

ACT Onco[®] + Report

PATIENT		
Identifier: 洪鳳玉		Patient ID: 48395068
Date of Birth: Feb 05, 1963		Gender: Female
Diagnosis: Lung cancer		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11152187A/B		Type: FFPE tissue
Collection site: Lung		
Date received: Dec 16, 2022	Lab ID: AA-22-07706	D/ID: NA

ABOUT ACT Onco[®]+

The test is a next-generation sequencing (NGS)-based assay developed for efficient and comprehensive genomic profiling of cancers. This test interrogates coding regions of 440 genes associated with cancer treatment, prognosis and diagnosis. Genetic mutations detected by this test include small-scale mutations like single nucleotide variants (SNVs), small insertions and deletions (InDels) (≤ 15 nucleotides) and large-scale genomic alterations like copy number alterations (CNAs). The test also includes an RNA test, detecting fusion transcripts of 13 genes.

SUMMARY FOR ACTIONABLE VARIANTS

VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Probable Effects in Patient's Cancer Type		Probable Sensitive in Other Cancer Types
	Sensitive	Resistant	
EGFR E746_A750del (Exon 19 deletion)	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	-	-

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
RB1 D330fs	-	Abemaciclib, Palbociclib, Ribociclib
KDR Amplification	Cabozantinib, Pazopanib, Sunitinib	-
MCL1 Amplification	Regorafenib, Sorafenib	-

Note:

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

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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
<i>EGFR</i>	E746_A750del (Exon 19 deletion)	33.2%
<i>RB1</i>	D330fs	50.4%
<i>SERPINB3</i>	K146N	61.4%
<i>TP53</i>	A70V	59.7%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr11	<i>ATM, MRE11</i>	Heterozygous deletion	1
Chr7	<i>KMT2C</i>	Heterozygous deletion	1
Chr1	<i>MCL1, NTRK1</i>	Amplification	6
Chr4	<i>KDR</i>	Amplification	6
Chr5	<i>TERT</i>	Amplification	15

- Fusions

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

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	1.3 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 62% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco[®] + to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is $< 30\%$.

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THERAPEUTIC IMPLICATIONS TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 1		
EGFR E746_A750del (Exon 19 deletion)	Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib	sensitive
Level 3B		
KDR Amplification	Cabozantinib	sensitive
Level 4		
KDR Amplification	Pazopanib, Sunitinib	sensitive
MCL1 Amplification	Regorafenib, Sorafenib	sensitive
RB1 D330fs	Abemaciclib, Palbociclib, Ribociclib	resistant

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

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

- Other Biomarkers with Potential Clinical Effects for ICIs

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

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

CHEMOTHERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
RB1 D330fs	Cisplatin	Sensitive	Clinical	Bladder carcinoma
	FAC	Sensitive	Clinical	Breast cancer
	T/FAC taxane/doxorubicin			

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
RB1 D330fs	Tamoxifen	Resistant	Clinical	Breast cancer

OTHERS

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

Note:

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

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VARIANT INTERPRETATION

EGFR E746_A750del (Exon 19 deletion)

Biological Impact

The EGFR gene encodes for the Epidermal Growth Factor Receptor, a receptor tyrosine kinase which binds to its ligands, including Epidermal Growth Factor (EGF) and Transforming Growth Factor- α (TGF- α), 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 E746_A750del is located within the protein kinase domain of the EGFR protein, resulting in the deletion of five amino acids from amino acids 746 to 750 (UniProtKB)^[5]. E746_A750del confers a gain of function to the EGFR protein, as demonstrated by increased EGFR kinase activity, activation of p44/42 MAPK and AKT, oncogenic transformation of the cells in vitro and promoting tumor growth in xenograft models^{[6][7][8]}.

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

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^[10] (Annals of Oncology (2017) 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376).

In a retrospective study, treatment with gefitinib resulted in partial response in 7 patients and stable disease in 1 patient who are with lung adenocarcinoma harboring EGFR E746_A750del^[11]. Preclinically, EGFR E746_A750del is sensitive to gefitinib, erlotinib, afatinib and osimertinib, demonstrated by the inhibition of EGFR signaling and cell proliferation in vitro^{[12][13][14]}.

The first- and second-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs), dacomitinib, erlotinib, gefitinib and afatinib have been approved by the U.S. Food and Drug Administration (FDA) as the first-line treatment in non-small cell lung cancer (NSCLC) patients whose tumor carries EGFR exon 19 deletion or L858R mutation^{[15][16][17]}, as detected by a U.S. FDA-approved test. A Phase III clinical trial (NCT01774721) show that dacomitinib significantly improved progression-free survival over gefitinib in first-line treatment of patients with EGFR-mutation-positive NSCLC^[15]. Another Phase III clinical trial (NCT00949650) demonstrated that median progression-free survival (PFS) among lung cancer patients with exon 19 deletion or L858R EGFR mutation (n=308) was 13.6 months for afatinib and 6.9 months for chemotherapy. The EGFR T790M mutation has been demonstrated to confer resistance to TKIs (dacomitinib, gefitinib, erlotinib, and afatinib) in preclinical and clinical studies^{[18][19][20][21]}.

Osimertinib, a third-generation irreversible EGFR-TKI that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations, has been approved by the U.S. FDA for NSCLC patient harboring T790M mutation-positive tumor^{[22][23][24]}. Results from a double-blind, Phase 3 trial further showed that osimertinib significantly demonstrated longer PFS than standard EGFR-TKIs (18.9 months vs. 10.2 months) in previously untreated EGFR mutation-positive (exon 19 deletion or L858R) advanced NSCLC^[25].

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RB1 D330fs

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication^[26]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis^[27]. 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^{[28][29][30]}. 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^[31].

D330fs mutation results in a change in the amino acid sequence beginning at 330, likely to cause premature truncation of the functional RB1 protein (UniProtKB). This mutation is predicted to lead to a loss of RB1 protein function, despite not being characterized in the literature.

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^[32]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytosine (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy^[33].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer^{[34][35]}.

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment^[36]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib^[37].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)^{[38][39]}. 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^{[35][40]}.

SERPINB3 K146N

Biological Impact

SERPINB3 encodes a protein of the serpin family of serine protease inhibitors. SERPINB3 is a close human homolog of SERPINB4 with which shares 92% protein sequence identity. SERPINB3 and SERPINB4 proteins have overlapping functions and are involved in both oncogenesis and immunity^{[41][42]}.

Therapeutic and prognostic relevance

Results from a clinical study showed that somatic mutations in SERPINB3 and SERPINB4 predicted improved survival from treatment with anti-CTLA4 therapy in two independent cohorts of patients with melanoma (n=174)^[43].

TP53 A70V

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[44]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[45].

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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)^[46].

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^[47]. 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^[48].

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^{[49][50][51]}. 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)^[52]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[53][54]}. 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^[55].

ATM Heterozygous deletion

Biological Impact

The ataxia-telangiectasia mutated protein kinase (ATM) gene encodes a PI3K-related serine/threonine protein kinase involved in genomic integrity maintenance and plays central roles in DNA double-strand break (DSB) repair, which can be induced by ionizing radiation, chemotherapy drugs, or oxidative stress^[56]. ATM is a well-characterized tumor suppressor gene, hereditary mutations and haploinsufficiency of ATM result in markedly increased susceptibility to a variety of cancer types^{[57][58][59][60][61]}. Results from a case-cohort study of colorectal cancer and cancer-free control individuals suggested that germline pathogenic mutations in ATM and PALB2 should be added to established CRC risk genes as part of standard tumor genetic testing panels^[62]. ATM is among the most commonly aberrant genes in sporadic cancers. Somatic ATM aberrations are frequently observed in hematologic malignancies^{[63][64][65][66]} and a broad range of tumors such as prostate cancer^[67], head and neck squamous cell carcinoma (HNSCC)^[68], pancreatic cancer^[69], lung adenocarcinoma^[70], breast cancer^[71], and ovarian cancer^[58].

Therapeutic and prognostic relevance

In May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate (NCT02987543)^[72].

In a phase II trial (TOPARP-A; NCT01682772), 3 out of 4 metastatic prostate cancer patients harboring only ATM inactivating mutations responded to olaparib treatment^[73]. Also, the phase II TOPARP-B trial (NCT01682772) demonstrated that olaparib treatment resulted in a RECIST 1.1 or PSA50 response rate of 10.5% (2/12) and a composite overall response rate of 36.8% (7/19) in prostate cancer patients harboring deleterious ATM mutations^[74]. In another randomized, double-blind phase II trial in Asian patients with metastatic gastric cancer has shown that addition of olaparib to paclitaxel significantly increased the OS in both the overall population and patients with low or undetectable ATM protein expression (NCT01063517)^[75]. However, in the subsequent phase III trial (GOLD; NCT01924533), addition of olaparib to paclitaxel did not significantly improve OS in the overall or the ATM-negative population of Asian gastric cancer patients^[76]. Besides, in a phase II trial (TBCRC 048; NCT03344965), 7 metastatic breast cancer patients harboring only ATM mutations were not responded to olaparib treatment (SD: n=2, PD: n=5)^[77]. In

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a phase II trial (TRITON2; NCT02952534), 49 mCRPC patients harboring ATM alteration had limited response to rucaparib treatment. The radiographic response rate was 10.5 % (n=2/19 evaluable patients), the prostate-specific antigen response rate was 4.1% (n=2/49), and the 6-month clinical benefit rate was 28.6% (n=12/42)^[78].

In preclinical studies, cells with ATM alternation were sensitive to olaparib, niraparib, and talazoparib treatment in vitro and in vivo^{[79][80][81][82]}.

In addition, ATM has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in breast cancer (NCT04053322) and advanced solid tumors (NCT03297606), rucaparib efficacy in ovarian cancer (NCT01968213)^[83] and prostate cancer (NCT02952534, NCT03533946)^[78], niraparib efficacy in pancreatic cancer (NCT03553004, NCT03601923), prostate cancer (NCT02854436), melanoma (NCT03925350), metastatic esophageal/gastroesophageal junction (GEJ)/proximal gastric adenocarcinoma (NCT03840967), and any malignancy, except prostate (NCT03207347), and talazoparib efficacy in advanced or metastatic cancer (NCT02286687), HER2-negative solid tumors (NCT02401347), prostate cancer (NCT03148795), and lung cancer (NCT03377556), respectively.

Also, a prospective study in muscle-invasive bladder cancer patients suggested that genomic alternations in the DNA repair genes ATMs, RB1 and FANCC could be recognized as biomarkers predictive of response to cisplatin-based neoadjuvant chemotherapy^[32]. However, loss-of-function of the ATM-CHEK2-TP53 cascade is associated with resistance to anthracycline/mitomycin-containing chemotherapy in patients with breast cancer^[84].

A retrospective study of VICTOR trial demonstrated that ATM loss was associated with worse prognosis in colorectal cancer^[85].

KDR Amplification

Biological Impact

KDR (kinase domain receptor), also known as VEGFR2 or Flk-1, is a tyrosine kinase receptor for the vascular endothelial growth factor (VEGF) and involves in angiogenesis pathway^[86]. Binding of VEGF to KDR results in activation of phospholipase C (PLC-gamma) and downstream signaling via protein kinase C (PKC) and RAF/MEK/ERK^[87]. Mutations of KDR are rare in tumors, and alterations of KDR activity typically occur via KDR amplification and subsequent overexpression^{[88][89]}.

Therapeutic and prognostic relevance

To date, there are four VEGF inhibitors (sorafenib, sunitinib, pazopanib, bevacizumab) and one VEGFR2 inhibitor cabozantinib that are FDA-approved for the treatment of cancers^{[90][91][92]}. Notably, a case report showed that an angiosarcoma patient with concurrent KDR and FLT4 amplification developed a progressive disease when treated with sorafenib, but experienced a potent antitumor response and achieved clinically stable disease for 6 months after receiving pazopanib therapy^[93]. Besides, an angiosarcoma patient with upregulated VEGFR2 responded to sunitinib treatment^[94]. VEGFR2 inhibitors like apatinib and vandetanib are in early clinical phase trial^{[95][96][97]}.

KDR amplification and/or mutation has been selected as an inclusion criteria for the trial examining cabozantinib in metastatic castrate resistant prostate cancer (mCRPC) (NCT04631744) and sunitinib in malignant solid tumors (NCT03297606). The increased copy number of KIT or KDR significantly correlated with a worse 5-year breast cancer-specific survival (BCSS) in triple-negative breast cancer (TNBC) patients^[98].

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KMT2C Heterozygous deletion

Biological Impact

Lysine methyltransferase 2C (KMT2C) gene encodes the histone methyltransferase MLL3, which methylates lysine residue four on the tail of histone H3 (H3K4)^[99] and regulates the gene expression during development and hematopoiesis^{[100][101][102]}. KMT2C is ubiquitously expressed, and its function is essential for normal embryonal development and cell proliferation^[103]. Genetic deletion of the region containing KMT2C is the most common chromosomal abnormality in acute myeloid leukemia^{[104][105]}, and KMT2C mutation has been reported in breast cancer, cutaneous squamous cell carcinoma, and leukemia^{[106][107][108][109][110]}. KMT2C was implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions^[111]. Animal studies revealed that MLL3 haploinsufficiency enhances hematopoietic stem cells (HSCs) self-renewal capacity and induces extensive division of HSCs (AACR; Cancer Res 2018;78(13 Suppl): Abstract nr 4996).

Therapeutic and prognostic relevance

Preclinical studies of cell lines and xenograft models demonstrated that cells with reduced KMT2C expression and activity are deficient in homologous recombination-mediated double-strand break DNA repair and therefore, are more sensitive to olaparib, a PARP1/2 inhibitor^[112].

A meta-analysis indicated that low levels of KMT2C expression was associated with better overall survival in pancreatic ductal adenocarcinoma (PDAC) patients^[113]. However, another study of ER-positive breast cancer patients (n = 401) demonstrated that low KMT2C expression was associated with worse overall survival^[114].

MCL1 Amplification

Biological Impact

The myeloid cell leukemia 1 (MCL1) gene encodes a member of the BCL2 pro-survival family^[115]. MCL1 is highly regulated by various oncogenic signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway^[116], the mTOR pathway^[117], and the phosphatidylinositol-3 kinase (PI3K) pathway^[118]. Oncogenic roles for MCL1 have been previously suggested by the report of increased rates of lymphoma in transgenic mice^[119]. Somatic amplification of MCL1 may be a common mechanism in cancer cells to increase cell survival^[120]. MCL1 overexpression was observed from a retrospective analysis of parotid gland carcinomas, including adenoid cystic carcinoma^[121].

Therapeutic and prognostic relevance

Therapies targeting MCL1 and other BCL2 family members with the pan-BCL2 family inhibitors are currently under investigation^[122]. 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^[123]. 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^{[124][125][126][127][128][129]}. Preclinical studies have also demonstrated the efficacy of regorafenib in reducing MCL1 expression in human colorectal cancer (CRC) cell lines^{[130][131]}. 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^[132].

MRE11 Heterozygous deletion

Biological Impact

The MRE11 gene encodes a protein that forms the MRE11-RAD50-NBS (MRN) complex involved in sensing and repairing DNA double-strand breaks via homologous recombination and non-homologous end joining^{[133][134]}. MRE11 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function^[133]. The carrier of MRE11 mutation may confer elevated risks

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for numerous types of cancers including breast cancer, ovarian cancer, endometrial cancer, colorectal cancer, and lymphoid cancer^{[133][134][135][136][137][138][139]}.

Therapeutic and prognostic relevance

In a Phase II clinical trial (n=50), one castration-resistant prostate cancer patient harboring an MRE11 inactivating mutation responded to olaparib^[73]. Preclinically, loss of MRE11 also predicted sensitivity to PARP inhibitor talazoparib and ABT-888 in endometrial cancer^[140] and microsatellite unstable colorectal cancer (CRC) cell lines^[141]. MRE11 has been selected as an inclusion criterion for the trial examining olaparib in metastatic biliary tract cancer (NCT04042831), and talazoparib in HER2-negative breast cancer (NCT02401347) and prostate cancer (NCT03148795).

CRC patients with tumor deficient of MRE11 showed initially reduced disease-free survival (DFS) and overall survival (OS) but improved long-term DFS and OS compared with patients with an intact MRE11^[142].

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^{[143][144]}. 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)^[145], 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^[146].

TERT Amplification

Biological Impact

The TERT gene encodes the catalytic subunit of telomerase, an enzyme that maintains telomere length and genomic integrity^[147]. Upregulation of TERT promotes cancer development and progression via modulation of Wnt-catenin and nuclear factor kappa B signaling^{[148][149]}, and mitochondrial RNA processing^[150]. 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^{[151][152][153][154][155]}.

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^[147].

TERT gene amplification is an independent poor prognostic marker for disease-free survival in non-small cell lung cancer (NSCLC) and breast cancer^{[156][157][158]}.

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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 ^[159] NCT01523587	Non-small cell lung carcinoma (Approved on 2016/04/15)
	EGFR ex19del or L858R
	Afatinib vs. Erlotinib [PFS(M): 2.4 vs. 1.9]
LUX-Lung 3 ^[160] NCT00949650	Non-small cell lung carcinoma (Approved on 2013/07/13)
	EGFR ex19del or L858R
	Afatinib vs. Pemetrexed + cisplatin [PFS(M): 11.1 vs. 6.9]

Cabozantinib (COMETRIQ)

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

- FDA Approval Summary of Cabozantinib (COMETRIQ)

EXAM ^[161] NCT00704730	Thyroid cancer (Approved on 2012/11/29)
	-
	Cabozantinib vs. Placebo [PFS(M): 11.2 vs. 4]

Cabozantinib (CABOMETYX)

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

- FDA Approval Summary of Cabozantinib (CABOMETYX)

COSMIC-311 NCT03690388	Differentiated thyroid cancer (dtc) (Approved on 2021/09/17)
	-
	Cabozantinib vs. Placebo [PFS(M): 11 vs. 1.9, ORR(%): 18.0 vs. 0]
CHECKMATE-9ER NCT03141177	Renal cell carcinoma (Approved on 2021/01/22)
	-
	Nivolumab + cabozantinib vs. Sunitinib [ORR(%): 55.7 vs. 27.1, PFS(M): 16.6 vs. 8.3, OS(M): NR vs. NR]
CELESTIAL ^[92] NCT01908426	Hepatocellular carcinoma (Approved on 2019/01/14)
	-
	Cabozantinib vs. Placebo [OS(M): 10.2 vs. 8]
CABOSUN ^[162] NCT01835157	Renal cell carcinoma (Approved on 2017/12/09)
	-
	Cabozantinib vs. Sunitinib [PFS(M): 8.6 vs. 5.3]

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METEOR^[163] NCT01865747	Renal cell carcinoma (Approved on 2016/04/25)
	-
	Cabozantinib vs. Everolimus [PFS(M): 7.4 vs. 3.8]

Dacomitinib (VIZIMPRO)

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

- FDA Approval Summary of Dacomitinib (VIZIMPRO)

ARCHER 1050^[15] NCT01774721	Non-small cell lung carcinoma (Approved on 2018/09/27)
	EGFR ex19del or L858R
	Dacomitinib vs. Gefitinib [PFS(M): 14.7 vs. 9.2]

Erlotinib (TARCEVA)

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

- FDA Approval Summary of Erlotinib (TARCEVA)

RELAY NCT02411448	Non-small cell lung carcinoma (Approved on 2020/05/29)
	EGFR ex19del or L858R
	Erlotinib + ramucirumab vs. Erlotinib + placebo [PFS(M): 19.4 vs. 12.4]
EURTAC^[164] NCT00446225	Non-small cell lung carcinoma (Approved on 2013/05/14)
	EGFR ex19del or L858R
	Erlotinib vs. Cisplatin + gemcitabine or cisplatin + docetaxel or carboplatin + gemcitabine or carboplatin + docetaxel [PFS(M): 10.4 vs. 5.2]
PA.3^[165] 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^[166] NCT01203917	Non-small cell lung carcinoma (Approved on 2015/07/13)
	EGFR ex19del or L858R
	Gefitinib [ORR(%): 50.0]

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Niraparib (ZEJULA)

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

- FDA Approval Summary of Niraparib (ZEJULA)

PRIMA NCT02655016	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2020/04/29)
	- Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
NOVA^[167] NCT01847274	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/03/27)
	- Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

Olaparib (LYNPARZA)

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

- FDA Approval Summary of Olaparib (LYNPARZA)

OlympiA NCT02032823	Her2-negative high-risk early breast cancer (Approved on 2022/03/11)
	HER2-/gBRCA mutation Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M):]
PROfound^[72] NCT02987543	Prostate cancer (Approved on 2020/05/19)
	HRR genes mutation Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1^[168] NCT02477644	Ovarian cancer (Approved on 2020/05/08)
	HRD+ Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO^[169] NCT02184195	Pancreatic adenocarcinoma (Approved on 2019/12/27)
	gBRCA mutation Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1^[170] NCT01844986	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2018/12/19)
	gBRCA mutation or sBRCA mutation Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD^[171] NCT02000622	Breast cancer (Approved on 2018/02/06)
	HER2-/gBRCA mutation Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21^[172] NCT01874353	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	gBRCA mutation Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19^[173] NCT00753545	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	- Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

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Osimertinib (TAGRISSO)

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

- FDA Approval Summary of Osimertinib (TAGRISSO)

ADAURA NCT02511106	Non-small cell lung carcinoma (Approved on 2020/12/18)
	EGFR ex19del or L858R
	Osimertinib vs. Placebo + adjuvant chemotherapy [DFS(M): NR vs. 19.6]
FLAURA^[25] NCT02296125	Non-small cell lung carcinoma (Approved on 2018/04/18)
	EGFR ex19del or L858R
	Osimertinib vs. Gefitinib or erlotinib [PFS(M): 18.9 vs. 10.2]
AURA3^[174] NCT02151981	Non-small cell lung carcinoma (Approved on 2017/03/30)
	EGFR T790M
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA^[24] NCT01802632	Non-small cell lung carcinoma (Approved on 2015/11/13)
	EGFR T790M
	Osimertinib [ORR(%): 59.0]

Pazopanib (VOTRIENT)

Pazopanib is an oral, small molecule, multi-kinase inhibitor that targets receptor tyrosine kinase including vascular endothelial growth factor receptor-1, -2, -3 (VEGFR-1, -2, -3), platelet-derived growth factor receptor- α , - β (PDGFR- α , - β), c-kit, fibroblast growth factor-1 and -3 (FGFR-1, -3), thereby inhibiting angiogenesis. Pazopanib is developed and marketed by GlaxoSmithKline under the trade name VOTRIENT.

- FDA Approval Summary of Pazopanib (VOTRIENT)

PALETTE^[175] NCT00753688	Sarcoma (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]
VEG105192^[176] NCT00334282	Renal cell carcinoma (Approved on 2009/10/19)
	-
	Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]

Regorafenib (STIVARGA)

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

- FDA Approval Summary of Regorafenib (STIVARGA)

RESORCE^[177] NCT01774344	Hepatocellular carcinoma, Hepatocellular carcinoma (Approved on 2017/04/27)
	-
	Bsc vs. Placebo [OS(M): 10.6 vs. 7.8]
GRID^[178] NCT01271712	Gastrointestinal stromal tumor (Approved on 2013/02/25)
	-
	Regorafenib vs. Placebo [PFS(M): 4.8 vs. 0.9]

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CORRECT ^[179] NCT01103323	Colorectal cancer (Approved on 2012/09/27)
	-
	Regorafenib vs. Placebo [OS(M): 6.4 vs. 5]

Rucaparib (RUBRACA)

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

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	Prostate cancer (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3 ^[83] NCT01968213	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2018/04/06)
	-
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]

Sorafenib (NEXAVAR)

Sorafenib is a small molecule multi-kinase inhibitor that targets multiple kinase families including VEGFR, PDGFRB, and the RAF family kinases. Sorafenib is co-developed and co-marketed by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals under the trade name NEXAVAR.

- FDA Approval Summary of Sorafenib (NEXAVAR)

DECISION ^[180] NCT00984282	Differentiated thyroid carcinoma (Approved on 2013/11/22)
	-
	Sorafenib vs. Placebo [PFS(M): 10.8 vs. 5.8]
SHARP ^[181] NCT00105443	Hepatocellular carcinoma (Approved on 2007/11/16)
	-
	Sorafenib vs. Placebo [OS(M): 10.7 vs. 7.9]
TARGET ^[182] NCT00073307	Renal cell carcinoma (Approved on 2005/12/20)
	-
	Sorafenib vs. Placebo [PFS(D): 167 vs. 84]

Sunitinib (SUTENT)

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

- FDA Approval Summary of Sunitinib (SUTENT)

[183][184][185] NCT00428597	Pancreatic cancer (Approved on 2011/05/20)
	-
	Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]

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[186][187] NCT00083889	Renal cell carcinoma (Approved on 2007/02/02)
	-
	Sunitinib vs. Ifn- α [PFS(W): 47.3 vs. 22]
[188][189][187] NCT00077974	Renal cell carcinoma (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 34.0]
[189][187] NCT00054886	Renal cell carcinoma (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 36.5]
[190] NCT00075218	Gastrointestinal stromal tumor (Approved on 2006/01/26)
	-
	Sunitinib vs. Placebo [TTP(W): 27.3 vs. 6.4]

Talazoparib (TALZENNA)

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

- FDA Approval Summary of Talazoparib (TALZENNA)

EMBRACA ^[191] NCT01945775	Breast cancer (Approved on 2018/10/16)
	HER2-/gBRCA mutation
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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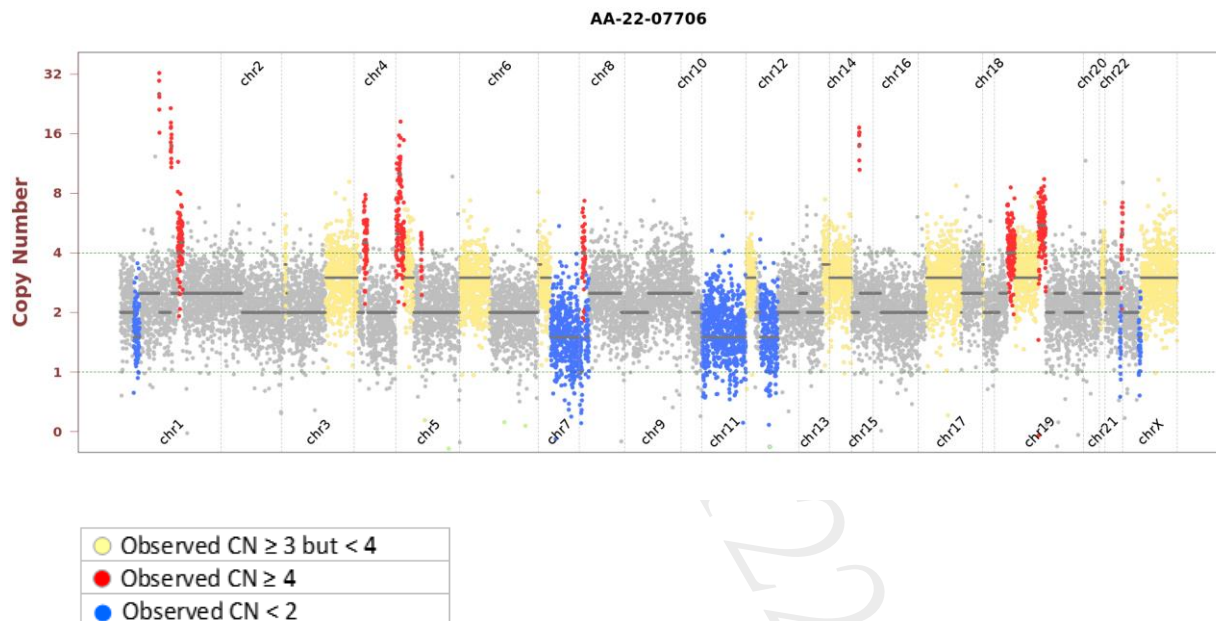
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
EGFR	E746_A750del (Exon 19 deletion)	19	c.2235_2249del	NM_005228	COSM6223	33.2%	1848
RB1	D330fs	10	c.988_995del	NM_000321	-	50.4%	246
SERPINB3	K146N	5	c.438G>T	NM_006919	-	61.4%	1351
TP53	A70V	4	c.209C>T	NM_000546	COSM6926092	59.7%	201

- Copy Number Alterations

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



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OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
ADAMTS13	C532Y	14	c.1595G>A	NM_139025	-	34.2%	602
BRCA2	S1832Y	11	c.5495C>A	NM_000059	-	83.1%	397
BUB1B	I625M	15	c.1875A>G	NM_001211	COSM98868	54.1%	1535
CREBBP	M2320L	31	c.6958A>C	NM_004380	-	55.5%	328
ERBB4	R979Q	24	c.2936G>A	NM_005235	COSM4090859	82.1%	1293
GATA3	P236S	3	c.706C>T	NM_001002295	-	60.3%	1180
HIST1H1C	A24V	1	c.71C>T	NM_005319	-	54.6%	997
LIG3	R867C	18	c.2599C>T	NM_013975	-	28.0%	927
MUC16	R13554C	56	c.40660C>T	NM_024690	-	65.7%	1039
MUC6	Splice region	-	c.1453+4C>T	NM_005961	COSM2108620	52.1%	142
MUTYH	R294H	10	c.881G>A	NM_001128425	-	70.3%	950
NFE2L2	P233S	5	c.697C>T	NM_006164	-	83.6%	749
PDGFRA	E219Q	5	c.655G>C	NM_006206	-	84.3%	1309
SYNE1	L1575F	36	c.4723C>T	NM_182961	COSM3726493	17.2%	761

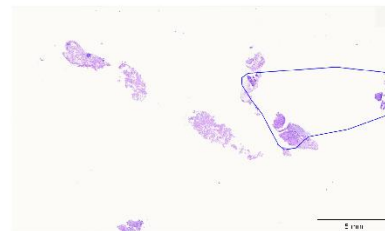
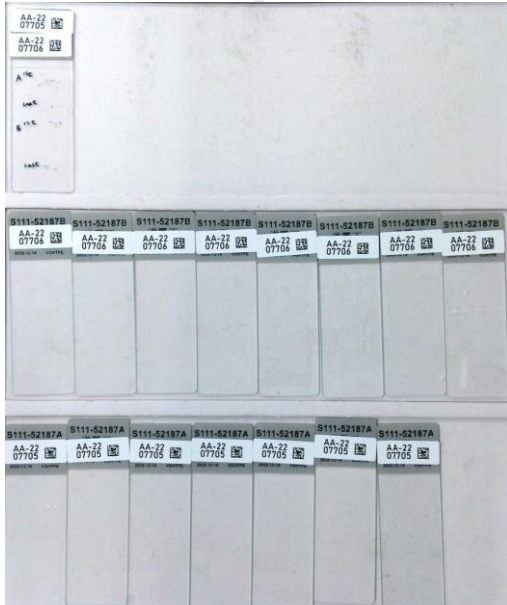
Note:

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

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TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Dec 13, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11152187A/B
- Collection site: Lung
- Examined by: Dr. Chien-Ta Chiang
 1. The percentage of viable tumor cells in total cells in the whole slide (%): 10%/20%
 2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 40%/60%
 3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 30%/10%
 4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%/5%
 5. Additional comment: NA/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: 937x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 150

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LIMITATIONS

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

The copy number alterations (CNAs) were predicted as described below:

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

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

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

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 .

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

DATABASE USED

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

Variant Analysis:

醫藥資訊研究員
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



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GENE LIST SNV & CNV

ABCB1*	ABCC2*	ABCG2*	ABL1	ABL2	ADAMTS1	ADAMTS13	ADAMTS15	ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9
ADAMTSL1	ADGRA2	ADH1C*	AKT1	AKT2	AKT3	ALDH1A1*	ALK	AMER1	APC	AR	ARAF
ARID1A	ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2	AXL
B2M	BAP1	BARD1	BCL10	BCL2*	BCL2L1	BCL2L2*	BCL6	BCL9	BCOR	BIRC2	BIRC3
BLM	BMPR1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2*	BTB	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*	SLC18A1*
SLC18A1*	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOC1*	SOX2*	SOX9	SPEN	SPOP
SRC	STAG2	STAT3	STK11	SUFU	SYK	SYNE1	TAF1	TAP1	TAP2	TAPBP	TBX3
TEK	TERT	TET1	TET2	TGFBR2	TMSB4X*	TNF	TNFAIP3	TNFRSF14	TNFSF11	TOP1	TP53
TPMT*	TSC1	TSC2	TSHR	TYMS	U2AF1	UBE2A*	UBE2K	UBR5	UGT1A1*	USH2A	VDR*
VEGFA	VEGFB	VHL	WT1	XIAP	XPO1	XRCC2	ZNF217				

*Analysis of copy number alterations NOT available.

FUSION

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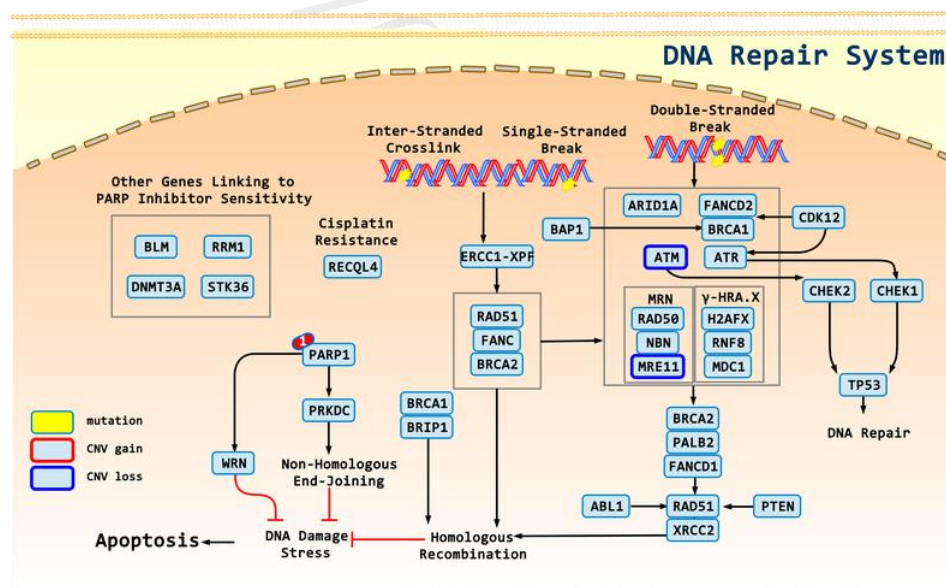
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
ATM	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
KMT2C	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
MRE11	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive

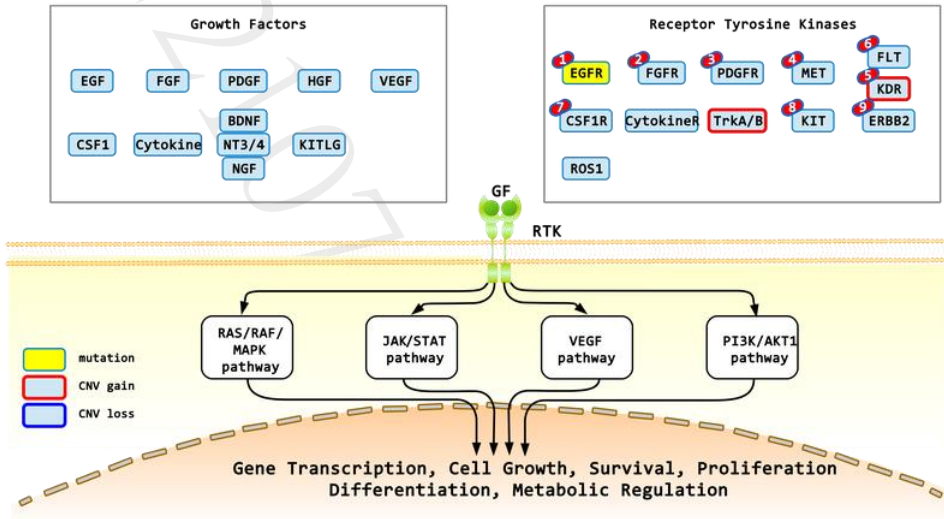
SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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Receptor Tyrosine Kinase/Growth Factor Signalling



1: Gefitinib, Afatinib, Erlotinib, Osimertinib, Dacomitinib; 2: Pazopanib; 3: Regorafenib, Sunitinib, Pazopanib; 4: Cabozantinib; 5: Sunitinib, Pazopanib, Cabozantinib; 6: Sunitinib, Pazopanib; 7: Sunitinib; 8: Sorafenib, Regorafenib, Sunitinib, Pazopanib; 9: Afatinib

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DISCLAIMER

法律聲明

本檢驗報告僅提供專業醫療參考，結果需經專業醫師解釋及判讀。基因突變資訊非必具備藥物或治療有效性指標，反之亦然。本檢驗報告提供之用藥指引不聲明或保證其臨床有效性，反之亦然。本基因檢測方法係由本公司研究開發，已經過有效性測試。

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本公司於提供檢驗報告後，即已完成本次契約義務，後續之報告解釋、判讀及用藥、治療，應自行尋求相關專業醫師協助，若需將報告移件其他醫師，本人應取得該醫師同意並填寫移件申請書，主動告知行動基因，行動基因僅能配合該醫師意願與時間提供醫師解說。

醫療決策需由醫師決定

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

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

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