

ACT Onco[®] + Report

| PATIENT | | |
|--------------------------------|-----------------------|----------------------|
| Identifier: 鄧宗雄 | | Patient ID: 38078498 |
| Date of Birth: Dec 07, 1941 | | Gender: Male |
| Diagnosis: Lung adenocarcinoma | | |
| ORDERING PHYSICIAN | | |
| Name: 陳育民醫師 | | 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: S11220388A | Collection site: Lung | Type: FFPE tissue |
| Date received: May 11, 2023 | Lab ID: AA-23-02969 | 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 L858R | Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib | - | - |

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

| Genomic Alterations/Biomarkers | Possibly Sensitive | | Possibly Resistant |
|--------------------------------|--------------------|--|--------------------------|
| | | | |
| CCNE1 Amplification | - | | Palbociclib, Trastuzumab |
| LYN Amplification | Dasatinib | | - |

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 |
|------|-------------------|------------------|
| EGFR | L858R | 35.7% |

- Copy Number Alterations

| Chromosome | Gene | Variation | Copy Number |
|------------|---------------|-----------------------|-------------|
| Chr11 | CHEK1 | Heterozygous deletion | 1 |
| Chr13 | BRCA2 | Heterozygous deletion | 1 |
| Chr16 | PALB2 | Heterozygous deletion | 1 |
| Chr9 | CDKN2A | Heterozygous deletion | 1 |
| Chr8 | LYN, MYC, NBN | Amplification | 6 |
| Chr19 | CCNE1 | Amplification | 7 |

- 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) | 0.7 muts/Mb |
| Microsatellite Instability (MSI) | Microsatellite stable (MSS) |

Note:

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

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THERAPEUTIC IMPLICATIONS TARGETED THERAPIES

| Genomic Alterations | Therapies | Effect |
|----------------------------|--|------------------|
| Level 1 | | |
| EGFR L858R | Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib | sensitive |
| Level 4 | | |
| LYN Amplification | Dasatinib | sensitive |
| CCNE1 Amplification | Palbociclib, Trastuzumab | 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 |
|----------------------|-------------------------|------------------|-------------------|----------------|
| MYC Amplification | FAC | Sensitive | Clinical | Breast cancer |
| | CMF and P-FEC regimens | | | |
| | Platinum-based regimens | Sensitive | Clinical | Ovarian cancer |

HORMONAL THERAPIES

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

OTHERS

Pharmacogenomic implication

| Gene | Detection Site | Genotype | Drug Impact | Level of Evidence* |
|--------|----------------|----------|---------------------------|--------------------|
| UGT1A1 | rs4148323 | AG | Irinotecan-based regimens | Level 1B |

Clinical Interpretation:

Patients with the AG genotype and cancer who are treated with irinotecan-based regimens may have an increased risk of diarrhea and neutropenia as compared to patients with the GG genotype, or a decreased risk of diarrhea and neutropenia compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk of diarrhea and neutropenia.

* Level of evidence was defined by PharmGKB (<https://www.pharmgkb.org/page/clinAnnLevels>)

Level 1A: Clinical annotations describe variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation.

Level 1B: Clinical annotations describe variant-drug combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label.

Level 2A: Variants in Level 2A clinical annotations are found in PharmGKB's Tier 1 Very Important Pharmacogenes (VIPs). These variants are in known pharmacogenes, implying causation of drug phenotype is more likely.

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 L858R

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 L858R is a missense mutation at position 858, located in exon 21, which encodes part of the kinase domain, from a leucine to an arginine residue^[5]. 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^[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).

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

A phase III trial (NCT01774721) show that dacomitinib significantly improved PFS over gefitinib in first-line treatment of patients with EGFR-mutation-positive NSCLC^[8]. Another phase III trial (NCT00949650) demonstrated that median PFS among lung cancer patients with exon 19 deletion or L858R EGFR mutation (n=308) was 13.6 months for afatinib and 6.9 months for chemotherapy^[9]. 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^[10].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair^[11]. 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^[12]. 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^[13]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers^[14].

Therapeutic and prognostic relevance

Multiple PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have been approved by the U.S. FDA

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for the treatment of cancer. Olaparib is approved for multiple settings in advanced ovarian cancer, metastatic breast cancer with BRCA mutations, metastatic pancreatic cancer, and mCRPC with HRR gene mutations, including BRCA mutations. Rucaparib is approved for maintenance treatment of recurrent ovarian cancer with BRCA mutations and mCRPC with BRCA mutations. Niraparib is approved for maintenance treatment of advanced ovarian cancer and recurrent ovarian cancer with BRCA mutations. Talazoparib is approved for locally advanced or metastatic breast cancer with BRCA mutations.

According to the NCCN guidelines, rucaparib is recommended as recurrence therapy for patients with BRCA-mutated ovarian cancer who have been treated with multiple lines of chemotherapy. It is also recommended as maintenance therapy for patients with metastatic pancreatic cancer who have undergone prior platinum-based therapy and harbor germline or somatic BRCA mutations. Additionally, niraparib is recommended as maintenance therapy for ovarian cancer patients with BRCA mutations.

CCNE1 Amplification

Biological Impact

The CCNE1 gene encodes the cyclin E1 protein, a regulator of the cell cycle that activates the cyclin-dependent protein kinase 2 (CDK2) and plays a role in regulating cells' transition from G1 to S phase and the maintenance of genomic stability^[15]. Increasing in cyclin E1 level, either by gene amplification or overexpression, is found in a diverse range of cancers and can be indicative of poor prognosis^[16].

Therapeutic and prognostic relevance

There are no FDA-approved therapies targeting cyclin E1 currently available^[17]. Dinaciclib, a CDK1/2 specific inhibitor, is currently under clinical evaluation^[18]. A combination of dinaciclib, a small molecule CDK2 inhibitor, and AKT inhibitors that may selectively target patients with CCNE1-amplified high-grade serous ovarian cancer (HGSC) in preclinical setting^[19]. A preclinical study in breast cancer cell lines showed that amplification of CCNE1 is associated with acquired resistance to CDK4/6 inhibition by palbociclib^[20]. A study of HER2-amplified breast cancer patients indicated that amplification of CCNE1 was associated with trastuzumab resistance and shorter progression-free survival^[21].

There are retrospective study and meta-analysis demonstrated that amplification and overexpression of CCNE1 are associated with poor survival in cancer patients^{[22][23]}. From the result of PALOMA-3 phase III trial, pre-treated hormone receptor-positive/HER2-negative metastatic breast cancer patients were resistant to palbociclib treatment when CCNE1 was highly expressed (median PFS: CCNE1 high, 7.6 months; CCNE1 low, 14.1 months)^[24]. CCNE1 amplification has been selected as an inclusion criteria for the trial examining palbociclib in malignant solid tumor (NCT02896335, NCT03155620, NCT01037790, NCT03526250).

CDKN2A Heterozygous deletion

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53^{[25][26][27]}. CDKN2A has been reported as a haploinsufficient tumor suppressor with one copy loss that may lead to weak protein expression and is insufficient to execute its original physiological functions^[28]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation^{[29][30]}.

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors^{[31][32]}. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments^{[33][34][35]}. However, there are clinical studies that demonstrated CDKN2A nuclear expression,

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CDKN2A/CDKN2B co-deletion, or CDKN2A inactivating mutation was not associated with clinical benefit from CDK4/6 inhibitors, such as palbociclib and ribociclib, in RB-positive patients^{[36][37][38]}. CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

The phase II TAPUR trial demonstrated clinical benefits to palbociclib monotherapy in advanced NSCLC or head and neck cancer harboring a CDKN2A mutation or copy number loss. However, pancreatic and biliary cancer patients harboring a CDKN2A mutation or copy number loss did not demonstrate an objective response or stable disease when treated with palbociclib monotherapy for 16 weeks (DOI: 10.1200/JCO.2021.39.15_suppl.6043)^{[39][40]}.

Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for the treatment of ER+ and HER2- breast cancer^{[32][41][42]}.

In a Phase I trial, a KRAS wild-type squamous non-small cell lung cancer (NSCLC) patient with CDKN2A loss had a partial response when treated with CDK4/6 inhibitor abemaciclib^[34]. Administration of combined palbociclib and MEK inhibitor PD-0325901 yield promising progression-free survival among patients with KRAS mutant non-small cell lung cancer (NSCLC) (AACR 2017, Abstract CT046). Moreover, MEK inhibitor in combination with CDK4/6 inhibitor demonstrates significant anti-KRAS-mutant NSCLC activity and radiosensitizing effect in preclinical models^[43].

A retrospective analysis demonstrated that concurrent deletion of CDKN2A with EGFR mutation in patients with non-small cell lung cancer (NSCLC), predicts worse overall survival after EGFR-TKI treatment^[44].

CHEK1 Heterozygous deletion

Biological Impact

The checkpoint kinase 1 (CHEK1 or CHK1) gene encodes a protein kinase involved in transducing DNA damage signals and is required for both the intra-S phase and G2/M checkpoints^[45]. CHEK1 heterozygosity has been shown to cause haploinsufficient phenotypes that can contribute to tumorigenesis through inappropriate S phase entry, accumulation of DNA damage during replication, and failure to restrain mitotic entry^{[46][47]}. Despite acting as a tumor suppressor, homozygous loss-of-function mutations in CHEK1 have not been identified in tumors^[48], and CHEK1 mutations are extremely rare^[45]. Overexpression of CHEK1 has been observed in a variety of tumors, including liver cancer^[49], breast cancer^[50], colorectal cancer^[51], non-small cell lung (NSCLC) cancer^[52], and nasopharyngeal cancer^[53].

Therapeutic and prognostic relevance

Olaparib is FDA-approved for treating mCRPC patients harboring mutations in homologous recombination repair (HRR) genes, including CHEK1.

CHEK1 mutation has been determined as an inclusion criterion for the trials evaluating olaparib, rucaparib, niraparib, and talazoparib efficacies in various types of solid tumors (NCT03297606, NCT01968213, NCT03533946, NCT03553004, NCT03377556).

Selective inhibitors for CHEK1 and CHEK2 alone or in combination with other agents are currently being investigated in clinical trials^[54].

LYN Amplification

Biological Impact

The LYN Proto-Oncogene, Src Family Tyrosine Kinase (LYN) gene encodes a non-receptor tyrosine protein kinase of the Src family (SFK)^[55]. LYN plays an important role in the regulation of immune responses, hematopoiesis, signal

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transduction of growth factors and cytokines and is activated in the cellular response to DNA damage and genotoxic agents^{[56][57][58][59]}. LYN has been described to promote tumor growth, invasion, epithelial to mesenchymal transition (EMT) and ERK signaling in different cancer types^{[60][61][62]}. Amplification of LYN has been identified in prostate cancer, breast cancer and ovarian cancer (cBioPortal).

Therapeutic and prognostic relevance

LYN could be pharmacologically targeted with Src-kinase inhibitors. Results of preclinical studies showed that dasatinib, a dual-specificity tyrosine kinase inhibitor of ABL and the Src-family tyrosine kinases, exerted antitumor activity in LYN-expressing breast cancer cells^[60].

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^{[63][64][65]}. Dysregulated MYC expression is implicated in a wide range of human cancers^[66].

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^{[67][68][69]}.

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^{[70][71]}.

Overexpression of MYC has been reported as a favorable prognostic biomarker in colorectal carcinoma (CRC)^{[72][73]}. However, the favorable prognostic value of MYC in CRC is abrogated by the TP53 mutation^[73].

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^{[70][74]}.

NBN Amplification

Biological Impact

The NBN gene encodes a component of the MRE11-RAD50-NBN (MRN) complex, which involves in DNA double-strand break sensing and repair^[75]. NBN mutation is related to Nijmegen breakage syndrome, increased cancer incidence and ionizing radiation sensitivity^{[75][76]}. NBN mutations have been found in various cancers, including cholangiocarcinoma, hepatocellular carcinoma^[77], prostate cancer^[78], leukemia, lymphoma^[79], and triple-negative breast cancer^[80].

Therapeutic and prognostic relevance

In a phase II trial (ARIEL2), an ovarian cancer patient harboring a NBN germline mutation showed responses to rucaparib treatment^[81]. NBN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer^[82]; the trials evaluating rucaparib efficacy in ovarian cancer^[83] or prostate cancer^[84]; the trials evaluating talazoparib efficacy in HER2-negative breast cancer (NCT02401347), prostate cancer (NCT03148795) or lung cancer (NCT03377556), and the trials evaluating niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate) cancer (NCT03207347).

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Germline and somatic mutations in homologous recombination genes, including NBN, have been suggested to be prognostic biomarkers for platinum-based treatment response and superior survival in patients with ovarian, fallopian tube, peritoneal carcinomas and pancreatic cancer^{[85][86]}.

In a retrospective study of localized prostate cancer, NBN gene amplification has been demonstrated to associate with overall tumor genomic instability and lower biochemical relapse-free rate following image-guided radiotherapy (IGRT)^[87].

Another retrospective study showed that amplification of the NBN gene is associated with protein overexpression and mostly correlated with poor prognosis in several cancer types, including ovarian cancer, breast invasive carcinoma, uterine corpus endometrial carcinoma, and sarcoma. Besides, in vivo and in vitro assays demonstrated that amplification of the NBN gene could induce cisplatin and PARP inhibitor resistance in breast and ovarian cancer cells^[88].

PALB2 Heterozygous deletion

Biological Impact

The partner and localizer of BRCA2 (PALB2) gene encodes a protein that plays a critical role in homologous recombination repair (HRR) through its ability to interact with BRCA2 in nuclear foci, promoting its localization and stability in key nuclear structures^[89]. The Fanconi anemia complementation group (FANC) which includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM and FANCN (also called PALB2) are involved in the repair of DNA double-strand breaks (DSBs) by homologous recombination (HR)^{[90][91][92]}. PALB2 is a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological function^[93]. Biallelic germline loss-of-function mutations in PALB2 cause Fanconi anemia, whereas monoallelic loss-of-function mutations are associated with an increased risk of breast cancer and pancreatic cancer^[94]. Fanconi Anemia is an autosomal recessive disease characterized by hematological abnormalities, bone marrow failure, limb deformities, skin hyperpigmentation, and susceptibility to hematologic and solid malignancies, such as acute myeloid leukemia and head and neck carcinoma^{[95][96]}.

Therapeutic and prognostic relevance

Olaparib is FDA-approved for treating mCRPC patients harboring mutations in homologous recombination repair (HRR) genes, including PALB2.

The NCCN guidelines recommend rucaparib as maintenance therapy for pancreatic adenocarcinoma patients with PALB2 mutations after platinum-based therapy. For breast cancer patients with stage IV disease and germline PALB2 alterations, olaparib treatment is recommended by the NCCN guidelines regardless of subtype.

PALB2 mutation has been determined as an inclusion criterion for the trials evaluating rucaparib, niraparib, and talazoparib efficacies in various types of solid tumors (NCT02401347, NCT03553004, NCT02952534)^{[83][84]}.

A case report demonstrated an exceptional response to mitomycin C and cisplatin treatment in a gemcitabine-resistant pancreatic cancer patient with biallelic inactivation of PALB2^[97].

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US FDA-APPROVED DRUG(S)

Abemaciclib (VERZENIO)

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

- FDA Approval Summary of Abemaciclib (VERZENIO)

| | |
|--|---|
| MONARCH E NCT03155997 | Breast cancer (Approved on 2021/10/12) |
| | HR+/HER2- Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0] |
| MONARCH 3^[98] NCT02246621 | Breast cancer (Approved on 2018/02/26) |
| | HR+/HER2- Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8] |
| MONARCH 2^[42] NCT02107703 | Breast cancer (Approved on 2017/09/28) |
| | HR+/HER2- Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3] |
| MONARCH 1^[99] NCT02102490 | Breast cancer (Approved on 2017/09/28) |
| | HR+/HER2- Abemaciclib [ORR(%): 19.7 vs. 17.4] |

Afatinib (GILOTRIF)

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

- FDA Approval Summary of Afatinib (GILOTRIF)

| | |
|--|--|
| LUX-Lung 8^[100] 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^[101] 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] |

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^[8] 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] |

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Dasatinib (SPRYCEL)

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

- FDA Approval Summary of Dasatinib (SPRYCEL)

| | |
|--|---|
| DASISION ^[102] NCT00481247 | Chronic myeloid leukemia (Approved on 2010/10/28) |
| | - |
| | Dasatinib vs. Imatinib [ORR(%): 76.8 vs. 66.2] |
| [103] NCT00123474 | Chronic myeloid leukemia (Approved on 2007/11/08) |
| | - |
| | Dasatinib [ORR(%): 63.0] |
| [104] NCT00123487 | Acute lymphocytic leukemia (Approved on 2006/06/28) |
| | - |
| | Dasatinib [ORR(%): 38.0] |

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 ^[105] 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 ^[106] 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 ^[107] 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) |
| | - |
| NOVA^[108] NCT01847274 | Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/03/27) |
| | - |
| | Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2] |
| | 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 |
| PROfound^[109] NCT02987543 | Prostate cancer (Approved on 2020/05/19) |
| | HRR genes mutation |
| PAOLA-1^[110] NCT02477644 | Ovarian cancer (Approved on 2020/05/08) |
| | HRD+ |
| POLO^[111] NCT02184195 | Pancreatic adenocarcinoma (Approved on 2019/12/27) |
| | gBRCA mutation |
| SOLO-1^[112] NCT01844986 | Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2018/12/19) |
| | gBRCA mutation or sBRCA mutation |
| OlympiAD^[113] NCT02000622 | Breast cancer (Approved on 2018/02/06) |
| | HER2-/gBRCA mutation |
| SOLO-2/ENGOT-Ov21^[114] NCT01874353 | Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17) |
| | gBRCA mutation |
| Study19^[115] 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^[10] 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^[116] NCT02151981 | Non-small cell lung carcinoma (Approved on 2017/03/30) |
| | EGFR T790M |
| | Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4] |
| AURA^[117] NCT01802632 | Non-small cell lung carcinoma (Approved on 2015/11/13) |
| | EGFR T790M |
| | Osimertinib [ORR(%): 59.0] |

Palbociclib (IBRANCE)

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

- FDA Approval Summary of Palbociclib (IBRANCE)

| | |
|--|---|
| PALOMA-2^[118] NCT01740427 | Breast cancer (Approved on 2017/03/31) |
| | ER+/HER2- |
| | Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5] |
| PALOMA-3^[119] NCT01942135 | Breast cancer (Approved on 2016/02/19) |
| | ER+/HER2- |
| | Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6] |

Ribociclib (KISQALI)

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

- FDA Approval Summary of Ribociclib (KISQALI)

| | |
|--|--|
| MONALEESA-2^[41] NCT01958021 | Breast cancer (Approved on 2017/03/13) |
| | HR+/HER2- |
| | Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7] |

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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] |

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 ^[120] 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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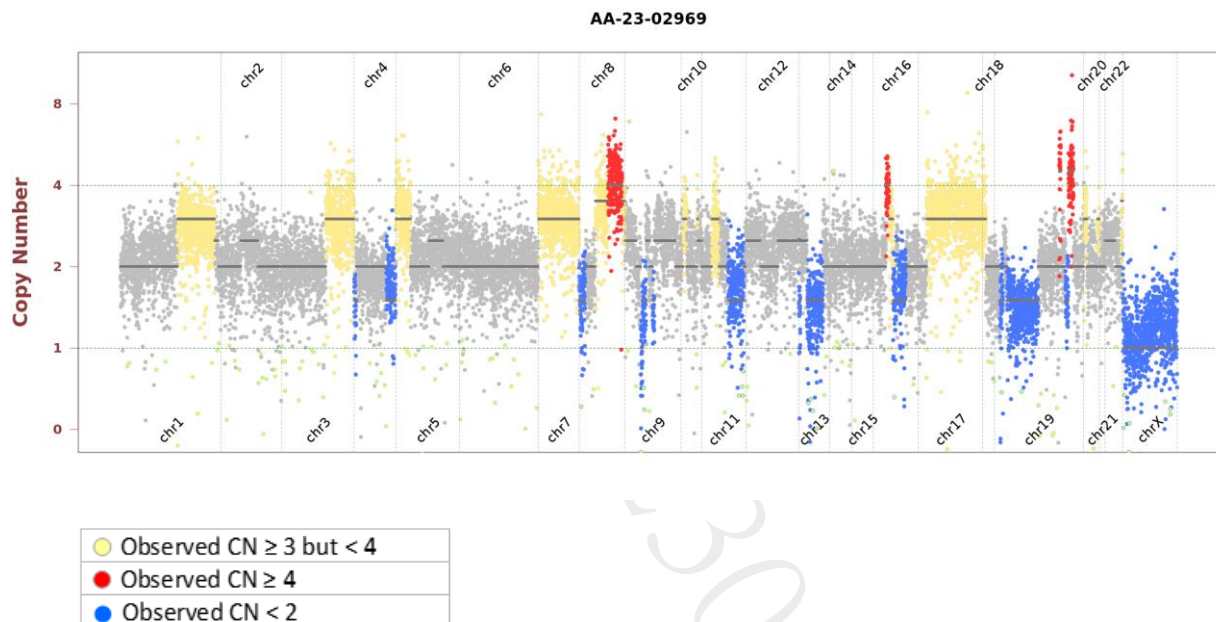
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

| Gene | Amino Acid Change | Exon | cDNA Change | Accession Number | COSMIC ID | Allele Frequency | Coverage |
|------|-------------------|------|-------------|------------------|-----------|------------------|----------|
| EGFR | L858R | 21 | c.2573T>G | NM_005228 | COSM6224 | 35.7% | 2438 |

- 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 |
|---------|-------------------|------|-------------|------------------|-------------|------------------|----------|
| ADAMTS9 | L1225V | 25 | c.3673C>G | NM_182920 | - | 52.7% | 664 |
| ADGRA2 | Splice region | - | c.1833+7G>A | NM_032777 | - | 76.8% | 125 |
| ADGRA2 | L474W | 10 | c.1421T>G | NM_032777 | - | 75.6% | 271 |
| CD19 | G149R | 3 | c.445G>A | NM_001178098 | - | 73.9% | 310 |
| MPL | S615F | 12 | c.1844C>T | NM_005373 | - | 44.8% | 737 |
| NFE2L2 | M235V | 5 | c.703A>G | NM_006164 | - | 58.8% | 981 |
| POLE | E1213Q | 30 | c.3637G>C | NM_006231 | COSM6917463 | 8.0% | 761 |
| SETD2 | P193L | 3 | c.578C>T | NM_014159 | - | 51.0% | 734 |
| SMARCA4 | Splice region | - | c.1812+6G>A | NM_001128844 | - | 23.7% | 447 |
| TET1 | L311F | 2 | c.931C>T | NM_030625 | - | 56.6% | 860 |

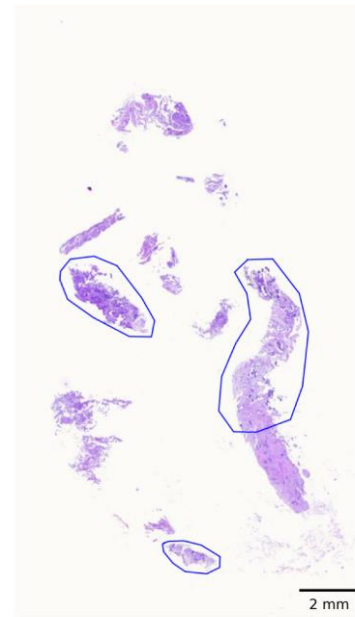
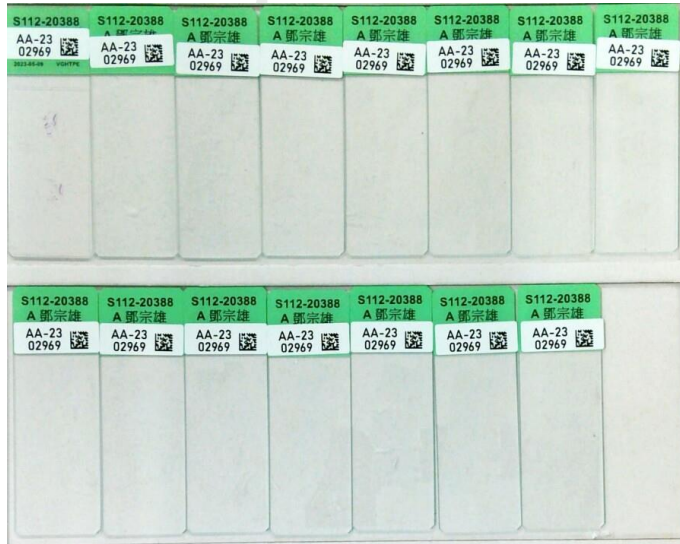
Note:

- 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: May 05, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11220388A
- Collection site: Lung
- Examined by: Dr. Yun-An Chen
- 1. The percentage of viable tumor cells in total cells in the whole slide (%): 15%
- 2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 40%
- 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: 750x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 108

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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:

解剖病理專科醫師朱盈霞
Ying-Hsia Chu, M.D.
病解字第 000653 號



Sign Off

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



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GENE LIST SNV & CNV

| | | | | | | | | | | | |
|----------|---------|---------|----------|----------|---------|-----------|-----------|----------|----------|----------|----------|
| ABCB1* | ABCC2* | ABCG2* | ABL1 | ABL2 | ADAMTS1 | ADAMTS13 | ADAMTS15 | ADAMTS16 | ADAMTS18 | ADAMTS6 | ADAMTS9 |
| ADAMTSL1 | ADGRA2 | ADH1C* | AKT1 | AKT2 | AKT3 | ALDH1A1* | ALK | AMER1 | APC | AR | ARAF |
| ARID1A | ARID1B | ARID2 | ASXL1 | ATM | ATR | ATRX | AURKA | AURKB | AXIN1 | AXIN2 | AXL |
| B2M | BAP1 | BARD1 | BCL10 | BCL2* | BCL2L1 | BCL2L2* | BCL6 | BCL9 | BCOR | BIRC2 | BIRC3 |
| BLM | BMPR1A | BRAF | BRCA1 | BRCA2 | BRD4 | BRIP1 | BTG1 | BTG2* | BTX | 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 | IKBK | IKBE | 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* | SLC01B1* |
| SLC01B3* | 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 |
|-----|------|------|-------|-------|-------|-----|------|-------|-------|-------|-----|------|

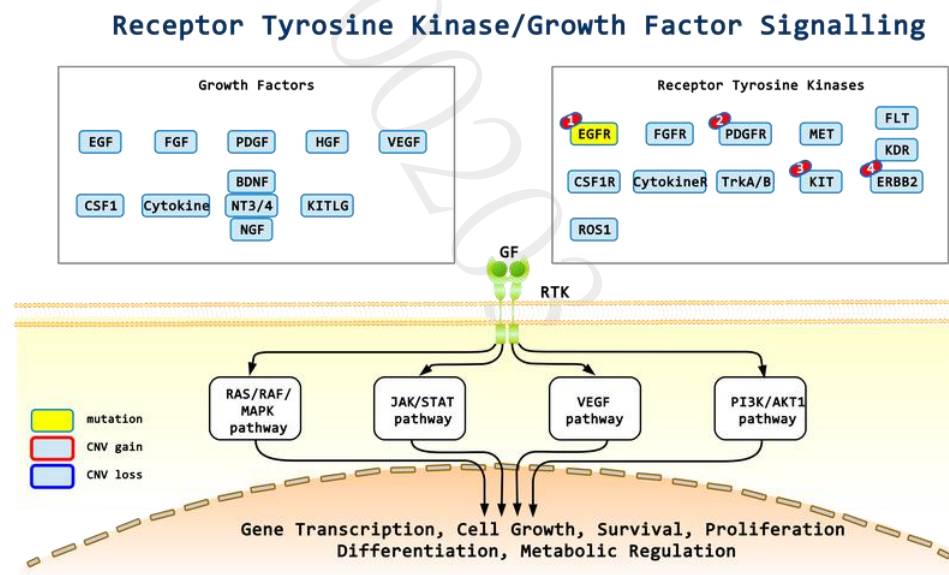
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

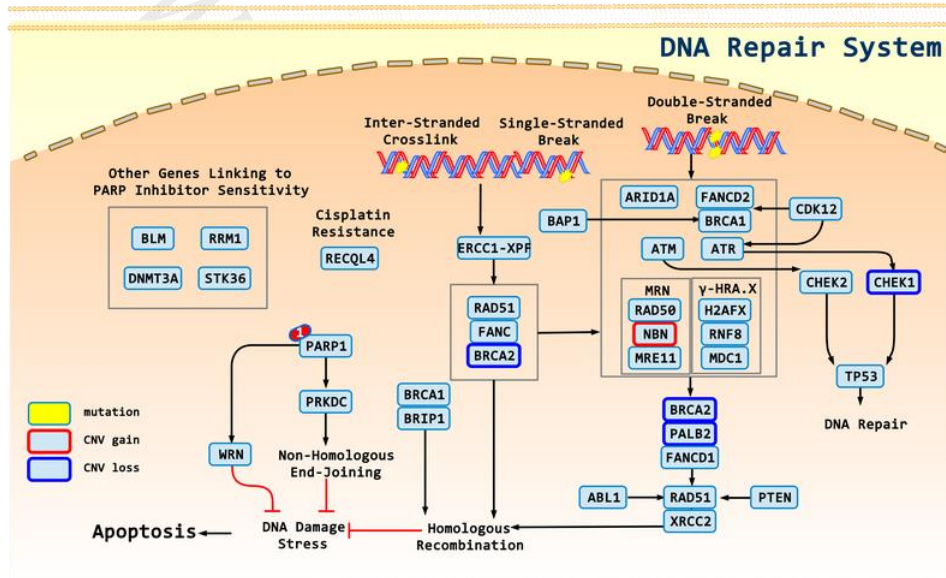
| Gene | Therapies | Possible effect |
|---------------|---|------------------|
| <i>CDKN2A</i> | Abemaciclib, Palbociclib, Ribociclib | sensitive |
| <i>BRCA2</i> | Niraparib, Olaparib, Rucaparib, Talazoparib | sensitive |
| <i>CHEK1</i> | Niraparib, Olaparib, Rucaparib, Talazoparib | sensitive |
| <i>PALB2</i> | Niraparib, Olaparib, Rucaparib, Talazoparib | sensitive |

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

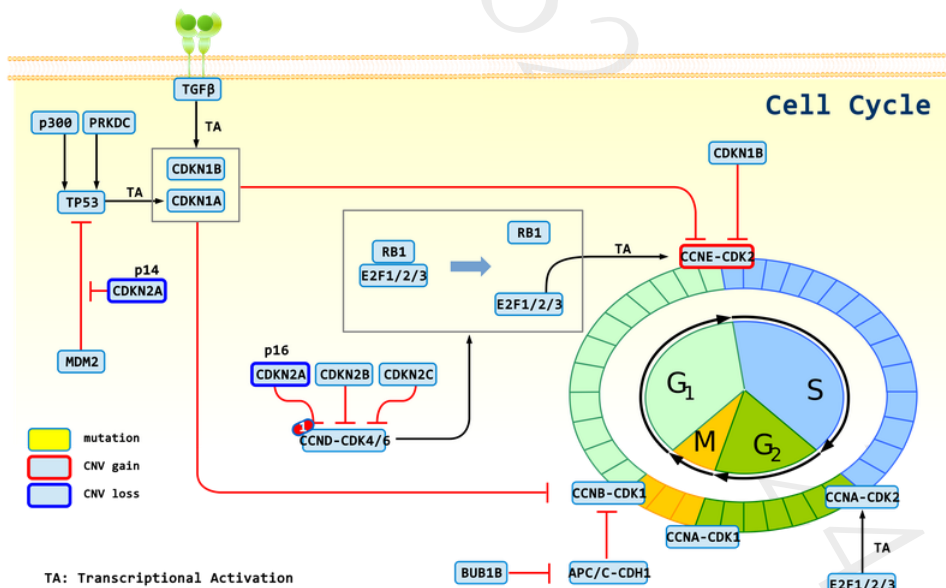


1: Gefitinib, Afatinib, Erlotinib, Osimertinib, Dacomitinib; 2: Dasatinib; 3: Dasatinib; 4: Afatinib

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1: Olaparib, Niraparib, Rucaparib, Talazoparib



1: Abemaciclib, Palbociclib, Ribociclib

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DISCLAIMER

法律聲明

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

本檢驗報告非經本公司許可，不得私自變造、塗改，或以任何方式作為廣告及其他宣傳之用途。

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

醫療決策需由醫師決定

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

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

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