ACT Onco® + Report

PATIENT	
Name: 曹劉秋香	Patient ID: 1175402
Date of Birth: May 06, 1951	Gender: Female
Diagnosis: Lung adenocarcinoma	
ORDERING PHYSICIAN	
Name: 趙恒勝醫師	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: S11176727A	Collection site: Lung	Type: FFPE tissue
Date received: Jul 07, 2022	Lab ID: AA-22-03959	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 A767_V769dup (Exon 20 insertion)	Amivantamab-vmjw, Mobocertinib	Afatinib, Dacomitinib, Erlotinib, Gefitinib	-

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
EGFR A767_V769dup (Exon 20 insertion)	Osimertinib	-
EGFR Amplification	Afatinib, Erlotinib, Gefitinib, Osimertinib, Cetuximab, Panitumumab, Necitumumab	-

Note:

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

ACT Onco® + Report

TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
EGFR	A767_V769dup (Exon 20 insertion)	52.1%
TP53	Y126*	64.7%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr13	*BRCA2, RB1*	Heterozygous deletion	1
Chr17	*TP53*	Heterozygous deletion	1
Chr6	*E2F3*	Amplification	6¥
Chr1	*MCL1, MDM4, NTRK1*	Amplification	7¥
Chr5	*FLT4, TERT*	Amplification	7¥
Chr8	*MYC*	Amplification	7¥
Chr7	*EGFR*	Amplification	9
Chr9	*CD274 (PD-L1), JAK2, PDCD1LG2 (PD-L2)*	Amplification	9

¥ Increased gene copy number was observed.

- 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)	5 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 54% 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 1		
EGFR A767_V769dup (Exon 20 insertion)	Amivantamab-vmjw, Mobocertinib	**sensitive**
Level 2		
EGFR A767_V769dup (Exon 20 insertion)	Afatinib, Dacomitinib, Erlotinib, Gefitinib	**resistant**
Level 3B		
EGFR A767_V769dup (Exon 20 insertion)	Osimertinib	**sensitive**
EGFR Amplification	Afatinib, Erlotinib, Gefitinib, Osimertinib, Cetuximab, Panitumumab, Necitumumab	**sensitive**

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
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

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

EGFR A767_V769dup (Exon 20 insertion), Amplification

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[1]. 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[2]. 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[3]. On the other hand, in the brain and colorectal cancers, the most prevalent EGFR alteration is copy number amplification that results in receptor overexpression[4].

EGFR A767_V769dup (also referred to as V769_D770insASV and M766insASV) mutation results in the insertion of three residues in the protein kinase domain of the EGFR protein between amino acids 769 and 770 (UniProtKB). A767_V769dup confers a gain of function to the EGFR protein as demonstrated by constitutive EGFR phosphorylation, downstream signaling activation, and transforming cells in vitro[5][6].

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[7](Annals of Oncology (2017) 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376).

Accumulating evidence showed that patients with tumor harboring EGFR exon 20 insertions or mutations, including A767, S768, D770, P772 and H773, display the lack of response to tyrosine kinase inhibitors, such as gefitinib and erlotinib[8][9][10]. In clinical studies, NSCLC patients harboring A767_V769dup (V769_D770insASV) demonstrated disease progression on gefitinib or erlotinib treatment[5][11]. Another clinical study showed that a patient with NSCLC harboring A767_V769dup achieved partial response to osimertinib treatment[12].

In preclinical studies, cells harboring A767_V769dup (V769_D770insASV, M766insASV) were sensitive to amivantamab and mobocertinib, as demonstrated by decreased EGFR phosphorylation and inhibited cell viability[13][14][15][16], but were resistant to gefitinib, erlotinib, and dacomitinib[5][17][14][6].

In May 2021, the U. S. FDA approved RYBREVANT (amivantamab-vmjw, a bispecific antibody targeting to EGFR and MET receptor) to treat adult patients with locally advanced or metastatic NSCLC harboring EGFR exon 20 insertion mutations based on CHRYSALIS trial (NCT02609776). In the CHRYSALIS trial, the ORR of 81 NSCLC patients who had progressive disease on or after platinum-based chemotherapy was 40%, the median duration of response (DOR) was 11.1 months, the mPFS was 8.3 months, and the mOS was 22.8 months (this endpoint remains immature)[18]. In September 2021, the U. S. FDA also approved Exkivity (mobocertinib, a selective TKI specifically target EGFR exon 20 insertion mutations) to treat adult patients with locally advanced or metastatic NSCLC harboring EGFR exon 20 insertion mutations based on Study 101 trial (NCT02716116). In the Study 101 trial, the ORR of 114 NSCLC patients who had progressive disease on or after platinum-based chemotherapy was 28%, and the median response duration was 17.5 months[19].

NCCN guidelines for non-small cell lung cancer (NSCLC) has suggested that EGFR exon 20 alternations are generally associated with lack of sensitivity to TKI therapy, except for A763_Y764insFQEA. Clinical data has reported that NSCLC patients harboring EGFR exon 20 insertion, outside of A763_Y764insFQEA, had a poor response to gefitinib and erlotinib[9][10][5][20]. In other clinical studies, afatinib showed lower clinical benefit in patients with EGFR exon 20 insertion mutations[9][21][22]. A case study showed that a combination therapy with afatinib plus cetuximab could overcome primary

EGFR TKI resistance in EGFR exon 20 insertion positive NSCLC patient[23].

Tumor inhibitory effect of osimertinib was observed in cells harboring EGFR exon 20 insertion in vitro and in vivo[24].

EGFR exon 20 insertion has been selected as an inclusion criteria for the trial examining osimertinib efficacy in NSCLC (NCT03414814).

Increased EGFR copy number is associated with tumor response to panitumumab, an EGFR-targeted antibody, in colorectal cancer patients, based on data from a phase III study[25]. A recent Phase II trial of cetuximab (another approved anti-EGFR antibody) oxaliplatin/leucovorin/5-fluorouracil therapy in first-line setting also demonstrated an association between higher EGFR copy number and better overall survival in gastric cancer patients[26]. The addition of cetuximab to chemotherapy reduced the risk of death by 44% for advanced squamous non–small cell lung cancer (NSCLC) patients with EGFR-amplified tumor, according to clinical trial findings presented at the 2015 World Conference on Lung Cancer. Preclinical data of gastric cancer (GC)-derived xenograft also showed that EGFR amplification or overexpression is associated with response to cetuximab[27]. Besides, a phase III study of necitumumab showed squamous cell lung cancer patients with EGFR amplification had improved overall survival (14.8 versus 7.6 months, p = 0.033) (NCT00981058)[28].

Increased EGFR copy number has been shown to be associated with better response and survival in gefitinib or erlotinib treatment for NSCLC[29][30][31][32][33][34], esophageal cancer[35], and mucinous urethral adenocarcinoma[36]. Concurrent amplification of EGFR and ERBB2 is associated with response to afatinib in patients with trastuzumab-refractory esophagogastric cancer[37]. However, dacomitinib has been reported with a limited single-agent activity in recurrent glioblastoma with EGFR amplification in a phase II trial[38]. EGFR amplification has been determined as an inclusion criterion for the trials evaluating erlotinib, afatinib, and osimertinib efficacy in PDAC with co-expressing EGFR and c-Met (NCT03213626), glioblastoma (NCT03732352), urothelial tract carcinoma (NCT02780687), and brain cancer (NCT02423525).

TP53 Y126*, Heterozygous deletion

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[39]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[40].

Y126* mutation results in a premature truncation of the p53 protein at amino acid 126 (UniProtKB). This mutation is predicted to lead to a loss of p53 function, despite not having characterized in the literature. Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

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)[41].

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[42]. 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[43].

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[44][45][46]. 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)[47]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[48][49]. In a retrospective study of non-small cell lung cancer (NSCLC), TP53 mutations were associated with high expression of VEGF-A, the primary target of bevacizumab, offering a mechanistic explanation for why patients exhibit improved outcomes after bevacizumab treatment when their tumors harbor mutant TP53 versus wild-type TP53[50].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[51]. BRCA2 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[52]. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia[53]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[54].

Therapeutic and prognostic relevance

The U.S. FDA has approved olaparib in advanced ovarian cancer under several settings including (1) first-line maintenance treatment for patients with deleterious or suspected deleterious germline or somatic BRCA mutation who are in complete or partial response to first-line platinum-based chemotherapy[55]; (2) in combination with bevacizumab as first-line maintenance treatment for patients with homologous recombination deficiency (HRD)-positive status[56]; (3) maintenance treatment for patients with germline BRCA-mutated recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy[57][58]; (4) treatment for patients with germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy[59]. In addition, olaparib has also been approved in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in either neoadjuvant, adjuvant, or metastatic setting[60]and germline BRCA-mutated metastatic pancreatic cancer[61]. Of note, in May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate[62].

Rucaparib has been approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and patients with BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more chemotherapies[63][64]. In May 2020, the U.S. FDA also approved rucaparib to treat adult patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy (TRITON2, NCT02952534).

The U.S. FDA also approved niraparib for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy and patients who have been treated with three or more prior lines of chemotherapy and associated with HRD positive status[65][66][67]. In addition, talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer[68].

CD274 (PD-L1) Amplification

Biological Impact

The CD274 gene encodes the programmed death ligand 1 (PD-L1), a member of a family of co-stimulatory immune receptor ligands. PD-L1 binds to the PD-1 cell surface receptor, which is expressed by T cells, B cells and natural killer cells to inhibit an immune response[69]. PD-1/PD-L1 pathways regulate immune suppression to allows tumor cells to evade the host immune system[70]. Amplification or overexpression of PD-L1 has been identified in some tumor types[71][72][73][74]and was associated with a high response rate to checkpoint inhibitor treatment[75].

Studies in Hodgkin's lymphoma[76], non-small cell lung cancer (NSCLC) and oral cavity squamous cell carcinoma showed that genomic amplification of PD-L1 correlated with PD-L1 protein expression[76][77][72].

Therapeutic and prognostic relevance

Expression of PD-L1 is an indication for pembrolizumab in non-small cell lung cancer (NSCLC) patients. The PD-L1 overexpression on tumor cell surface and/or tumor-infiltrating immune cells (TIICs) was associated with better response to the immune checkpoint inhibitor therapies[78][79][80][81]. However, some clinical studies showed that the PD-L1 expression is not a biomarker for the use of PD-1 inhibitors[82][83].

E2F3 Amplification

Biological Impact

The E2F3 gene encodes a transcription factor that interacts directly with the retinoblastoma protein (pRB) to regulate the expression of genes involved in the cell cycle and DNA replication[84][85][86].

Amplification or overexpression of E2F3 has been reported in various types of cancers, including bladder cancer, hepatocellular carcinoma, retinoblastomas, and melanoma[87][88][89][90][91].

Therapeutic and prognostic relevance

A tissue microarray analysis indicated that amplification of the E2F3 gene is associated with increased E2F3 protein overexpression, accelerated cell proliferation, and poor prognosis in bladder cancer[88]. Besides, elevated E2F genes and E2F transcriptional targets in tumors have been linked with poor prognosis in the liver and pancreatic cancers[86].

FLT4 Amplification

Biological Impact

The FLT4 (FMS-like tyrosine kinase 4) gene encodes for a vascular endothelial growth factor receptor 3 (VEGFR3), which involves in lymphangiogenesis and the maintenance of lymphatic endothelium[92]. VEGFR3 has been shown to mediate cell proliferation, survival, and chemoresistance in leukemia[93], and to promote invasion and metastasis of human lung adenocarcinoma cells[94]. Mutations in FLT4 cause hereditary Nonne-Milroy disease, an autosomal dominant form of primary lymphedema type IA[95]. In addition to lymphatic endothelial cells, FLT4 is also expressed in lung adenocarcinoma[96], colorectal adenocarcinoma[97], head and neck carcinoma[98], prostate carcinoma[99], leukemia[93], and Kaposi's sarcoma[100]. FLT4 expression levels were also shown to correlate with different stages of cervical carcinogenesis[101].

Therapeutic and prognostic relevance

In a phase II trial of sorafenib in radiation-associated breast angiosarcomas, patients with co-amplification of MYC and FLT4 achieved complete or partial response (DOI: 10.1200/jco.2012.30.15_suppl.10019). In clinical studies, a subset of patients with secondary angiosarcoma, mostly related to radiation-induced breast cancer and postlymphedema, co-harbored MYC and FLT4 amplification. The MYC and FLT4 amplification was associated to poor prognosis[102][103].

A case report showed that angiosarcoma patient with concurrent KDR and FLT4 amplification experienced a potent antitumor response and achieved clinically stable disease for 6 months after receiving pazopanib therapy[104].

JAK2 Amplification

Biological Impact

The JAK2 (Janus kinase 2) gene encodes one of four members of the JAK family of non-receptor tyrosine kinases and is involved in the interferon-alpha/beta/gamma pathway and is a member of the JAK/STAT signaling pathway[105][106]. JAK2 signaling is required for the normal production of blood cells such as erythrocytes and thrombocytes[107].

Therapeutic and prognostic relevance

Biallelic inactivation of JAK1/2 was associated with primary and acquired resistance to PD-1 blockade due to defects in the pathways involved in interferon-receptor signaling[108][109].

JAK2-amplified triple-negative breast cancers were shown to be JAK2-dependent and more sensitive to JAK2-specific inhibitor (BSK805) than dual JAK1/2 inhibitor ruxolitinib[110]. Efficacy of ruxolitinib was also evidenced in a non-breast cancer cell line harboring JAK2-amplification[111].

MCL1 Amplification

Biological Impact

The myeloid cell leukemia 1 (MCL1) gene encodes a member of the BCL2 pro-survival family[112]. MCL1 is highly regulated by various oncogenic signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway[113], the mTOR pathway[114], and the phosphatidylinositol-3 kinase (PI3K) pathway[115]. Oncogenic roles for MCL1 have been previously suggested by the report of increased rates of lymphoma in transgenic mice[116]. Somatic amplification of MCL1 may be a common mechanism in cancer cells to increase cell survival[117]. MCL1 overexpression was observed from a retrospective analysis of parotid gland carcinomas, including adenoid cystic carcinoma[118].

Therapeutic and prognostic relevance

Therapies targeting MCL1 and other BCL2 family members with the pan-BCL2 family inhibitors are currently under investigation[119]. A case report has demonstrated clinical efficacy of sorafenib, when combined with vorinostat, in a metastatic triple-negative breast cancer (TNBC) patient with MCL1-amplified tumor[120]. Several in vitro studies also showed that sorafenib induces cell death via inhibition of MCL1 expression in multiple cancer types including, hepatocellular carcinoma (HCC), lung cancer, breast cancer, cholangiocarcinoma, endometrial cancer and chronic lymphocytic leukemia[121][122][123][124][125][126]. Preclinical studies have also demonstrated the efficacy of regorafenib in reducing MCL1 expression in human colorectal cancer (CRC) cell lines[127][128], and shown clinical benefit in two CRC patients when combined with 5-fluorouracil[128]. In vivo models of colon cancer showed that MCL-1 expression is inhibited by targeting of the mTOR pathway using everolimus, promoting increased tumor cell killing of cancers with KRAS or BRAF mutations[129].

MDM4 Amplification

Biological Impact

The MDM4 gene encodes a E3-ubiquitin ligase that exerts its oncogenic roles via blocking the transactivation and enhancing the degradation of the p53 tumor suppressor[130][131][132]. Similar to MDM2, dysregulation of MDM4 has been reported in various tumor types such as retinoblastoma[133], Ewing sarcoma[134], cutaneous melanoma[135]and glioma[136].

Therapeutic and prognostic relevance

Several small molecules that disrupt the interaction between p53 and MDM4, such as CTX1, ATSP-7041, SAH-p53-8, SJ-172550 have demonstrated p53-dependent tumor growth suppression in preclinical models[137][138][139][140]. Results

from a study showed that patients with MDM2 family amplification, including MDM2 and MDM4, or EGFR aberrations has a poor clinical outcome and significantly increased rate of tumor growth (hyper-progression) after receiving immune checkpoint (PD-1/PD-L1) therapy[7].

MYC Amplification

Biological Impact

The v-myc avian myelocytomatosis viral oncogene homolog, also known as c-myc (MYC) gene encodes a transcription factor involved in cellular proliferation, inhibiting exit from the cell cycle, stimulating vascularization and enhancing genomic instability[141][142][143]. Dysregulated MYC expression is implicated in a wide range of human cancers[144].

Therapeutic and prognostic relevance

MYC amplification was associated with better clinical outcome in breast cancer patients treated with FAC (5-fluorouracil, doxorubicin, and cyclophosphamide), CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and P-FEC (paclitaxel followed by 5-fluorouracil, epirubicin and cyclophosphamide) and higher expression of MYC was also associated with a better response rate in platinum-treated ovarian cancer patients[145][146][147].

CDK inhibition using the dinaciclib, a CDK1, 2, 5 and 9 inhibitors, exerted antitumor activity in triple-negative breast cancer (TNBC) tumor xenograft and cell lines with increased activity of the MYC pathway[148][149].

Overexpression of MYC has been reported as a favorable prognostic biomarker in colorectal carcinoma (CRC)[150][151]. However, the favorable prognostic value of MYC in CRC is abrogated by the TP53 mutation[151].

MYC amplification with the loss of tumor suppressor pathways such as p53 and RB has been shown to be associated with poor outcomes and was correlated with shortened disease-free survival in breast cancer with BRCA1 deficiency in TNBC[148][152].

NTRK1 Amplification

Biological Impact

The NTRK1 gene encodes the TRKA (tropomyosin receptor kinase) receptor which plays an important role in the development and function of the nervous system. Gene fusions of NTRK1 lead to constitutive activation of MAP-kinase, PI3-kinase, and PLC-γ pathways, and represent the main molecular alterations with known oncogenic and transforming potential in various malignancies, including soft tissue sarcoma, non-small cell lung cancer (NSCLC), glioblastoma multiforme (GBM), thyroid carcinoma, and pilocytic astrocytomas[153][154]. A pan-cancer study (n=1250) demonstrated that 2.2% of the metastatic cancer patients harbored NTRK amplification and NTRK protein overexpression was observed in 14.8% of NTRK-amplified tumors (doi.org/10.23838/pfm.2017.00142).

Therapeutic and prognostic relevance

Patients with NTRK1 amplification had only limited benefit from larotrectinib treatment according to the few clinical studies. One of them had a partial response with larotrectinib of short duration (3.7 months)[155], and the other one with metastatic NTRK1-amplified (copy number=8) esophageal carcinoma showed clinical efficacy for six weeks, and then a progressive disease of new lesions were observed[156].

PDCD1LG2 (PD-L2) Amplification

Biological Impact

The PDCD1LG2 gene encodes the programmed cell death 1 ligand 2 (PD-L2) protein. Similar to PD-L1, PD-L2 overexpression by tumor cells and antigen presenting cells (APC) lead to negative regulation of T-cell receptor (TCR) signaling and the subsequent tumor immune evasion[157][71]. PD-L2 binding affinity for PD-1 is higher than PD-L1,

although the biological consequences remain unknown[158].

Genomic amplification of PD-L2 was not correlated with PD-L2 expression in non-small cell lung cancer (NSCLC)[77].

Therapeutic and prognostic relevance

PD-L2 is a predictor of poor prognosis in esophageal cancer and triple negative breast cancer (TNBC)[159][160]. PD-L2 positivity was significantly associated with shorter progression-free survival (PFS) and cancer-specific survival in clear cell renal cell carcinoma, but not in papillary renal cell carcinoma[161].

RB1 Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[162]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[163]. 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[164][165][166]. 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[167].

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[168]. 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[169].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[170][171].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[172]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[173].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[174][175]. 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[171][176].

TERT Amplification

Biological Impact

The TERT gene encodes the catalytic subunit of telomerase, an enzyme that maintains telomere length and genomic integrity[177]. Upregulation of TERT promotes cancer development and progression via modulation of Wnt-catenin and nuclear factor kappa B signaling[178][179], and mitochondrial RNA processing[180]. Activating mutations in the TERT promoter have been identified in a number of cancer types including melanoma, hepatocellular carcinoma, urothelial carcinoma, medulloblastoma, and glioma whereas TERT gene amplification is implicated in lung cancer, cervical cancer, breast cancer, Merkel cell carcinoma, neuroblastoma and adrenocortical carcinoma[181][182][183][184][185].

ACT Onco® + Report

Therapeutic and prognostic relevance

Imetelstat (GRN163L), a telomere inhibitor which has been shown to inhibit cell proliferation in various cancer cell lines and tumor xenografts is currently in clinical trials[177].

TERT gene amplification is an independent poor prognostic marker for disease-free survival in non-small cell lung cancer (NSCLC) and breast cancer[186][187][188].

ACT Onco® + Report

US FDA-APPROVED DRUG(S)

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[189] NCT01523587	**Non-small cell lung carcinoma** (Approved on 2016/04/15)
	EGFR Del19/L858R
	Afatinib vs. Erlotinib [PFS(M): 2.4 vs. 1.9]
LUX-Lung 3[190] NCT00949650	**Non-small cell lung carcinoma** (Approved on 2013/07/13)
	EGFR Del19/L858R
	Afatinib vs. Pemetrexed + cisplatin [PFS(M): 11.1 vs. 6.9]

Amivantamab-vmjw (RYBREVANT)

Amivantamab-vmjw is a bispecific antibody directed against epidermal growth factor (EGF) and MET receptors. Amivantamab-vmjw is developed and marketed by Janssen Biotech, Inc. under the trade name RYBREVANT.

- FDA Approval Summary of Amivantamab-vmjw (RYBREVANT)

CHRYSALIS NCT02609776	**Non-small cell lung carcinoma** (Approved on 2021/05/21)
	EGFR exon 20 insertion mutations
	Amivantamab-vmjw [ORR(%): 40, DOR(M): 11.1]

Cetuximab (ERBITUX)

Cetuximab is a recombinant, chimeric (human/mouse) monoclonal antibody that binds to the extracellular domain and inhibits epidermal growth factor receptor (EGFR). Cetuximab is developed by ImClone and marketed by Eli Lilly under the trade name ERBITUX.

- FDA Approval Summary of Cetuximab (ERBITUX)

CRYSTAL[191] NCT00154102	**Colorectal cancer** (Approved on 2012/07/06)
	EGFR-expressing, K-Ras Wild-type
	Cetuximab + 5-fluorouracil + folinic acid + irinotecan vs. 5-fluorouracil + folinic acid + irinotecan [PFS(M): 8.9 vs. 8.1]
EXTREME[192] NCT00122460	**Head and neck cancer** (Approved on 2011/11/07)
	-
	Cetuximab + cisplatin/carboplatin + 5-fu vs. Cisplatin/carboplatin + 5-fu [OS(M): 10.1 vs. 7.4]
[193] NCT00004227	**Head and neck cancer** (Approved on 2006/03/01)
	-
	Cetuximab + radiation vs. Radiation [OS(M): 49 vs. 29.3]
[194] NCT00063141	**Colorectal cancer** (Approved on 2004/02/12)
	EGFR-expressing
	Cetuximab + irinotecan vs. Irinotecan [DOR(M): 5.7 vs. 4.2]

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 exon 19 deletion or exon 21 (L858R)
	Erlotinib + ramucirumab vs. Erlotinib + placebo [PFS(M): 19.4 vs. 12.4]
EURTAC[195] NCT00446225	**Non-small cell lung carcinoma** (Approved on 2013/05/14)
	Exon 19 Del/Exon 21 substitution (L858R)
	Erlotinib vs. Cisplatin + gemcitabine or cisplatin + docetaxel or carboplatin + gemcitabine or carboplatin + docetaxel [PFS(M): 10.4 vs. 5.2]
PA.3[196] NCT00026338	**Pancreatic cancer** (Approved on 2005/11/02)
	-
	Gemcitabine vs. Placebo [OS(M): 6.4 vs. 6]

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[197] NCT01203917	**Non-small cell lung carcinoma** (Approved on 2015/07/13)
	Exon 19 Del/Exon 21 substitution (L858R)
	Gefitinib [ORR(%): 50.0]

Mobocertinib (EXKIVITY)

Mobocertinib is a first-in-class, oral tyrosine kinase inhibitor (TKI) specifically designed to selectively target epidermal growth factor receptor (EGFR) Exon 20 insertion mutations. Mobocertinib is developed and marketed by Takeda under the trade name EXKIVITY.

- FDA Approval Summary of Mobocertinib (EXKIVITY)

Study 101[19] NCT02716116	**Non-small cell lung carcinoma** (Approved on 2021/09/15)
	EGFR Exon 20 insertion mutations
	Mobocertinib [ORR(%): 28.0, DOR(M): 17.5]

ACT Onco® + Report

Necitumumab (PORTRAZZA)

Necitumumab is a recombinant human IgG1 monoclonal antibody against the human epidermal growth factor receptor (EGFR) and blocks the binding of EGFR to its ligands. Necitumumab is developed and marketed by Eli Lilly under the trade name PORTRAZZA.

- FDA Approval Summary of Necitumumab (PORTRAZZA)

SQUIRE[198] NCT00981058	**Lung squamous cell carcinoma** (Approved on 2015/11/14)
	-
	Gemcitabine + cisplatin vs. Placebo [OS(M): 11.5 vs. 9.9]

Niraparib (ZEJULA)

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

- FDA Approval Summary of Niraparib (ZEJULA)

PRIMA NCT02655016	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2020/04/29)
	-
	Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
QUADRA[67] NCT02354586	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2019/10/23)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Niraparib [ORR(%): 24.0, DOR(M): 8.3]
NOVA[66] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/03/27)
	-
	Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

Olaparib (LYNPARZA)

Olaparib is an oral, small molecule inhibitor of poly (ADP-ribose) polymerase-1, -2, and -3 (PARP-1, -2, -3). Olaparib is developed by KuDOS Pharmaceuticals and marketed by AstraZeneca under the trade name LYNPARZA.

- FDA Approval Summary of Olaparib (LYNPARZA)

OlympiA NCT02032823	**Her2-negative high-risk early breast cancer** (Approved on 2022/03/11)
	gBRCA
	Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound[62] NCT02987543	**Prostate cancer** (Approved on 2020/05/19)
	ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm, RAD54Lm
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1[56] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]

POLO[61] NCT02184195	**Pancreatic adenocarcinoma** (Approved on 2019/12/27)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1[55] NCT01844986	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19)
	Germline or somatic BRCA-mutated (gBRCAm or sBRCAm)
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD[60] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[199] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA+
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19[200] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]
Study 42[201] NCT01078662	**Ovarian cancer** (Approved on 2014/12/19)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

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 exon 19 deletions or exon 21 L858R mutations
	Osimertinib vs. Placebo + adjuvant chemotherapy [DFS(M): NR vs. 19.6]
FLAURA[202] NCT02296125	**Non-small cell lung carcinoma** (Approved on 2018/04/18)
	EGFR Del19/L858R
	Osimertinib vs. Gefitinib or erlotinib [PFS(M): 18.9 vs. 10.2]
AURA3[203] NCT02151981	**Non-small cell lung carcinoma** (Approved on 2017/03/30)
	EGFR T790M+
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA[204] NCT01802632	**Non-small cell lung carcinoma** (Approved on 2015/11/13)
	EGFR T790M+
	Osimertinib [ORR(%): 59.0]

ACT Onco® + Report

Panitumumab (VECTIBIX)

Panitumumab is a fully human monoclonal antibody against the human epidermal growth factor receptor (EGFR) and binds to the extracellular domain to prevent its activation. Panitumumab is developed by Abgenix and Amgen, and marketed by the latter under the trade name VECTIBIX.

- FDA Approval Summary of Panitumumab (VECTIBIX)

Study 20050203[205] NCT01412957	**Colorectal cancer** (Approved on 2017/06/29)
	-
	Panitumumab + bsc vs. Bsc [OS(M): 10 vs. 6.9]
PRIME[206] NCT00364013	**Colorectal cancer** (Approved on 2014/05/23)
	-
	Panitumumab + folfox vs. Folfox [PFS(M): 9.6 vs. 8]
ASPECCT[207] NCT01001377	**Colorectal cancer** (Approved on 2014/05/23)
	-
	Panitumumab vs. Cetuximab [OS(M): 10.4 vs. 10]
Study 20080763[208] NCT00113763	**Colorectal cancer** (Approved on 2006/09/27)
	-
	Panitumumab + bsc vs. Bsc [PFS(M): 3.2 vs. 2]

Rucaparib (RUBRACA)

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

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA+, sBRCA
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[63] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	All|HRD|tBRCA
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]
ARIEL2[209] NCT01482715, NCT01891344	**Ovarian cancer** (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation
	Rucaparib [ORR(%): 54.0]

ACT Onco® + Report

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

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.

Amivantamab-vmjw

(NCT04538664, Phase 3)

The purpose of this study is to compare the efficacy, as demonstrated by progression-free survival (PFS), in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone in participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) characterized by EGFR Exon 20ins mutations.

- Contact

Name: Study Contact
Phone: 844-434-4210
Email: Participate-In-This-Study@its.jnj.com

- Location

Status: Recruiting Country: Taiwan City: Kaohsiung Name: Kaohsiung Medical University Chung-Ho Memorial Hospital	Status: Recruiting Country: Taiwan City: Kaohsiung Name: Chang Gung Medical Foundation
Status: Recruiting Country: Taiwan City: New Taipei Name: Taipei Medical University Shuang Ho Hospital	Status: Recruiting Country: Taiwan City: Taichung Name: Chung Shan Medical University Hospital
Status: Recruiting Country: Taiwan City: Taichung Name: China Medical University Hospital	Status: Recruiting Country: Taiwan City: Taipei City Name: National Taiwan University Hospital

Mobocertinib

(NCT04129502, Phase 3)

The purpose of this study is to compare the effectiveness of TAK-788 as first-line treatment with that of platinum-based chemotherapy in participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors has epidermal growth factor receptor (EGFR) exon 20 insertion mutations.

Participants will be randomly assigned to one of the two treatment groups- TAK-788 group or Platinum-based chemotherapy group.

ACT Onco® + Report

Participants will receive TAK-788 orally and pemetrexed/cisplatin or pemetrexed/carboplatin via vein until the participants experience worsening disease (PD) as assessed by blinded independent review committee (IRC), intolerable harmful effects or another discontinuation criteria.

- Contact

Name: Takeda Contact
Phone: +1-877-825-3327
Email: medinfoUS@takeda.com

- Location

Status: Recruiting Country: Taiwan City: Dalin Name: Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation	Status: Recruiting Country: Taiwan City: Douliu Name: National Taiwan University Hospital - YunLin Branch
Status: Recruiting Country: Taiwan City: Kaohsiung Name: Kaohsiung Medical University - Chung-Ho Memorial Hospital	Status: Recruiting Country: Taiwan City: Kaohsiung Name: E-DA hospital
Status: Recruiting Country: Taiwan City: Taichung City Name: Taichung Veterans General Hospital	Status: Recruiting Country: Taiwan City: Taichung Name: Taichung Veterans General Hospital
Status: Recruiting Country: Taiwan City: Tainan City Name: Chi Mei Medical Center, Liouying	Status: Recruiting Country: Taiwan City: Tainan Name: National Cheng Kung University Hospital
Status: Recruiting Country: Taiwan City: Taipei Name: National Taiwan University Hospital	Status: Recruiting Country: Taiwan City: Taipei Name: Taipei Veterans General Hospital

ACT Onco® + Report

SUPPLEMENTARY INFORMATION OF TESTING RESULTS

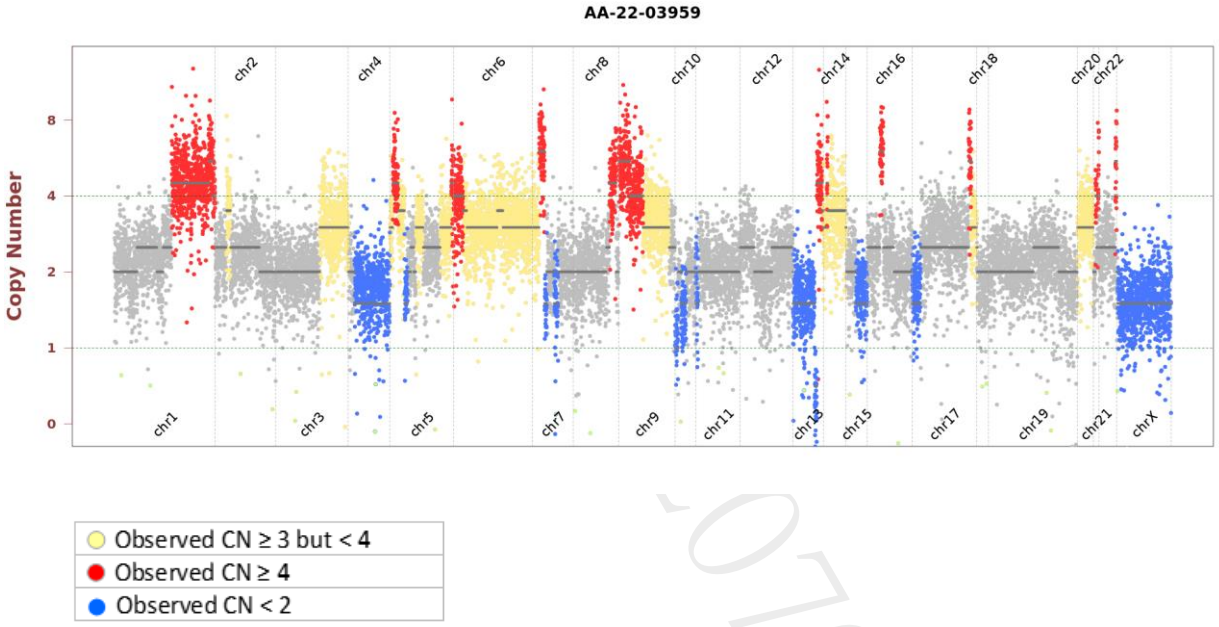
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
EGFR	A767_V769dup (Exon 20 insertion)	20	c.2300_2308dup	NM_005228	COSM12376	52.1%	1442
TP53	Y126*	5	c.378C>G	NM_000546	COSM10862	64.7%	890

- 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
ADAMTS13	V154I	5	c.460G>A	NM_139025	-	16.7%	281
CASP8	Q49P	3	c.146A>C	NM_033355	-	45.7%	1827
CSF1R	T621M	14	c.1862C>T	NM_005211	COSM4970976	15.2%	875
EPCAM	R153T	4	c.458G>C	NM_002354	-	63.8%	1182
GRIN2A	D731N	12	c.2191G>A	NM_000833	COSM3513466	5.2%	3999
HSPA4	Splice donor	-	c.429+1G>T	NM_002154	-	5.4%	482
KMT2C	R380L	8	c.1139G>T	NM_170606	COSM225885	6.0%	3999
MET	G134fs	2	c.393_400dup	NM_001127500	-	73.0%	984
MUC16	N12965S	36	c.38894A>G	NM_024690	-	42.3%	1081
MUC16	T5029R	3	c.15086C>G	NM_024690	-	25.0%	1822
MUC6	Splice region	-	c.1453+4C>T	NM_005961	COSM2108620	64.2%	279
PRKDC	V3792I	80	c.11374G>A	NM_006904	COSM1457256	87.1%	426
PTPRD	N244I	17	c.731A>T	NM_002839	-	50.6%	2544
PTPRD	Y300F	17	c.899A>T	NM_002839	-	9.5%	3513
RUNX1	S346L	6	c.1037C>T	NM_001001890	COSM6919607	80.6%	1930
ZNF217	I211V	1	c.631A>G	NM_006526	-	53.8%	3058

Note:

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

ACT Onco® + Report

TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW

- Collection date: Jul 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11176727A
- Collection site: Lung
- Examined by: Dr. Chien-Ta Chiang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 10%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 35%
    3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
    4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
    5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 1168x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 80

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).

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.

ACT Onco® + Report

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:
醫藥資訊研究員
楊杭哲 博士
Hang-Che Yang Ph.D.

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

ACT Onco® + Report

GENE LIST

SNV & CNV

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

*Analysis of copy number alterations NOT available.

FUSION

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

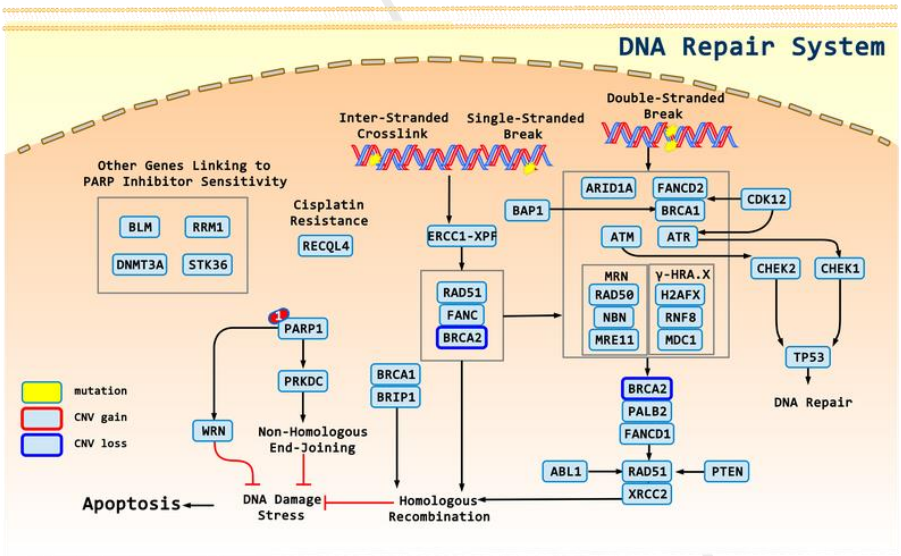
ACT Onco® + Report

APPENDIX

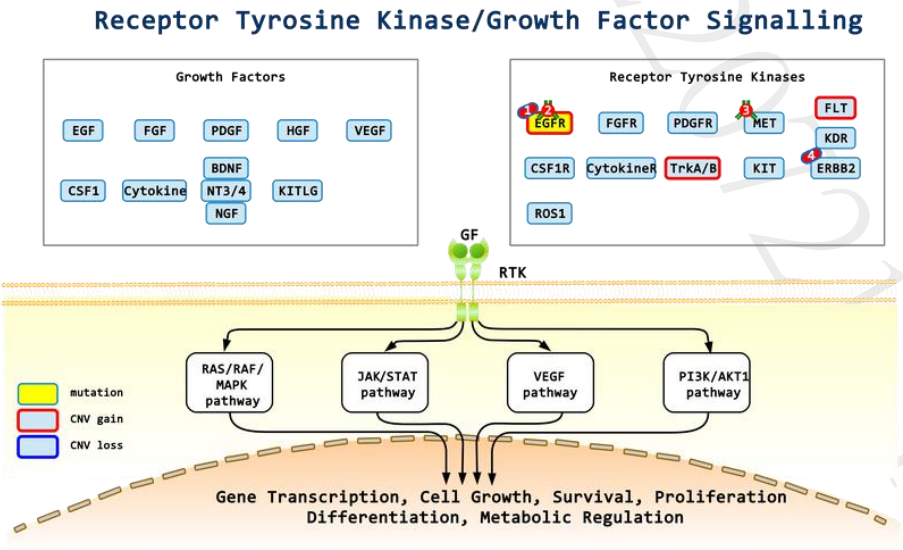
POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RB1	Abemaciclib, Palbociclib, Ribociclib	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib



1: Osimertinib, Erlotinib, Gefitinib, Afatinib, Mobocertinib; 2: Cetuximab, Panitumumab, Amivantamab-vmjw, Necitumumab;

3: Amivantamab-vmjw; 4: Afatinib

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。

REFERENCE

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

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

3. 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.

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

5. PMID: 24353160; 2013, Sci Transl Med;5(216):216ra177
Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer.

6. PMID: 28363995; 2017, Cancer Res;77(10):2712-2721
Response Heterogeneity of EGFR and HER2 Exon 20 Insertions to Covalent EGFR and HER2 Inhibitors.

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

8. PMID: 18676761; 2008, Clin Cancer Res;14(15):4877-82
Lung cancer with epidermal growth factor receptor exon 20 mutations is associated with poor gefitinib treatment response.

9. PMID: 21531810; 2011, Clin Cancer Res;17(11):3812-21
Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer.

10. PMID: 21764376; 2012, Lancet Oncol;13(1):e23-31
EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications.

11. PMID: 31859066; 2020, Clin Lung Cancer;21(3):e191-e204
Clinicopathologic Characteristics, Treatment Outcomes, and Acquired Resistance Patterns of Atypical EGFR Mutations and HER2 Alterations in Stage IV Non-Small-Cell Lung Cancer.

12. PMID: 31208370; 2019, BMC Cancer;19(1):595
EGFR exon 20 insertion mutations and response to osimertinib in non-small-cell lung cancer.

13. PMID: 32414908; 2020, Cancer Discov;10(8):1194-1209
Antitumor Activity of Amivantamab (JNJ-61186372), an EGFR-MET Bispecific Antibody, in Diverse Models of EGFR Exon 20 Insertion-Driven NSCLC.

14. PMID: 33395611; 2021, Lung Cancer;152():135-142
Extensive functional evaluation of exon 20 insertion mutations of EGFR.

15. PMID: 33728415; 2021, JTO Clin Res Rep;2(3):
Preclinical characterization of mobocertinib highlights the putative therapeutic window of this novel EGFR inhibitor to EGFR exon 20 insertion mutations.

16. PMID: 33632773; 2021, Cancer Discov;11(7):1672-1687
Mobocertinib (TAK-788): A Targeted Inhibitor of EGFR Exon 20 Insertion Mutants in Non-Small Cell Lung Cancer.

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

18. PMID: 34339292; 2021, J Clin Oncol;39(30):3391-3402

Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study.

19. PMID: 33632775; 2021, Cancer Discov;11(7):1688-1699
Activity and Safety of Mobocertinib (TAK-788) in Previously Treated Non-Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations from a Phase I/II Trial.

20. PMID: 28652772; 2017, Onco Targets Ther;10():2903-2908
Epidermal growth factor receptor exon 20 mutation in lung cancer: types, incidence, clinical features and impact on treatment.

21. PMID: 26354527; 2015, Oncologist;20(10):1167-74
Afatinib in Non-Small Cell Lung Cancer Harboring Uncommon EGFR Mutations Pretreated With Reversible EGFR Inhibitors.

22. PMID: 29508940; 2018, Asia Pac J Clin Oncol;14 Suppl 1():7-9
Afatinib for an EGFR exon 20 insertion mutation: A case report of progressive stage IV metastatic lung adenocarcinoma with 54 months' survival.

23. PMID: 29702285; 2018, J Thorac Oncol;13(8):1222-1226
Afatinib and Cetuximab in Four Patients With EGFR Exon 20 Insertion-Positive Advanced NSCLC.

24. PMID: 29483211; 2018, Mol Cancer Ther;17(5):885-896
Antitumor Activity of Osimertinib, an Irreversible Mutant-Selective EGFR Tyrosine Kinase Inhibitor, in NSCLC Harboring EGFR Exon 20 Insertions.

25. PMID: 17664472; 2007, J Clin Oncol;25(22):3238-45
Epidermal growth factor receptor gene copy number and clinical outcome of metastatic colorectal cancer treated with panitumumab.

26. PMID: 22152101; 2011, BMC Cancer;11():509
Biomarker analysis of cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric and oesophago-gastric junction cancer: results from a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO).

27. PMID: 24141978; 2013, Sci Rep;3():2992
A subset of gastric cancers with EGFR amplification and overexpression respond to cetuximab therapy.

28. PMID: 29158193; 2018, J Thorac Oncol;13(2):228-236
EGFR Gene Copy Number by FISH May Predict Outcome of Necitumumab in Squamous Lung Carcinomas: Analysis from the SQUIRE Study.

29. PMID: 19102716; 2009, Pharmacogenomics;10(1):59-68
EGFR-targeted therapies in lung cancer: predictors of response and toxicity.

30. PMID: 15870435; 2005, J Natl Cancer Inst;97(9):643-55
Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer.

31. PMID: 15998906; 2005, J Clin Oncol;23(28):6838-45
Increased epidermal growth factor receptor gene copy number detected by fluorescence in situ hybridization associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: a Southwest Oncology Group Study.

32. PMID: 16204011; 2005, J Clin Oncol;23(31):8081-92
Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials.

33. PMID: 23557218; 2013, J Transl Med;11():90
High EGFR copy number predicts benefits from tyrosine kinase inhibitor treatment for non-small cell lung cancer patients with wild-type EGFR.

34. PMID: 26141217; 2015, Lung Cancer;89(3):337-42
Concurrence of EGFR amplification and sensitizing mutations indicate a better survival benefit from EGFR-TKI therapy in lung adenocarcinoma patients.

35. PMID: 28537764; 2017, J Clin Oncol;35(20):2279-2287
Gefitinib and EGFR Gene Copy Number Aberrations in Esophageal Cancer.

36. PMID: 28057415; 2017, Clin Genitourin Cancer;15(4):e727-e734
Comprehensive Genomic Analysis of Metastatic Mucinous Urethral Adenocarcinoma Guides Precision Oncology Treatment: Targetable EGFR Amplification Leading to Successful Treatment With Erlotinib.

37. PMID: 30463996; 2019, Cancer Discov;9(2):199-209
EGFR and MET Amplifications Determine Response to HER2 Inhibition in ERBB2-Amplified Esophagogastric Cancer.

38. PMID: 28575464; 2017, Neuro Oncol;19(11):1522-1531
Phase II trial of dacomitinib, a pan-human EGFR tyrosine kinase inhibitor, in recurrent glioblastoma patients with EGFR amplification.

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

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

41. 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.

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

43. 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.

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

45. 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.

46. 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.

47. 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.

48. 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.

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

50. 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.

51. PMID: 11239455; 2001, Mol Cell;7(2):263-72
BRCA2 is required for homology-directed repair of chromosomal breaks.

52. PMID: 17597348; 2007, Ann Surg Oncol;14(9):2510-8
Heterogenic loss of the wild-type BRCA allele in human breast tumorigenesis.

53. PMID: 22193408; 2011, Nat Rev Cancer;12(1):68-78
BRCA1 and BRCA2: different roles in a common pathway of genome protection.

54. PMID: 27283171; 2016, J Natl Compr Canc Netw;14(6):795-806

The Relevance of Hereditary Cancer Risks to Precision Oncology: What Should Providers Consider When Conducting Tumor Genomic Profiling?

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

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

57. PMID: 28884698; 2017, Lancet Oncol;18(9):e510
Correction to Lancet Oncol 2017; 18: 1274-84.

58. PMID: 22452356; 2012, N Engl J Med;366(15):1382-92
Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer.

59. PMID: 26187614; 2015, Clin Cancer Res;21(19):4257-61
FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy.

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

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

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

63. 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.

64. PMID: 28882436; 2017, Gynecol Oncol;147(2):267-275
Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2.

65. PMID: 31562799; 2019, N Engl J Med;381(25):2391-2402
Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.

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

67. PMID: 30948273; 2019, Lancet Oncol;20(5):636-648
Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial.

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

69. PMID: 17629517; 2007, Immunity;27(1):111-22
Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses.

70. PMID: 19426216; 2009, Immunol Rev;229(1):88-100
Yin-Yang of costimulation: crucial controls of immune tolerance and function.

71. PMID: 22437870; 2012, Nat Rev Cancer;12(4):252-64
The blockade of immune checkpoints in cancer immunotherapy.

72. PMID: 26918453; 2016, Oncotarget;7(11):12024-34
CD274/PD-L1 gene amplification and PD-L1 protein expression are common events in squamous cell carcinoma of the oral cavity.

ACT Onco® + Report

73. PMID: 28652380; 2017, Cancer Discov;7(10):1098-1115
Immune Escape in Breast Cancer During In Situ to Invasive Carcinoma Transition.

74. PMID: 27620277; 2017, Clin Cancer Res;23(5):1220-1226
Genomic Amplification of CD274 (PD-L1) in Small-Cell Lung Cancer.

75. PMID: 29902298; 2018, JAMA Oncol;4(9):1237-1244
Prevalence of PDL1 Amplification and Preliminary Response to Immune Checkpoint Blockade in Solid Tumors.

76. PMID: 25482239; 2015, N Engl J Med;372(4):311-9
PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma.

77. PMID: 27050074; 2016, Oncotarget;7(22):32113-28
Clinical significance of PD-L1 and PD-L2 copy number gains in non-small-cell lung cancer.

78. PMID: 25795410; 2015, Lancet Oncol;16(4):375-84
Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial.

79. PMID: 26412456; 2015, N Engl J Med;373(17):1627-39
Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer.

80. PMID: 26970723; 2016, Lancet;387(10030):1837-46
Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial.

81. PMID: 26952546; 2016, Lancet;387(10031):1909-20
Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial.

82. PMID: 25399552; 2015, N Engl J Med;372(4):320-30
Nivolumab in previously untreated melanoma without BRAF mutation.

83. PMID: 26028407; 2015, N Engl J Med;373(2):123-35
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer.

84. PMID: 10733529; 2000, Genes Dev;14(6):690-703
E2f3 is critical for normal cellular proliferation.

85. PMID: 24901045; 2014, Cell Death Dis;5():e1274
Retinoblastoma protein (RB) interacts with E2F3 to control terminal differentiation of Sertoli cells.

86. PMID: 31053804; 2019, Nat Rev Cancer;19(6):326-338
The broken cycle: E2F dysfunction in cancer.

87. PMID: 12782593; 2003, Cancer Res;63(11):2872-80
Array-based comparative genomic hybridization for genome-wide screening of DNA copy number in bladder tumors.

88. PMID: 15122326; 2004, Oncogene;23(33):5616-23
E2F3 amplification and overexpression is associated with invasive tumor growth and rapid tumor cell proliferation in urinary bladder cancer.

89. PMID: 28134624; 2017, J Clin Invest;127(3):830-842
Dosage-dependent copy number gains in E2f1 and E2f3 drive hepatocellular carcinoma.

90. PMID: 16007192; 2005, Oncogene;24(42):6441-9
Gains and overexpression identify DEK and E2F3 as targets of chromosome 6p gains in retinoblastoma.

91. PMID: 30214236; 2018, Onco Targets Ther;11():5303-5313
E2F3 promotes cancer growth and is overexpressed through copy number variation in human melanoma.

92. PMID: 10762646; 2000, Int J Mol Med;5(5):447-56
Signaling pathways induced by vascular endothelial growth factor (review).

93. PMID: 11877295; 2002, Blood;99(6):2179-84
Vascular endothelial growth factor (VEGF)-C signaling through FLT-4 (VEGFR-3) mediates leukemic cell proliferation, survival, and resistance to chemotherapy.

94. PMID: 16530705; 2006, Cancer Cell;9(3):209-23
The VEGF-C/Flt-4 axis promotes invasion and metastasis of cancer cells.

95. PMID: 11292664; 2001, FASEB J;15(6):1028-36
VEGFR3 gene structure, regulatory region, and sequence polymorphisms.

96. PMID: 12875690; 2003, Chin Med J (Engl);116(5):727-30
Clinical significance of co-expression of VEGF-C and VEGFR-3 in non-small cell lung cancer.

97. PMID: 12168824; 2002, Anticancer Res;22(3):1463-6
Expression of the vascular endothelial growth factor receptor-3 (VEGFR-3) and its ligand VEGF-C in human colorectal adenocarcinoma.

98. PMID: 12784238; 2003, Head Neck;25(6):464-74
Vascular endothelial growth factor C and vascular endothelial growth factor receptor 3 expression in squamous cell carcinomas of the head and neck.

99. PMID: 15701844; 2005, Clin Cancer Res;11(2 Pt 1):584-93
Stage-specific characterization of the vascular endothelial growth factor axis in prostate cancer: expression of lymphangiogenic markers is associated with advanced-stage disease.

100. PMID: 10068212; 1999, Lab Invest;79(2):243-51
Expression of vascular endothelial growth factor receptor-3 and podoplanin suggests a lymphatic endothelial cell origin of Kaposi's sarcoma tumor cells.

101. PMID: 14648657; 2003, J Pathol;201(4):544-54
Expression of vascular endothelial growth factor (VEGF)-C and VEGF-D, and their receptor VEGFR-3, during different stages of cervical carcinogenesis.

102. PMID: 20949568; 2011, Genes Chromosomes Cancer;50(1):25-33
Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions.

103. PMID: 26735859; 2016, Am J Surg Pathol;40(5):645-55
Recurrent CIC Gene Abnormalities in Angiosarcomas: A Molecular Study of 120 Cases With Concurrent Investigation of PLCG1, KDR, MYC, and FLT4 Gene Alterations.

104. PMID: 27160228; 2016, J Natl Compr Canc Netw;14(5):499-502
Antitumor Response of VEGFR2- and VEGFR3-Amplified Angiosarcoma to Pazopanib.

105. PMID: 25057888; 2014, Biochem J;462(1):1-13
The molecular regulation of Janus kinase (JAK) activation.

106. PMID: 15575979; 2004, Genome Biol;5(12):253
The Janus kinases (Jaks).

107. PMID: 9590173; 1998, Cell;93(3):385-95
Jak2 is essential for signaling through a variety of cytokine receptors.

108. PMID: 27903500; 2017, Cancer Discov;7(2):188-201
Primary Resistance to PD-1 Blockade Mediated by JAK1/2 Mutations.

109. PMID: 27433843; 2016, N Engl J Med;375(9):819-29
Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma.

ACT Onco® + Report

110. PMID: 27075627; 2016, Sci Transl Med;8(334):334ra53
Triple-negative breast cancers with amplification of JAK2 at the 9p24 locus demonstrate JAK2-specific dependence.

111. PMID: 22875628; 2013, Haematologica;98(3):404-8
Ruxolitinib as potential targeted therapy for patients with JAK2 rearrangements.

112. PMID: 18955968; 2008, Oncogene;27(50):6398-406
Bcl-2 family proteins and cancer.

113. PMID: 18676833; 2008, Cancer Res;68(15):6109-17
Down-regulation of myeloid cell leukemia-1 through inhibiting Erk/Pin 1 pathway by sorafenib facilitates chemosensitization in breast cancer.

114. PMID: 18664580; 2008, Proc Natl Acad Sci U S A;105(31):10853-8
mTORC1 promotes survival through translational control of Mcl-1.

115. PMID: 11314001; 2001, Oncogene;20(6):677-85
The involvement of PI 3-K/Akt-dependent up-regulation of Mcl-1 in the prevention of apoptosis of Hep3B cells by interleukin-6.

116. PMID: 11389033; 2001, Blood;97(12):3902-9
MCL1 transgenic mice exhibit a high incidence of B-cell lymphoma manifested as a spectrum of histologic subtypes.

117. PMID: 20164920; 2010, Nature;463(7283):899-905
The landscape of somatic copy-number alteration across human cancers.

118. PMID: 21734342; 2011, Dis Markers;30(5):229-33
Mcl-1 expression is up-regulated in malignancies of the parotid gland.

119. PMID: 26045609; 2015, Blood;126(3):363-72
Inhibition of Mcl-1 with the pan-Bcl-2 family inhibitor (-)BI97D6 overcomes ABT-737 resistance in acute myeloid leukemia.

120. PMID: 27293397; 2016, Case Rep Oncol;9(1):112-8
A Combination of Targeted Therapy with Chemotherapy Backbone Induces Response in a Treatment-Resistant Triple-Negative MCL1-Amplified Metastatic Breast Cancer Patient.

121. PMID: 17178882; 2006, Cancer Res;66(24):11851-8
Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5.

122. PMID: 23392173; 2013, Cell Death Dis;4():e485
Mcl-1-dependent activation of Beclin 1 mediates autophagic cell death induced by sorafenib and SC-59 in hepatocellular carcinoma cells.

123. PMID: 16007148; 2005, Oncogene;24(46):6861-9
The role of Mcl-1 downregulation in the proapoptotic activity of the multikinase inhibitor BAY 43-9006.

124. PMID: 19821497; 2009, Hepatology;50(6):1861-70
Sorafenib inhibits signal transducer and activator of transcription-3 signaling in cholangiocarcinoma cells by activating the phosphatase shatterproof 2.

125. PMID: 20071162; 2010, Eur J Cancer;46(4):836-50
The multikinase inhibitor Sorafenib induces apoptosis and sensitises endometrial cancer cells to TRAIL by different mechanisms.

126. PMID: 21979753; 2012, Mol Med;18():19-28
Sorafenib-induced apoptosis of chronic lymphocytic leukemia cells is associated with downregulation of RAF and myeloid cell leukemia sequence 1 (Mcl-1).

127. PMID: 24763611; 2014, Clin Cancer Res;20(13):3472-84
Regorafenib inhibits colorectal tumor growth through PUMA-mediated apoptosis.

128. PMID: 26561209; 2015, Cancer Biol Ther;16(12):1710-9

Regorafenib with a fluoropyrimidine for metastatic colorectal cancer after progression on multiple 5-FU-containing combination therapies and regorafenib monotherapy.

129. PMID: 24163374; 2014, Cancer Discov;4(1):42-52
mTOR inhibition specifically sensitizes colorectal cancers with KRAS or BRAF mutations to BCL-2/BCL-XL inhibition by suppressing MCL-1.

130. PMID: 21730163; 2011, Proc Natl Acad Sci U S A;108(29):12001-6
The p53 inhibitors MDM2/MDMX complex is required for control of p53 activity in vivo.

131. PMID: 14507994; 2003, Proc Natl Acad Sci U S A;100(21):12009-14
HdmX stimulates Hdm2-mediated ubiquitination and degradation of p53.

132. PMID: 12162806; 2002, DNA Cell Biol;21(7):519-25
MDMX inhibits the p300/CBP-mediated acetylation of p53.

133. PMID: 17080083; 2006, Nature;444(7115):61-6
Inactivation of the p53 pathway in retinoblastoma.

134. PMID: 21098696; 2011, Clin Cancer Res;17(3):494-504
Nutlin-3a is a potential therapeutic for ewing sarcoma.

135. PMID: 22820643; 2012, Nat Med;18(8):1239-47
MDM4 is a key therapeutic target in cutaneous melanoma.

136. PMID: 12640683; 2003, Int J Cancer;104(6):752-7
Refined mapping of 1q32 amplicons in malignant gliomas confirms MDM4 as the main amplification target.

137. PMID: 23946421; 2013, Proc Natl Acad Sci U S A;110(36):E3445-54
Stapled α-helical peptide drug development: a potent dual inhibitor of MDM2 and MDMX for p53-dependent cancer therapy.

138. PMID: 26883273; 2016, Mol Cancer Ther;15(4):574-582
Identification of a Small Molecule That Overcomes HdmX-Mediated Suppression of p53.

139. PMID: 21075307; 2010, Cancer Cell;18(5):411-22
A stapled p53 helix overcomes HDMX-mediated suppression of p53.

140. PMID: 20080970; 2010, J Biol Chem;285(14):10786-96
Identification and characterization of the first small molecule inhibitor of MDMX.

141. PMID: 19029958; 2008, Nat Rev Cancer;8(12):976-90
Reflecting on 25 years with MYC.

142. PMID: 22464321; 2012, Cell;149(1):22-35
MYC on the path to cancer.

143. PMID: 10378696; 1999, Oncogene;18(19):3004-16
MYC oncogenes and human neoplastic disease.

144. PMID: 16934487; 2006, Semin Cancer Biol;16(4):318-30
The Myc oncoprotein as a therapeutic target for human cancer.

145. PMID: 22113465; 2012, Clin Exp Med;12(4):217-23
C-myc as a predictive marker for chemotherapy in metastatic breast cancer.

146. PMID: 21741827; 2011, Eur J Cancer;47(12):1779-88
Association between c-myc amplification and pathological complete response to neoadjuvant chemotherapy in breast cancer.

147. PMID: 15132769; 2004, Cancer Sci;95(5):418-23
Expression of the c-myc gene as a predictor of chemotherapy response and a prognostic factor in patients with ovarian cancer.

ACT Onco® + Report

148. PMID: 22430491; 2012, J Exp Med;209(4):679-96
MYC pathway activation in triple-negative breast cancer is synthetic lethal with CDK inhibition.

149. PMID: 27486754; 2016, Oncotarget;7(35):56864-56875
Inhibition of cyclin dependent kinase 9 by dinaciclib suppresses cyclin B1 expression and tumor growth in triple negative breast cancer.

150. PMID: 24503701; 2014, PLoS One;9(2):e87456
Immunohistochemistry for myc predicts survival in colorectal cancer.

151. PMID: 9816266; 1996, Clin Cancer Res;2(6):1049-53
Overexpression of the c-myc proto-oncogene in colorectal carcinoma is associated with a reduced mortality that is abrogated by point mutation of the p53 tumor suppressor gene.

152. PMID: 23860775; 2013, Tumour Biol;34(6):3945-58
MYC overexpression and poor prognosis in sporadic breast cancer with BRCA1 deficiency.

153. PMID: 24162815; 2013, Nat Med;19(11):1469-1472
Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer.

154. PMID: 27843590; 2016, ESMO Open;1(2):e000023
NTRK gene fusions as novel targets of cancer therapy across multiple tumour types.

155. PMID: 30624546; 2019, Ann Oncol;30(2):325-331
Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study.

156. PMID: 32323889; 2020, Oncologist;25(6):e881-e886
Antitumor Activity of Larotrectinib in Esophageal Carcinoma with NTRK Gene Amplification.

157. PMID: 15599732; 2005, Cancer Immunol Immunother;54(4):307-14
Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy.

158. PMID: 12893276; 2003, Biochem Biophys Res Commun;307(3):672-7
Differential binding properties of B7-H1 and B7-DC to programmed death-1.

159. PMID: 15837746; 2005, Clin Cancer Res;11(8):2947-53
Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer.

160. PMID: 26317899; 2015, Oncotarget;6(28):26483-93
Genomic amplification of 9p24.1 targeting JAK2, PD-L1, and PD-L2 is enriched in high-risk triple negative breast cancer.

161. PMID: 26464193; 2016, Ann Surg Oncol;23(2):694-702
Clinicopathologic Analysis of PD-L1 and PD-L2 Expression in Renal Cell Carcinoma: Association with Oncogenic Proteins Status.

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

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

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

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

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

167. 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.

168. 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.

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

170. 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.

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

172. 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.

173. 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.

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

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

176. 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.

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

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

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

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

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

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

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

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

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

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

187. PMID: 27982019; 2017, Cancer Gene Ther;24(1):20-27

The associations of TERT-CLPTM1L variants and TERT mRNA expression with the prognosis of early stage non-small cell lung cancer.

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

189. 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.

190. 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.

191. PMID: 19339720; 2009, N Engl J Med;360(14):1408-17
Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer.

192. PMID: 18784101; 2008, N Engl J Med;359(11):1116-27
Platinum-based chemotherapy plus cetuximab in head and neck cancer.

193. PMID: 16467544; 2006, N Engl J Med;354(6):567-78
Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.

194. PMID: 15269313; 2004, N Engl J Med;351(4):337-45
Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.

195. 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.

196. 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.

197. 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.

198. PMID: 26045340; 2015, Lancet Oncol;16(7):763-74
Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial.

199. 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.

200. 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.

201. PMID: 25366685; 2015, J Clin Oncol;33(3):244-50
Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation.

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

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

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

205. PMID: 27736842; 2016, Br J Cancer;115(10):1206-1214

ACT Onco® + Report

A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer.

206. PMID: 24024839; 2013, N Engl J Med;369(11):1023-34
Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer.

207. PMID: 24739896; 2014, Lancet Oncol;15(6):569-79
Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study.

208. PMID: 17470858; 2007, J Clin Oncol;25(13):1658-64
Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer.

209. PMID: 27908594; 2017, Lancet Oncol;18(1):75-87
Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial.