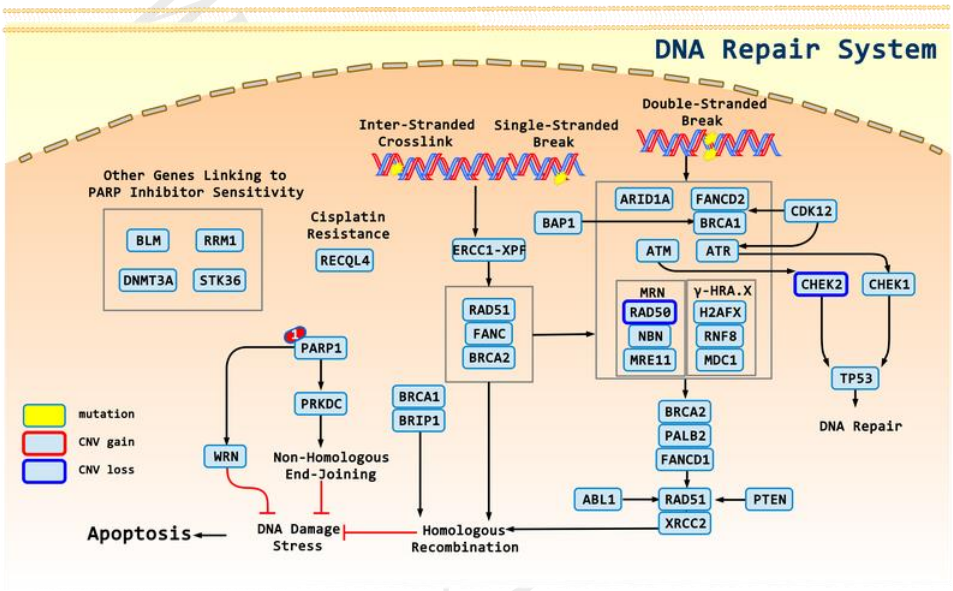

1: Olaparib, Niraparib, Rucaparib, Talazoparib

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DISCLAIMER

法律聲明

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

醫療決策需由醫師決定

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

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

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REFERENCE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17. PMID: 9065402; 1997, Science;275(5307):1787-90
Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC.

18. PMID: 10433945; 1999, Am J Pathol;155(2):527-36
beta-catenin expression pattern in stage I and II ovarian carcinomas : relationship with beta-catenin gene mutations, clinicopathological features, and clinical outcome.

19. PMID: 26861905; 2016, Ann Surg Oncol;23(6):1924-7

Correlation of CTNNB1 Mutation Status with Progression Arrest Rate in RECIST Progressive Desmoid-Type Fibromatosis Treated with Imatinib: Translational Research Results from a Phase 2 Study of the German Interdisciplinary Sarcoma Group (GISG-01).

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

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

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

23. PMID: 18045542; 2007, Cell;131(5):1018
SnapShot: EGFR signaling pathway.

24. PMID: 10880430; 2000, EMBO J;19(13):3159-67
The ErbB signaling network: receptor heterodimerization in development and cancer.

25. PMID: 15329413; 2004, Proc Natl Acad Sci U S A;101(36):13306-11
EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib.

26. PMID: 11426640; 2000, Oncogene;19(56):6550-65
The EGF receptor family as targets for cancer therapy.

27. PMID: 25939061; 2015, Nat Med;21(6):560-2
Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M.

28. PMID: 27323238; 2016, Cancer Sci;107(9):1179-86
Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy.

29. PMID: 27785061; 2016, Onco Targets Ther;9():6137-6145
Effectiveness of tyrosine kinase inhibitors on uncommon E709X epidermal growth factor receptor mutations in non-small-cell lung cancer.

30. PMID: 30055651; 2018, Cancer Commun (Lond);38(1):51
First-generation EGFR tyrosine kinase inhibitor therapy in 106 patients with compound EGFR-mutated lung cancer: a single institution's clinical practice experience.

31. PMID: 16205628; 2006, Oncogene;25(8):1205-15
Distinctive activation patterns in constitutively active and gefitinib-sensitive EGFR mutants.

32. PMID: 26206867; 2015, Clin Cancer Res;21(23):5305-13
EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs.

33. PMID: 23387505; 2013, Cancer Sci;104(5):584-9
Sensitivity and kinase activity of epidermal growth factor receptor (EGFR) exon 19 and others to EGFR-tyrosine kinase inhibitors.

34. PMID: 22263017; 2010, J Thorac Dis;2(1):48-51
Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update.

35. PMID: 28351930; 2017, Clin Cancer Res;23(15):4242-4250
Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate.

36. PMID: 25948633; 2015, Clin Cancer Res;21(17):3913-23
EGFR Mutations and Resistance to Irreversible Pyrimidine-Based EGFR Inhibitors.

37. PMID: 27448564; 2016, J Hematol Oncol;9(1):59
EGFR C797S mutation mediates resistance to third-generation inhibitors in T790M-positive non-small cell lung cancer.

38. PMID: 28625641; 2017, Lung Cancer;108():228-231
Emergence of novel and dominant acquired EGFR solvent-front mutations at Gly796 (G796S/R) together with C797S/R and L792F/H mutations in one EGFR (L858R/T790M) NSCLC patient who progressed on osimertinib.

39. PMID: 28843359; 2017, J Thorac Oncol;12(11):1728-1732
Combination Osimertinib and Gefitinib in C797S and T790M EGFR-Mutated Non-Small Cell Lung Cancer.

40. PMID: 28662863; 2017, J Thorac Oncol;12(11):1723-1727
Lung Adenocarcinoma Harboring EGFR T790M and In Trans C797S Responds to Combination Therapy of First- and Third-Generation EGFR TKIs and Shifts Allelic Configuration at Resistance.

41. PMID: 28287083; 2017, Nat Commun;8():14768
Brigatinib combined with anti-EGFR antibody overcomes osimertinib resistance in EGFR-mutated non-small-cell lung cancer.

42. PMID: 30233215; 2018, Onco Targets Ther;11():5545-5550
Effective treatment of pulmonary adenocarcinoma harboring triple EGFR mutations of L858R, T790M, and cis-C797S by osimertinib, bevacizumab, and brigatinib combination therapy: a case report.

43. PMID: 26051236; 2015, Lancet Oncol;16(7):830-8
Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6.

44. PMID: 31715539; 2020, Lung Cancer;139():35-40
Detection of rare and novel EGFR mutations in NSCLC patients: Implications for treatment-decision.

45. PMID: 29141884; 2017, Sci Transl Med;9(416):
A method of high-throughput functional evaluation of EGFR gene variants of unknown significance in cancer.

46. PMID: 30683294; 2019, J Thorac Oncol;14(2):e27-e29
Novel SPECC1L-MET Fusion Detected in Circulating Tumor DNA in a Patient with Lung Adenocarcinoma following Treatment with Erlotinib and Osimertinib.

47. PMID: 33225315; 2020, JTO Clin Res Rep;1(4):100071
Acquired Resistance to Osimertinib Plus Savolitinib Is Mediated by MET-D1228 and MET-Y1230 Mutations in EGFR-Mutated MET-Amplified Lung Cancer.

48. PMID: 28958502; 2017, Lancet Oncol;18(11):1454-1466
Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial.

49. PMID: 29653820; 2018, Clin Lung Cancer;19(4):e465-e479
Afatinib as First-line Treatment of Older Patients With EGFR Mutation-Positive Non-Small-Cell Lung Cancer: Subgroup Analyses of the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 Trials.

50. PMID: 29151359; 2018, N Engl J Med;378(2):113-125
Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer.

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

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

53. PMID: 22713868; 2012, Genes Dev;26(12):1268-86
Mutant p53: one name, many proteins.

54. PMID: 23264849; 2012, Genes Cancer;3(7-8):491-502
Gain-of-Function Activity of Mutant p53 in Lung Cancer through Up-Regulation of Receptor Protein Tyrosine Kinase Axl.

55. PMID: 23612969; 2013, J Biol Chem;288(23):16704-14
A novel p53 mutant found in iatrogenic urothelial cancers is dysfunctional and can be rescued by a second-site global suppressor mutation.

56. PMID: 29970031; 2018, BMC Cancer;18(1):709
Mutant p53 gain of function induces HER2 over-expression in cancer cells.

57. PMID: 27998224; 2016, J Clin Oncol;34(36):4354-4361
Phase II Study of WEE1 Inhibitor AZD1775 Plus Carboplatin in Patients With TP53-Mutated Ovarian Cancer Refractory or Resistant to First-Line Therapy Within 3 Months.

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

59. PMID: 25669829; 2015, Ann Oncol;26(5):1012-8
Phase I study of pazopanib and vorinostat: a therapeutic approach for inhibiting mutant p53-mediated angiogenesis and facilitating mutant p53 degradation.

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

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

62. PMID: 17145525; 2006, Semin Oncol;33(5 Suppl 10):S8-14
Bevacizumab in combination with chemotherapy: first-line treatment of patients with metastatic colorectal cancer.

63. PMID: 21399868; 2011, Int J Oncol;38(5):1445-52
p53, HER2 and tumor cell apoptosis correlate with clinical outcome after neoadjuvant bevacizumab plus chemotherapy in breast cancer.

64. PMID: 20549698; 2011, Int J Cancer;128(8):1813-21
p53 status influences response to tamoxifen but not to fulvestrant in breast cancer cell lines.

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

66. PMID: 25672981; 2015, Cancer Res;75(7):1187-90
VEGF-A Expression Correlates with TP53 Mutations in Non-Small Cell Lung Cancer: Implications for Antiangiogenesis Therapy.

67. PMID: 25385265; 2015, Int J Oncol;46(2):607-18
TP53 oncomorphic mutations predict resistance to platinum□ and taxane□based standard chemotherapy in patients diagnosed with advanced serous ovarian carcinoma.

68. PMID: 11278692; 2001, J Biol Chem;276(15):11877-82
CARD11 and CARD14 are novel caspase recruitment domain (CARD)/membrane-associated guanylate kinase (MAGUK) family members that interact with BCL10 and activate NF-kappa B.

69. PMID: 26260210; 2015, Mol Immunol;68(2 Pt C):546-57
TCR signaling to NF-κB and mTORC1: Expanding roles of the CARMA1 complex.

70. PMID: 18323416; 2008, Science;319(5870):1676-9
Oncogenic CARD11 mutations in human diffuse large B cell lymphoma.

71. PMID: 26212909; 2015, Am J Pathol;185(9):2354-63
Novel CARD11 Mutations in Human Cutaneous Squamous Cell Carcinoma Lead to Aberrant NF-κB Regulation.

72. PMID: 22397314; 2012, Leuk Lymphoma;53(10):1971-7
Role of nuclear factor-κB regulators TNFAIP3 and CARD11 in Middle Eastern diffuse large B-cell lymphoma.

73. PMID: 26668357; 2015, Proc Natl Acad Sci U S A;112(52):E7230-8

Lymphomagenic CARD11/BCL10/MALT1 signaling drives malignant B-cell proliferation via cooperative NF-κB and JNK activation.

74. PMID: 26876250; 2016, Zhonghua Xue Ye Xue Za Zhi;37(1):30-4
[Expression and prognostic value of CARD11 in diffuse large B cell lymphoma].

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

76. 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.

77. 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.

78. 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.

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

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

81. 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.

82. 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.

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

84. 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.

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

86. 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.

87. 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.

88. 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.

89. 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.

90. 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.

91. PMID: 27717303; 2016, N Engl J Med;375(18):1738-1748

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer.

92. 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.

93. 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.

94. 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.

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

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

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

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

99. 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.

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

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

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

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

104. 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.

105. 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.

106. 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.

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

108. 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.

109. 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.

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

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

112. 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.

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

114. 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.

115. 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.

116. 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.

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

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

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

120. 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.

121. 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.

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

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

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

125. 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.

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

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

128. PMID: 24934408; 2014, Cancer Discov;4(9):1014-21

Synthetic lethality in ATM-deficient RAD50-mutant tumors underlies outlier response to cancer therapy.

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

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

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

132. 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.

133. PMID: 26156651; 2015, Lancet Oncol;16(8):897-907
Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial.

134. PMID: 23816960; 2013, J Clin Oncol;31(27):3327-34
Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.

135. PMID: 22285168; 2012, Lancet Oncol;13(3):239-46
Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial.

136. PMID: 17452677; 2007, J Clin Oncol;25(15):1960-6
Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group.

137. 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.

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

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

140. 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.

141. 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.

142. PMID: 24263064; 2014, Br J Cancer;110(1):55-62
First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study.

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

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

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

146. PMID: 30345884; 2018, N Engl J Med;379(26):2495-2505

ACT Onco® + Report

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.

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

148. 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.

149. 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.

150. PMID: 27959700; 2017, N Engl J Med;376(7):629-640
Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer.

151. PMID: 25923549; 2015, N Engl J Med;372(18):1689-99
AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer.

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

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

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

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