

ACT Onco[®] + Report

PATIENT		
Identifier: 郭淑美		Patient ID: 48433303
Date of Birth: Jul 15, 1967		Gender: Female
Diagnosis: Lung adenocarcinoma		
ORDERING PHYSICIAN		
Name: 陳育民醫師		Tel: 886-228712121
Facility: 臺北榮總		
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SPECIMEN		
Specimen ID: S11115872D	Collection site: Lung	Type: FFPE tissue
Date received: Apr 26, 2023	Lab ID: AA-23-02475	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
EGFR L833V	Afatinib, Erlotinib, Osimertinib, Cetuximab	Gefitinib
EGFR Amplification	Afatinib, Erlotinib, Gefitinib, Osimertinib, Necitumumab, Cetuximab, Panitumumab	-

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>	L858R	70.6%
<i>EGFR</i>	L833V	69.2%
<i>TP53</i>	R248W	64.2%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr16	<i>PALB2</i>	Heterozygous deletion	1
Chr18	<i>SMAD4</i>	Heterozygous deletion	1
Chr19	<i>ERCC1</i>	Heterozygous deletion	1
Chr7	<i>EGFR</i>	Amplification	8

- 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:

- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 47% 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 3B		
EGFR Amplification	Afatinib, Erlotinib, Gefitinib, Osimertinib, Necitumumab, Cetuximab, Panitumumab	sensitive
Level 4		
EGFR L833V	Afatinib, Erlotinib, Osimertinib, Cetuximab	sensitive
EGFR L833V	Gefitinib	resistant

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

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

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

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

- Other Biomarkers with Potential Clinical Effects for ICIs

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

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

CHEMOTHERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
TP53 R248W	Platinum- and taxane-based regimens	Less sensitive	Clinical	Ovarian cancer

HORMONAL THERAPIES

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

OTHERS

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

Note:

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

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VARIANT INTERPRETATION

EGFR L833V, L858R, Amplification

Biological Impact

The EGFR gene encodes for the Epidermal Growth Factor Receptor, a receptor tyrosine kinase which binds to its ligands, including Epidermal Growth Factor (EGF) and Transforming Growth Factor-alpha (TGF-alpha), activates downstream signaling pathways, including the canonical oncogenic MAPK and PI3K/AKT/mTOR signaling cascades^[1]. Increased EGFR activity by mutations and/or amplification of the EGFR gene has been described in a wide range of cancers, such as lung, brain, colorectal and head and neck cancer^[2]. Mutations in the kinase domain of EGFR are commonly observed in non-small cell lung cancer (NSCLC), resulting in a constitutively activated form of the receptor^[3]. On the other hand, in the brain and colorectal cancers, the most prevalent EGFR alteration is copy number amplification that results in receptor overexpression^[4].

EGFR L833V is located within the kinase domain of the EGFR protein, specifically within exon 21 and is known as an activating/oncogenic mutation as demonstrated by colony formation in vitro^[5]. This mutation has been detected in combination with EGFR H835L or G719S in several lung adenocarcinoma patients of Asian descent^{[6][7][8][9][10]}.

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^[11]. 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^[12].

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^[13] (Annals of Oncology (2017) 28 (suppl_5): v403-v427. 10.1093/annonc/mdx376).

The cell-based assay revealed that compared with L858R or the exon 19 deletion, exon 21 mutations like L833V was insensitive to gefitinib, but displayed sensitivity to cetuximab, erlotinib, afatinib, and osimertinib^[5]. However, case studies demonstrated that NSCLC patients with in cis EGFR L833V/H835L mutations responded to gefitinib^{[8][10][14]}. A patient with NSCLC harboring L833V/H835L showed a partial response to afatinib and the PFS was over 10 months^[15]. Another patient with advanced NSCLC harboring L833V/H835F was responding to osimertinib for 9 months (DOI: 10.36000/hbT.OH.2020.03.011). Furthermore, a NSCLC patient with L858R/L833V mutation also showed stable disease for 5 months after treated with first generation EGFR TKI^[16]. Of note, there are case reports showing that patients with EGFR E709K/L833V/H835L or R670W/L833V/H835L triple mutations responded to afatinib treatment^{[17][18]}.

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^[19]. 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^[20]. 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^[21].

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Increased EGFR copy number is associated with tumor response to panitumumab, an EGFR-targeted antibody, in colorectal cancer patients, based on data from a phase III study^[22]. A recent Phase II trial of cetuximab (another approved anti-EGFR antibody) oxaliplatin/leucovorin/5-fluorouracil therapy in first-line setting also demonstrated an association between higher EGFR copy number and better overall survival in gastric cancer patients^[23]. The addition of cetuximab to chemotherapy reduced the risk of death by 44% for advanced squamous non-small cell lung cancer (NSCLC) patients with EGFR-amplified tumor, according to clinical trial findings presented at the 2015 World Conference on Lung Cancer. Preclinical data of gastric cancer (GC)-derived xenograft also showed that EGFR amplification or overexpression is associated with response to cetuximab^[24]. Besides, a phase III study of necitumumab showed squamous cell lung cancer patients with EGFR amplification had improved overall survival (14.8 versus 7.6 months, $p = 0.033$) (NCT00981058)^[25].

Increased EGFR copy number has been shown to be associated with better response and survival in gefitinib or erlotinib treatment for NSCLC^{[26][27][28][29][30][31]}, esophageal cancer^[32], and mucinous urethral adenocarcinoma^[33]. Concurrent amplification of EGFR and ERBB2 is associated with response to afatinib in patients with trastuzumab-refractory esophagogastric cancer^[34]. However, dacomitinib has been reported with a limited single-agent activity in recurrent glioblastoma with EGFR amplification in a phase II trial^[35]. EGFR amplification has been determined as an inclusion criterion for the trials evaluating erlotinib, afatinib, and osimertinib efficacy in PDAC with co-expressing EGFR and c-Met (NCT03213626), glioblastoma (NCT03732352), urothelial tract carcinoma (NCT02780687), and brain cancer (NCT02423525).

TP53 R248W

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[36]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[37].

R248W is a missense mutation located in the DNA-binding domain (DBD) of the p53 protein^[38]. This mutation results in abrogation of the p53 tumor suppressor activity and a gain-of-function in ATM inactivation, resulting in increased genetic instability and increased tumorigenesis in mouse models^[39].

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)^[40].

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^[41]. 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^[42].

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^{[43][44][45]}. 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)^[46]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[47][48]}. 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^[49].

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TP53 oncomorphic mutations, including P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L, and R282W have been shown to predict resistance to platinum- and taxane-based chemotherapy in advanced serous ovarian carcinoma patients^[50].

ERCC1 Heterozygous deletion

Biological Impact

The Excision Repair Cross-Complementation Group 1 (ERCC1) gene encodes a non-catalytic component of a structure-specific DNA repair endonuclease that is responsible for 5' incision. This endonuclease is a heterodimer containing ERCC1 and ERCC4 and is involved in recombinational DNA repair and in the repair of inter-strand crosslinks (ICL). In addition, ERCC1 participates in the processing of anaphase bridge-generating DNA structures. Other genes associated with the nucleotide excision repair pathway includes ERCC1-5, CDK7, DDB1-2, XPA, and XPC^[51]. ERCC1 haploinsufficiency is associated with tumorigenesis in the mouse model^[52].

Therapeutic and prognostic relevance

Loss of expression of ERCC1 has long been implicated in increased sensitivity towards cisplatin in non-small cell lung cancer (NSCLC) and ovarian carcinoma^{[53][54][55][56]}. PARP inhibitors demonstrated anti-tumor activity against ERCC1-deficient non-small cell lung cancer (NSCLC) cell line^{[57][58][59]}. Preclinical studies also showed that inhibiting topoisomerase I and PARP1 in combination, as was demonstrated with the combination of ABT-888 and CPT-11, may result in the synergistic decrease in tumor regression for women with triple-negative breast cancer (TNBC)^[60].

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^[61]. 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)^{[62][63][64]}. 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^[65]. 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^[66]. 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^{[67][68]}.

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)^{[69][70]}.

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^[71].

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SMAD4 Heterozygous deletion

Biological Impact

The SMAD family member 4 (SMAD4) gene encodes a transcription factor that acts as a downstream effector in the TGF- β signaling pathway. Upon phosphorylated and activated by serine-threonine receptor kinase, Smad4 is the Co-Smad which recruits other activated R-Smad proteins to the Smad transcriptional complex and regulate TGF- β -targeted genes^[72]. Smad4 has been identified as a haploinsufficient gene with one copy loss may lead to a weak protein expression and is insufficient to execute its original physiological function^[73]. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)^{[74][75][76][77]}. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer^[78], colorectal cancer (CRC)^{[76][79][80]}, and less frequently seen in other cancers such as lung adenocarcinoma^[81], head and neck cancer^{[82][83]}, and cutaneous squamous cell carcinoma^[84].

Therapeutic and prognostic relevance

In Chinese patients with metastatic colorectal cancer, SMAD4 or NF1 mutations are suggested as a potential biomarker for poor prognosis to cetuximab-based therapy^[85]. Preclinical data demonstrated that depletion of SMAD4 by shRNA knockdown increased clonogenic survival and cetuximab resistance in HPV-negative head and neck squamous cell carcinoma cells^[86].

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)^{[87][88]}. CRC patients with normal SMAD4 diploidy exhibited three-fold higher benefit of 5-FU/mitomycin-based adjuvant therapy when compared with those with SMAD4 deletion^[89].

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis^{[90][91][92][93][94][95][96][97]}. In cervical cancer patients, weak cytoplasmic SMAD4 expression and absent nuclear SMAD4 expression were shown to be significantly associated with poor disease-free and overall 5-year survival^[98].

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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 ^[99] 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 ^[100] 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]

Cetuximab (ERBITUX)

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

- FDA Approval Summary of Cetuximab (ERBITUX)

BEACON CRC ^[101] NCT02928224	Colorectal cancer (Approved on 2020/04/08)
	BRAF V600E
	Encorafenib in combination with cetuximab vs. Irinotecan or folfox with cetuximab [OS(M): 8.4 vs. 5.4]
CRYSTAL ^[102] NCT00154102	Colorectal cancer (Approved on 2012/07/06)
	KRAS Wild-type/EGFR-expressing
	Cetuximab + 5-fluorouracil + folinic acid + irinotecan vs. 5-fluorouracil + folinic acid + irinotecan [PFS(M): 8.9 vs. 8.1]
EXTREME ^[103] NCT00122460	Head and neck cancer (Approved on 2011/11/07)
	-
	Cetuximab + cisplatin/carboplatin + 5-fu vs. Cisplatin/carboplatin + 5-fu [OS(M): 10.1 vs. 7.4]
^[104] NCT00004227	Head and neck cancer (Approved on 2006/03/01)
	-
	Cetuximab + radiation vs. Radiation [OS(M): 49 vs. 29.3]
^[105] NCT00063141	Colorectal cancer (Approved on 2004/02/12)
	KRAS Wild-type/EGFR-expressing
	Cetuximab + irinotecan vs. Irinotecan [DOR(M): 5.7 vs. 4.2]

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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 ^[19] 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 ^[106] 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 ^[107] 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 ^[108] NCT01203917	Non-small cell lung carcinoma (Approved on 2015/07/13)
	EGFR ex19del or L858R
	Gefitinib [ORR(%): 50.0]

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Necitumumab (PORTRAZZA)

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

- FDA Approval Summary of Necitumumab (PORTRAZZA)

SQUIRE ^[109] NCT00981058	Lung squamous cell carcinoma (Approved on 2015/11/14)
	-
	Gemcitabine + cisplatin vs. Placebo [OS(M): 11.5 vs. 9.9]

Niraparib (ZEJULA)

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

- FDA Approval Summary of Niraparib (ZEJULA)

PRIMA NCT02655016	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2020/04/29)
	-
	Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
NOVA ^[110] 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 ^[111] 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 ^[112] NCT02477644	Ovarian cancer (Approved on 2020/05/08)
	HRD+
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO ^[113] 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 ^[114] 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]

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OlympiAD ^[115] NCT02000622	Breast cancer (Approved on 2018/02/06)
	HER2-/gBRCA mutation
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21 ^[116] 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 ^[117] NCT00753545	Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

Osimertinib (TAGRISSO)

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

- FDA Approval Summary of Osimertinib (TAGRISSO)

ADAURA NCT02511106	Non-small cell lung carcinoma (Approved on 2020/12/18)
	EGFR ex19del or L858R
	Osimertinib vs. Placebo + adjuvant chemotherapy [DFS(M): NR vs. 19.6]
FLAURA ^[21] 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 ^[118] NCT02151981	Non-small cell lung carcinoma (Approved on 2017/03/30)
	EGFR T790M
	Osimertinib vs. Chemotherapy [PFS(M): 10.1 vs. 4.4]
AURA ^[119] NCT01802632	Non-small cell lung carcinoma (Approved on 2015/11/13)
	EGFR T790M
	Osimertinib [ORR(%): 59.0]

Panitumumab (VECTIBIX)

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

- FDA Approval Summary of Panitumumab (VECTIBIX)

Study 20050203 ^[120] NCT01412957	Colorectal cancer (Approved on 2017/06/29)
	KRAS Wild-type
	Panitumumab + bsc vs. Bsc [OS(M): 10 vs. 6.9]
PRIME ^[121] NCT00364013	Colorectal cancer (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab + folfox vs. Folfox [PFS(M): 9.6 vs. 8]
ASPECCT ^[122] NCT01001377	Colorectal cancer (Approved on 2014/05/23)
	KRAS Wild-type
	Panitumumab vs. Cetuximab [OS(M): 10.4 vs. 10]

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Study 20080763 ^[123] NCT00113763	Colorectal cancer (Approved on 2006/09/27)
	KRAS Wild-type
	Panitumumab + bsc vs. Bsc [PFS(M): 3.2 vs. 2]

Rucaparib (RUBRACA)

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

- FDA Approval Summary of Rucaparib (RUBRACA)

TRITON2 NCT02952534	Prostate cancer (Approved on 2020/05/15)
	gBRCA mutation or sBRCA mutation
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3 ^[69] 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 ^[124] 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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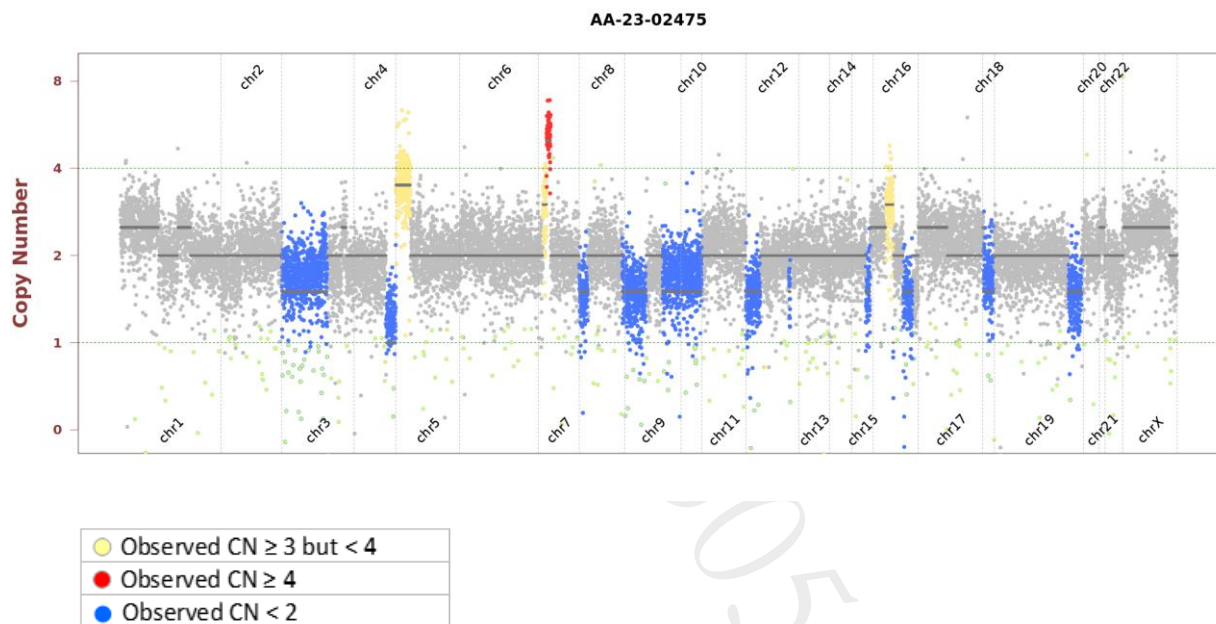
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
EGFR	L833V	21	c.2497T>G	NM_005228	COSM13424	69.2%	3995
EGFR	L858R	21	c.2573T>G	NM_005228	COSM6224	70.6%	3979
TP53	R248W	7	c.742C>T	NM_000546	COSM10656	64.2%	2393

- 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
ADAMTSL1	R331H	9	c.992G>A	NM_001040272	-	32.0%	1270
APC	T562M	14	c.1685C>T	NM_000038	COSM6602026	25.4%	338
ATM	T1504A	30	c.4510A>G	NM_000051	-	43.2%	1334
AXIN2	G429S	6	c.1285G>A	NM_004655	-	42.3%	1124
CALR	I147V	4	c.439A>G	NM_004343	-	44.7%	830
DDR2	E586Q	14	c.1756G>C	NM_006182	-	21.4%	1481
FANCD2	N791S	25	c.2372A>G	NM_001018115	COSM9118330	58.0%	609
GATA1	A120V	3	c.359C>T	NM_002049	COSM1122170	52.0%	2530
IKZF1	M476I	8	c.1428G>T	NM_006060	-	6.7%	1472
MSH6	K567N	4	c.1701G>C	NM_000179	-	75.7%	1046
MTOR	F1148S	23	c.3443T>C	NM_004958	-	45.7%	2098
POLD1	Splice region	-	c.3218+5G>A	NM_001256849	-	63.8%	472
RUNX1	R244K	5	c.731G>A	NM_001001890	-	53.1%	1224

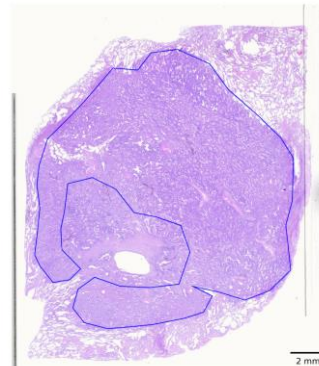
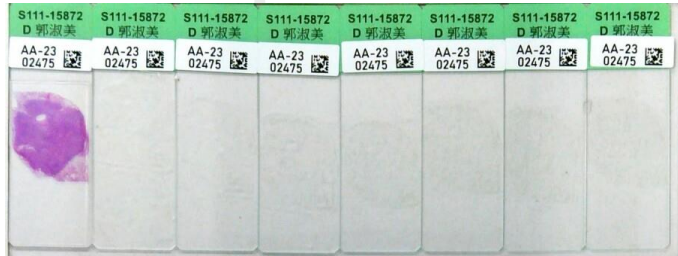
Note:

- 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: Apr 18, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11115872D
- Collection site: Lung
- Examined by: Dr. Yun-An Chen
 1. The percentage of viable tumor cells in total cells in the whole slide (%): 20%
 2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 35%
 3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
 4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
 5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco[®]+

DNA test

- Mean Depth: 984x
- Target Base Coverage at 100x: 95%

RNA test

- Average unique RNA Start Sites per control GSP2: 48

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.

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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 .

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.

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DATABASE USED

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

Variant Analysis:

醫檢師陳韻鈺 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

Sign Off

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

Yeh

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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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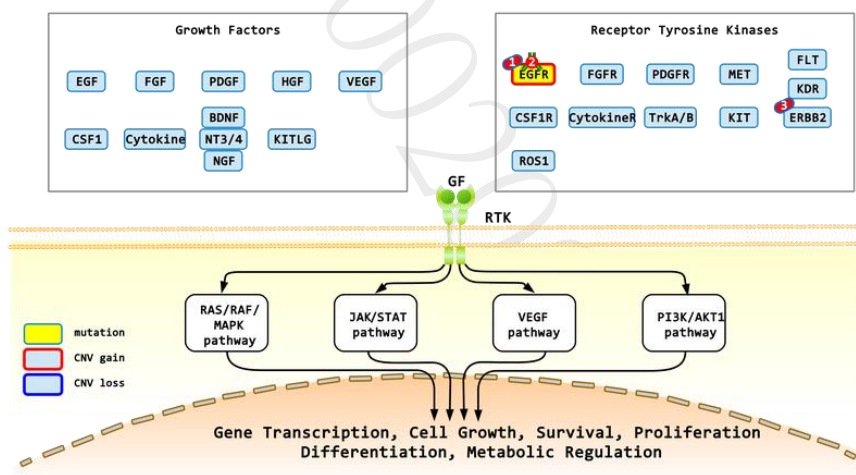
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

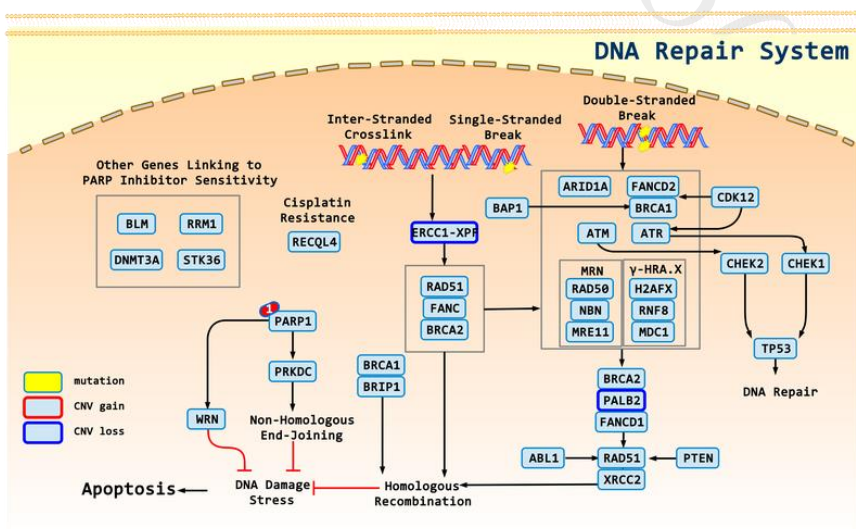
Gene	Therapies	Possible effect
<i>ERCC1</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<i>PALB2</i>	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
<i>SMAD4</i>	Cetuximab	resistant

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS

Receptor Tyrosine Kinase/Growth Factor Signalling



1: Afatinib, Osimertinib, Gefitinib, Erlotinib, Dacomitinib; 2: Cetuximab, Panitumumab, Necitumumab; 3: Afatinib



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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DISCLAIMER

法律聲明

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

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

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

醫療決策需由醫師決定

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

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

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

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REFERENCE

1. PMID: 18045542; 2007, Cell;131(5):1018
SnapShot: EGFR signaling pathway.
2. PMID: 10880430; 2000, EMBO J;19(13):3159-67
The ErbB signaling network: receptor heterodimerization in development and cancer.
3. PMID: 15329413; 2004, Proc Natl Acad Sci U S A;101(36):13306-11
EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib.
4. PMID: 11426640; 2000, Oncogene;19(56):6550-65
The EGF receptor family as targets for cancer therapy.
5. PMID: 29141884; 2017, Sci Transl Med;9(416):
A method of high-throughput functional evaluation of EGFR gene variants of unknown significance in cancer.
6. PMID: 15623594; 2004, Clin Cancer Res;10(24):8195-203
High frequency of epidermal growth factor receptor mutations with complex patterns in non-small cell lung cancers related to gefitinib responsiveness in Taiwan.
7. PMID: 17236554; 2006, Zhonghua Zhong Liu Za Zhi;28(8):599-602
[Epithelial growth factor receptor (EGFR) exon double-sequencing analysis in NSCIC].
8. PMID: 21422421; 2011, J Clin Oncol;29(16):e468-9
Good response to gefitinib in a lung adenocarcinoma harboring a heterozygous complex mutation of L833V and H835L in epidermal growth factor receptor gene.
9. PMID: 23313172; 2013, Clin Lung Cancer;14(3):295-300
A sequential method of epidermal growth factor receptor mutation detection reduces false negatives: a new case with doublet mutations of L833V and H835L in China.
10. PMID: 29780256; 2018, Onco Targets Ther;11():2637-2646
The utilization of next-generation sequencing to detect somatic mutations and predict clinical prognosis of Chinese non-small cell lung cancer patients.
11. PMID: 17318210; 2007, Nat Rev Cancer;7(3):169-81
Epidermal growth factor receptor mutations in lung cancer.
12. PMID: 22263017; 2010, J Thorac Dis;2(1):48-51
Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update.
13. PMID: 28351930; 2017, Clin Cancer Res;23(15):4242-4250
Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate.
14. PMID: 30990107; 2019, Cancer Biol Ther;20(8):1097-1104
The in cis compound EGFR mutations in Chinese advanced non-small cell lung cancer patients.
15. PMID: 33116645; 2020, Onco Targets Ther;13():10689-10692
Great Efficacy of Afatinib in a Patient with Lung Adenocarcinoma Harboring EGFR L833V/H835L Mutations: A Case Report.
16. PMID: 30055651; 2018, Cancer Commun (Lond);38(1):51
First-generation EGFR tyrosine kinase inhibitor therapy in 106 patients with compound EGFR-mutated lung cancer: a single institution's clinical practice experience.
17. PMID: 27131295; 2016, J Thorac Oncol;11(5):e63-e64
A Triple Rare E709K and L833V/H835L EGFR Mutation Responsive to an Irreversible Pan-HER Inhibitor: A Case Report of Lung Adenocarcinoma Treated with Afatinib.

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18. PMID: 30127622; 2018, Onco Targets Ther;11():4739-4745
The effectiveness of afatinib and osimertinib in a Chinese patient with advanced lung adenocarcinoma harboring a rare triple EGFR mutation (R670W/H835L/L833V): a case report and literature review.
19. PMID: 28958502; 2017, Lancet Oncol;18(11):1454-1466
Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial.
20. PMID: 29653820; 2018, Clin Lung Cancer;19(4):e465-e479
Afatinib as First-line Treatment of Older Patients With EGFR Mutation-Positive Non-Small-Cell Lung Cancer: Subgroup Analyses of the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 Trials.
21. PMID: 29151359; 2018, N Engl J Med;378(2):113-125
Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer.
22. PMID: 17664472; 2007, J Clin Oncol;25(22):3238-45
Epidermal growth factor receptor gene copy number and clinical outcome of metastatic colorectal cancer treated with panitumumab.
23. PMID: 22152101; 2011, BMC Cancer;11():509
Biomarker analysis of cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric and oesophago-gastric junction cancer: results from a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO).
24. PMID: 24141978; 2013, Sci Rep;3():2992
A subset of gastric cancers with EGFR amplification and overexpression respond to cetuximab therapy.
25. PMID: 29158193; 2018, J Thorac Oncol;13(2):228-236
EGFR Gene Copy Number by FISH May Predict Outcome of Necitumumab in Squamous Lung Carcinomas: Analysis from the SQUIRE Study.
26. PMID: 19102716; 2009, Pharmacogenomics;10(1):59-68
EGFR-targeted therapies in lung cancer: predictors of response and toxicity.
27. PMID: 15870435; 2005, J Natl Cancer Inst;97(9):643-55
Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer.
28. PMID: 15998906; 2005, J Clin Oncol;23(28):6838-45
Increased epidermal growth factor receptor gene copy number detected by fluorescence in situ hybridization associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: a Southwest Oncology Group Study.
29. PMID: 16204011; 2005, J Clin Oncol;23(31):8081-92
Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials.
30. PMID: 23557218; 2013, J Transl Med;11():90
High EGFR copy number predicts benefits from tyrosine kinase inhibitor treatment for non-small cell lung cancer patients with wild-type EGFR.
31. PMID: 26141217; 2015, Lung Cancer;89(3):337-42
Concurrence of EGFR amplification and sensitizing mutations indicate a better survival benefit from EGFR-TKI therapy in lung adenocarcinoma patients.
32. PMID: 28537764; 2017, J Clin Oncol;35(20):2279-2287
Gefitinib and EGFR Gene Copy Number Aberrations in Esophageal Cancer.
33. PMID: 28057415; 2017, Clin Genitourin Cancer;15(4):e727-e734
Comprehensive Genomic Analysis of Metastatic Mucinous Urethral Adenocarcinoma Guides Precision Oncology Treatment: Targetable EGFR Amplification Leading to Successful Treatment With Erlotinib.
34. PMID: 30463996; 2019, Cancer Discov;9(2):199-209
EGFR and MET Amplifications Determine Response to HER2 Inhibition in ERBB2-Amplified Esophagogastric Cancer.

ACT Onco[®] + Report

35. PMID: 28575464; 2017, Neuro Oncol;19(11):1522-1531
Phase II trial of dacomitinib, a pan-human EGFR tyrosine kinase inhibitor, in recurrent glioblastoma patients with EGFR amplification.
36. PMID: 24739573; 2014, Nat Rev Cancer;14(5):359-70
Unravelling mechanisms of p53-mediated tumour suppression.
37. PMID: 21125671; 2011, J Pathol;223(2):137-46
Haplo-insufficiency: a driving force in cancer.
38. PMID: 22713868; 2012, Genes Dev;26(12):1268-86
Mutant p53: one name, many proteins.
39. PMID: 17417627; 2007, Nat Cell Biol;9(5):573-80
p53 gain-of-function cancer mutants induce genetic instability by inactivating ATM.
40. PMID: 27998224; 2016, J Clin Oncol;34(36):4354-4361
Phase II Study of WEE1 Inhibitor AZD1775 Plus Carboplatin in Patients With TP53-Mutated Ovarian Cancer Refractory or Resistant to First-Line Therapy Within 3 Months.
41. PMID: 26646755; 2016, Ann Oncol;27(3):539-43
TP53 mutational status is predictive of pazopanib response in advanced sarcomas.
42. PMID: 25669829; 2015, Ann Oncol;26(5):1012-8
Phase I study of pazopanib and vorinostat: a therapeutic approach for inhibiting mutant p53-mediated angiogenesis and facilitating mutant p53 degradation.
43. PMID: 27466356; 2016, Mol Cancer Ther;15(10):2475-2485
TP53 Alterations Correlate with Response to VEGF/VEGFR Inhibitors: Implications for Targeted Therapeutics.
44. PMID: 23670029; 2013, Oncotarget;4(5):705-14
P53 mutations in advanced cancers: clinical characteristics, outcomes, and correlation between progression-free survival and bevacizumab-containing therapy.
45. PMID: 17145525; 2006, Semin Oncol;33(5 Suppl 10):S8-14
Bevacizumab in combination with chemotherapy: first-line treatment of patients with metastatic colorectal cancer.
46. PMID: 21399868; 2011, Int J Oncol;38(5):1445-52
p53, HER2 and tumor cell apoptosis correlate with clinical outcome after neoadjuvant bevacizumab plus chemotherapy in breast cancer.
47. PMID: 20549698; 2011, Int J Cancer;128(8):1813-21
p53 status influences response to tamoxifen but not to fulvestrant in breast cancer cell lines.
48. PMID: 10786679; 2000, Cancer Res;60(8):2155-62
Complete sequencing of TP53 predicts poor response to systemic therapy of advanced breast cancer.
49. PMID: 25672981; 2015, Cancer Res;75(7):1187-90
VEGF-A Expression Correlates with TP53 Mutations in Non-Small Cell Lung Cancer: Implications for Antiangiogenesis Therapy.
50. PMID: 25385265; 2015, Int J Oncol;46(2):607-18
TP53 oncomorphic mutations predict resistance to platinum and taxane based standard chemotherapy in patients diagnosed with advanced serous ovarian carcinoma.
51. PMID: 19023283; 2008, Nat Rev Mol Cell Biol;9(12):958-70
Transcription-coupled DNA repair: two decades of progress and surprises.
52. PMID: 21952828; 2012, Cell Mol Life Sci;69(5):727-40
Haploinsufficiency in mouse models of DNA repair deficiency: modifiers of penetrance.
53. PMID: 12114432; 2002, Clin Cancer Res;8(7):2286-91
Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer.

ACT Onco[®] + Report

54. PMID: 18024864; 2007, J Clin Oncol;25(33):5172-9
ERCC1 genotype and phenotype in epithelial ovarian cancer identify patients likely to benefit from paclitaxel treatment in addition to platinum-based therapy.
55. PMID: 1433335; 1992, J Natl Cancer Inst;84(19):1512-7
ERCC1 and ERCC2 expression in malignant tissues from ovarian cancer patients.
56. PMID: 8040325; 1994, J Clin Invest;94(2):703-8
Messenger RNA levels of XPAC and ERCC1 in ovarian cancer tissue correlate with response to platinum-based chemotherapy.
57. PMID: 23275151; 2013, Carcinogenesis;34(4):739-49
PARP inhibition selectively increases sensitivity to cisplatin in ERCC1-low non-small cell lung cancer cells.
58. PMID: 23934192; 2013, Oncogene;32(47):5377-87
A high-throughput screen identifies PARP1/2 inhibitors as a potential therapy for ERCC1-deficient non-small cell lung cancer.
59. PMID: 30589644; 2019, J Clin Invest;129(3):1211-1228
PARP inhibition enhances tumor cell-intrinsic immunity in ERCC1-deficient non-small cell lung cancer.
60. PMID: 25774912; 2015, PLoS One;10(3):e0119614
Protein expression of DNA damage repair proteins dictates response to topoisomerase and PARP inhibitors in triple-negative breast cancer.
61. PMID: 16793542; 2006, Mol Cell;22(6):719-29
Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2.
62. PMID: 23325218; 2013, Nature;493(7432):356-63
Fanconi anaemia and the repair of Watson and Crick DNA crosslinks.
63. PMID: 15905196; 2005, Carcinogenesis;26(10):1731-40
The Fanconi anemia group A protein modulates homologous repair of DNA double-strand breaks in mammalian cells.
64. PMID: 27037238; 2016, EMBO J;35(9):909-23
Interplay between Fanconi anemia and homologous recombination pathways in genome integrity.
65. PMID: 24153426; 2013, Nat Commun;4():2578
Heterozygous mutations in PALB2 cause DNA replication and damage response defects.
66. PMID: 20858716; 2010, Cancer Res;70(19):7353-9
PALB2/FANCN: recombining cancer and Fanconi anemia.
67. PMID: 25754594; 2015, Hum Mutat;36(5):562-8
Loss-of-Function FANCL Mutations Associate with Severe Fanconi Anemia Overlapping the VACTERL Association.
68. PMID: 28678401; 2017, Cancer;123(20):3943-3954
Assessing the spectrum of germline variation in Fanconi anemia genes among patients with head and neck carcinoma before age 50.
69. PMID: 28916367; 2017, Lancet;390(10106):1949-1961
Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial.
70. PMID: 32086346; 2020, Clin Cancer Res;26(11):2487-2496
Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: Analysis From the Phase II TRITON2 Study.
71. PMID: 21135251; 2011, Mol Cancer Ther;10(1):3-8
Personalizing cancer treatment in the age of global genomic analyses: PALB2 gene mutations and the response to DNA damaging agents in pancreatic cancer.
72. PMID: 25935112; 2015, Trends Biochem Sci;40(6):296-308

ACT Onco[®] + Report

Structural determinants of Smad function in TGF- β signaling.

73. PMID: 19014666; 2008, Pathogenetics;1(1):2
Smad4 haploinsufficiency: a matter of dosage.
74. PMID: 9545410; 1998, Am J Hum Genet;62(5):1129-36
A gene for familial juvenile polyposis maps to chromosome 18q21.1.
75. PMID: 8553070; 1996, Science;271(5247):350-3
DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1.
76. PMID: 8673134; 1996, Nat Genet;13(3):343-6
Evaluation of candidate tumour suppressor genes on chromosome 18 in colorectal cancers.
77. PMID: 18662538; 2008, Cell;134(2):215-30
TGFbeta in Cancer.
78. PMID: 9135016; 1997, Cancer Res;57(9):1731-4
Tumor-suppressive pathways in pancreatic carcinoma.
79. PMID: 23139211; 2013, Cancer Res;73(2):725-35
SMAD2, SMAD3 and SMAD4 mutations in colorectal cancer.
80. PMID: 22810696; 2012, Nature;487(7407):330-7
Comprehensive molecular characterization of human colon and rectal cancer.
81. PMID: 25890228; 2015, World J Surg Oncol;13():128
Clinical outcome and expression of mutant P53, P16, and Smad4 in lung adenocarcinoma: a prospective study.
82. PMID: 19841540; 2009, J Clin Invest;119(11):3208-11
Smad4: gatekeeper gene in head and neck squamous cell carcinoma.
83. PMID: 15867212; 2005, Clin Cancer Res;11(9):3191-7
Differences in Smad4 expression in human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck squamous cell carcinoma.
84. PMID: 25589618; 2015, Clin Cancer Res;21(6):1447-56
Genomic analysis of metastatic cutaneous squamous cell carcinoma.
85. PMID: 29703253; 2018, BMC Cancer;18(1):479
SMAD4 and NF1 mutations as potential biomarkers for poor prognosis to cetuximab-based therapy in Chinese metastatic colorectal cancer patients.
86. PMID: 28522603; 2017, Clin Cancer Res;23(17):5162-5175
SMAD4 Loss Is Associated with Cetuximab Resistance and Induction of MAPK/JNK Activation in Head and Neck Cancer Cells.
87. PMID: 16144935; 2005, Clin Cancer Res;11(17):6311-6
SMAD4 levels and response to 5-fluorouracil in colorectal cancer.
88. PMID: 24384683; 2014, Br J Cancer;110(4):946-57
Loss of Smad4 in colorectal cancer induces resistance to 5-fluorouracil through activating Akt pathway.
89. PMID: 12237773; 2002, Br J Cancer;87(6):630-4
SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer.
90. PMID: 25749173; 2015, Transl Oncol;8(1):18-24
A Meta-Analysis of SMAD4 Immunohistochemistry as a Prognostic Marker in Colorectal Cancer.
91. PMID: 19478385; 2009, Cell Oncol;31(3):169-78
Presence of a high amount of stroma and downregulation of SMAD4 predict for worse survival for stage I-II colon cancer patients.

ACT Onco[®] + Report

92. PMID: 25681512; 2015, J Clin Pathol;68(5):341-5
Smad4 inactivation predicts for worse prognosis and response to fluorouracil-based treatment in colorectal cancer.
93. PMID: 26861460; 2016, Clin Cancer Res;22(12):3037-47
Reduced Expression of SMAD4 Is Associated with Poor Survival in Colon Cancer.
94. PMID: 26947875; 2016, Transl Oncol;9(1):1-7
Prognostic Value of SMAD4 in Pancreatic Cancer: A Meta-Analysis.
95. PMID: 25760429; 2015, Pancreas;44(4):660-4
SMAD4 expression predicts local spread and treatment failure in resected pancreatic cancer.
96. PMID: 22504380; 2012, Pancreas;41(4):541-6
SMAD4 genetic alterations predict a worse prognosis in patients with pancreatic ductal adenocarcinoma.
97. PMID: 19584151; 2009, Clin Cancer Res;15(14):4674-9
SMAD4 gene mutations are associated with poor prognosis in pancreatic cancer.
98. PMID: 18425078; 2008, Mod Pathol;21(7):866-75
Expression of Smad2 and Smad4 in cervical cancer: absent nuclear Smad4 expression correlates with poor survival.
99. PMID: 26156651; 2015, Lancet Oncol;16(8):897-907
Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial.
100. PMID: 23816960; 2013, J Clin Oncol;31(27):3327-34
Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.
101. PMID: 33503393; 2021, J Clin Oncol;39(4):273-284
Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated BRAF V600E-Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study.
102. PMID: 19339720; 2009, N Engl J Med;360(14):1408-17
Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer.
103. PMID: 18784101; 2008, N Engl J Med;359(11):1116-27
Platinum-based chemotherapy plus cetuximab in head and neck cancer.
104. PMID: 16467544; 2006, N Engl J Med;354(6):567-78
Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.
105. PMID: 15269313; 2004, N Engl J Med;351(4):337-45
Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.
106. PMID: 22285168; 2012, Lancet Oncol;13(3):239-46
Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial.
107. PMID: 17452677; 2007, J Clin Oncol;25(15):1960-6
Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group.
108. PMID: 24263064; 2014, Br J Cancer;110(1):55-62
First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study.
109. PMID: 26045340; 2015, Lancet Oncol;16(7):763-74
Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial.

ACT Onco[®] + Report

110. PMID: 27717299; 2016, N Engl J Med;375(22):2154-2164
Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer.
111. PMID: 32343890; 2020, N Engl J Med;382(22):2091-2102
Olaparib for Metastatic Castration-Resistant Prostate Cancer.
112. PMID: 31851799; 2019, N Engl J Med;381(25):2416-2428
Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer.
113. PMID: 31157963; 2019, N Engl J Med;381(4):317-327
Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer.
114. PMID: 30345884; 2018, N Engl J Med;379(26):2495-2505
Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer.
115. PMID: 28578601; 2017, N Engl J Med;377(6):523-533
Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation.
116. PMID: 28754483; 2017, Lancet Oncol;18(9):1274-1284
Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial.
117. PMID: 27617661; 2016, Lancet Oncol;17(11):1579-1589
Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial.
118. PMID: 27959700; 2017, N Engl J Med;376(7):629-640
Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer.
119. PMID: 25923549; 2015, N Engl J Med;372(18):1689-99
AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer.
120. PMID: 27736842; 2016, Br J Cancer;115(10):1206-1214
A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer.
121. PMID: 24024839; 2013, N Engl J Med;369(11):1023-34
Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer.
122. PMID: 24739896; 2014, Lancet Oncol;15(6):569-79
Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study.
123. PMID: 17470858; 2007, J Clin Oncol;25(13):1658-64
Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer.
124. PMID: 30110579; 2018, N Engl J Med;379(8):753-763
Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation.