

ACT Onco[®] + Report

PATIENT		
Identifier: 廖俐婷		Patient ID: 37487551
Date of Birth: Oct 25, 1981		Gender: Female
Diagnosis: Cholangiocarcinoma		
ORDERING PHYSICIAN		
Name: 陳明晃醫師		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: S11171944A	Collection site: Liver	Type: FFPE tissue
Date received: May 15, 2023	Lab ID: AA-23-03010	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	
Not detected			

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
KRAS G12D	-	Cetuximab, Panitumumab
CDK4 Amplification	Abemaciclib, Palbociclib, Ribociclib	-

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
KRAS	G12D	30.0%
TP53	G245V	39.5%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr9	CDKN2A	Heterozygous deletion	1
Chr12	CDK4, ERBB3	Amplification	7
Chr8	KAT6A	Amplification	7
Chr18	TYMS	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)	0.1 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:

- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 33% 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 3A		
KRAS G12D	Cetuximab, Panitumumab	resistant
Level 3B		
CDK4 Amplification	Abemaciclib, Palbociclib, Ribociclib	sensitive

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

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

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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
Not detected	

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
TYMS Amplification	Fluorouracil	Less sensitive	Clinical	Colorectal cancer
	Pemetrexed	Less sensitive	Clinical	Lung 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

KRAS G12D

Biological Impact

The V-Ki-Ras2 Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (KRAS) gene encodes a small GTPase protein, a member of the RAS family of small GTPases, which catalyze the hydrolysis of GTP to GDP. RAS proteins cycle between an active (GTP-bound) and an inactive (GDP-bound) state, to activate the downstream oncogenic pathways, including the PI3K/AKT/mTOR and MAPK pathways^[1]. KRAS mutations occur primarily in three hotspots G12, G13 and Q61, and less frequently in codon A146^{[1][2]}. These are activating mutations that lead to constitutive activation and persistent stimulation of the downstream signaling pathways^{[3][4]}. Mutations in KRAS have been reported in a diverse spectrum of human malignancies, including pancreatic carcinomas (>80%)^{[1][5]}, colon carcinomas (40-50%)^{[6][7]}, and lung carcinomas (30-50%)^{[8][9]}, but are also present in biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer, liver cancer, myeloid leukemia and breast cancer^[2].

G12D is a hotspot mutation located in the GTP binding region of the KRAS protein (UniProtKB). This mutation results in decreased KRAS GTPase activity, increased activation of downstream signaling, and promotes tumor formation in preclinical studies^{[10][11][12]}.

Therapeutic and prognostic relevance

Cetuximab and panitumumab are FDA-approved for treating RAS wild-type metastatic colorectal cancer. The NCCN for CRC recommends cetuximab and panitumumab use only if both KRAS and NRAS genes are normal.

KRAS mutation has been determined as an inclusion criterion for the trials evaluating MEK inhibitors efficacies in various types of solid tumors (NCT03704688, NCT02399943, NCT02285439, NCT03637491, NCT04214418).

KRAS mutations are associated with a lack of efficacy of EGFR TKIs^{[13][14][15]}. Some case reports suggest that MEK inhibitors may benefit patients with KRAS mutations, as shown in cervical and ovarian cancer cases (Am J Clin Exp Obstet Gynecol 2015;2(3):140-143)^{[16][17]}. However, a randomized Phase II study did not find trametinib to be superior to docetaxel in KRAS-mutant non-small cell lung cancer patients^[18]. MEK inhibitors as a monotherapy have limited response^[19].

Combining MEK and mTOR inhibitors is being evaluated as a potential strategy in RAS-mutant CRC^{[20][21]}. The combination of trametinib and palbociclib has resulted in objective responses in KRAS mutant models^[22].

Sorafenib has been shown to be beneficial in KRAS-mutant CRC/NSCLC, and KRAS-amplified melanoma^{[23][24][25]}. KRAS mutations in exon 2 (codon 12 or 13) and codon 61 have been associated with poor prognosis in CRC^[26].

Patients with KRAS or BRAF mutations in low-grade serous carcinoma of the ovary or peritoneum had better overall survival than those with wild-type genes^[27]. In ovarian serous borderline tumor, KRAS G12V mutation was linked to shorter survival time^[28].

TP53 G245V

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis^[29]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation^[30].

TP53 G245V is a missense mutation locates within the DNA-binding domain (DBD) of the p53 protein (UniProtKB).

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TP53 G245V was demonstrated as a loss-of-function mutation with decreased transactivation activity and suppress cell growth when compared with wild type TP53^[31].

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)^[32].

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^[33]. 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^[34].

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^{[35][36][37]}. 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)^[38]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy^{[39][40]}. 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^[41].

CDK4 Amplification

Biological Impact

The cyclin-dependent kinase 4 (CDK4) gene encodes a serine/threonine kinase that functions in the regulation of CDK kinases in the cell cycle. CDK4 forms a complex with cyclin-dependent kinase 6 (CDK6) and cyclin D, leading to G1-S cell-cycle transition by inhibiting the retinoblastoma (RB) protein^[42]. Dysregulation of CDK4/6 activity by gene amplification, activating mutations or loss of CDKN2A has been reported in breast cancer, melanoma, glioblastoma and sarcomas^{[43][44][45][46][47]}.

Therapeutic and prognostic relevance

Results from clinical studies of liposarcoma and endocrine-resistant, hormone receptor-positive breast cancer showed that CDK4 amplification is predictive of sensitivity to CDK4/6 inhibitor palbociclib in RB-expressing tumors^{[48][49][50]}.

Abemaciclib, another CDK4/6 inhibitor, showed acceptable toxicity profile and preliminary efficacy in a Phase I trial of multiple tumor types, including breast cancer, non-small cell lung cancer (NSCLC) and other solid tumors^[51].

In a phase 0 trial (NCT02933736), recurrent glioblastoma patients with intact RB1 expression and harboring CDKN2A deletion or CDK4/6 amplification demonstrated good CNS penetration, inhibited RB1 phosphorylation, and reduced tumor cell proliferation to ribociclib treatment, resulting in a median progression-free survival of 9.7 weeks and a median overall survival of 7.8 months^[52].

Of note, CDK4 amplification has been selected as an inclusion criterion for the trial examining CDK4/6 inhibitors in different types of malignant solid tumors (NCT03310879, NCT02187783, NCT02154490).

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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^{[53][54][55]}. 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^[56]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation^{[57][47]}.

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors^{[58][59]}. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments^{[60][51][61]}. However, there are clinical studies that demonstrated CDKN2A nuclear expression, CDKN2A/CDKN2B co-deletion, or CDKN2A inactivating mutation was not associated with clinical benefit from CDK4/6 inhibitors, such as palbociclib and ribociclib, in RB-positive patients^{[50][62][63]}.

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)^{[64][65]}.

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^{[59][66][67]}.

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^[51]. 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^[68].

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^[69].

ERBB3 Amplification

Biological Impact

The ERBB3 (also known as HER3) gene encodes a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases^[70]. HER3 lacks or has little intrinsic tyrosine kinase activity. Upon binding of its ligand, neu differentiation factor (NDF), HER3 forms a heterodimer with ErbB2^[71] and subsequently activates various mitogenic signaling cascades, including the PI3K/AKT/mTOR, STAT and RAS/RAF/MAPK^{[72][73][74]}. Aberrant expression or alterations of the ErbB family play crucial roles in the development and progression of cancer^[75]. Enhanced expression of HER2 has been observed in a broad spectrum of human cancers, including gastric, bladder, uterine, colorectal, and breast cancers^[76]. HER3 is the preferred heterodimeric partner for EGFR in melanoma and pancreatic carcinoma^{[77][78]}, while in breast cancer, HER3 preferably heterodimerizes with HER2 and plays a critical role in HER2-mediated tumorigenesis.

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Therapeutic and prognostic relevance

Currently, there are no FDA-approved anti-HER3 therapies for patients with solid tumors. A variety of strategies targeting HER3 including pan HER approach, abrogating its dimerization partners' kinase activity using small molecule inhibitors (e.g. lapatinib, erlotinib, gefitinib, afatinib, and neratinib) or direct targeting of its extracellular domain (e.g. including AV-203 (Abstract nr 2509, AACR 2012)) are under investigation^{[79][80]}.

Preclinical data indicated that HER3 expression level is a predictive biomarker of pertuzumab (an anti-HER2 antibody) efficacy in HER2 low-expressing pancreatic cancer^[81].

ERBB3 mutation has been selected as an inclusion criteria for the trial examining afatinib in urothelial tract carcinoma, non-small cell lung carcinoma (NSCLC) and malignant solid tumor (NCT02780687, NCT01523587, NCT03810872)^{[82][83]}.

Accumulating evidence indicates that overexpression of HER3 associates with worse survival in cancer patients with solid tumors^[84], besides, HER3 signaling plays a major role causing treatment failure in cancer therapy^{[85][86][79]}. For example, elevated HER3 expression of HER3 in HER2-overexpressing breast cancer cells results in resistance to hormone therapy (tamoxifen)^[87], HER2-targeted therapy (trastuzumab and lapatinib)^[88], and chemotherapy (paclitaxel). Besides, the high expression of ERBB3 has associated with gefitinib resistance in head and neck squamous cell carcinoma (HNSCC) cell lines^[89].

The amplification of ERBB3 was associated with poor response to chemotherapy, higher distant metastasis rate, poor PFS and OS of primary osteosarcoma patients^[90].

In a prospective study, a gallbladder cancer patient harboring ERBB3 amplification demonstrated a partial response for 1.8 months by lapatinib and capecitabine treatment^[91].

KAT6A Amplification

Biological Impact

The KAT6A (Lysine Acetyltransferase 6A) gene encodes for a member of the MOZ, YBFR2, SAS2, TIP60 family of histone acetyltransferases. KAT6A is a HAT enzyme that controls fundamental cellular processes, including gene transcription and maintenance of normal hematopoietic stem cell^[92]. Analysis of the genomic dataset from The Cancer Genome Atlas (TCGA) showed that KAT6A is amplified in at least 11% of breast tumors, at a higher frequency (22%) in the Luminal B subtype (HER2-)^[93].

Therapeutic and prognostic relevance

A study of the TCGA data demonstrated a strong correlation between KAT6A copy number and mRNA expression levels. Besides, high level of KAT6A expression was associated with significant reduction in overall survival^[94].

Preclinical study of gliomas showed that overexpression of KAT6A promotes PI3K/AKT signaling pathway activation by upregulating PIK3CA expression. Besides, the pan-PI3K inhibitor LY294002 is capable of abrogating the growth-promoting effect of KAT6A^[95].

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TYMS Amplification

Biological Impact

TYMS (Thymidylate Synthetase) gene encodes the thymidylate synthase that catalyzes the methylation of deoxyuridylate to deoxythymidylate. The enzyme is critical for DNA replication and repair^{[96][97][98]}. TYMS polymorphisms may be associated with etiology of neoplasia, including acute lymphoblastic leukemia^[99], breast cancer, and response to chemotherapy^[100].

Therapeutic and prognostic relevance

Thymidylate synthase gene amplification was associated with pemetrexed resistance in patients with advanced non-small cell lung cancer^{[101][102][103][104]}, and 5-FU resistance in CRC patients^[105]

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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 ^[106] 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 ^[67] NCT02107703	Breast cancer (Approved on 2017/09/28)
	HR+/HER2- Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1 ^[107] NCT02102490	Breast cancer (Approved on 2017/09/28)
	HR+/HER2- Abemaciclib [ORR(%): 19.7 vs. 17.4]

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 ^[108] NCT01740427	Breast cancer (Approved on 2017/03/31)
	ER+/HER2- Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3 ^[109] 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 ^[66] NCT01958021	Breast cancer (Approved on 2017/03/13)
	HR+/HER2- Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

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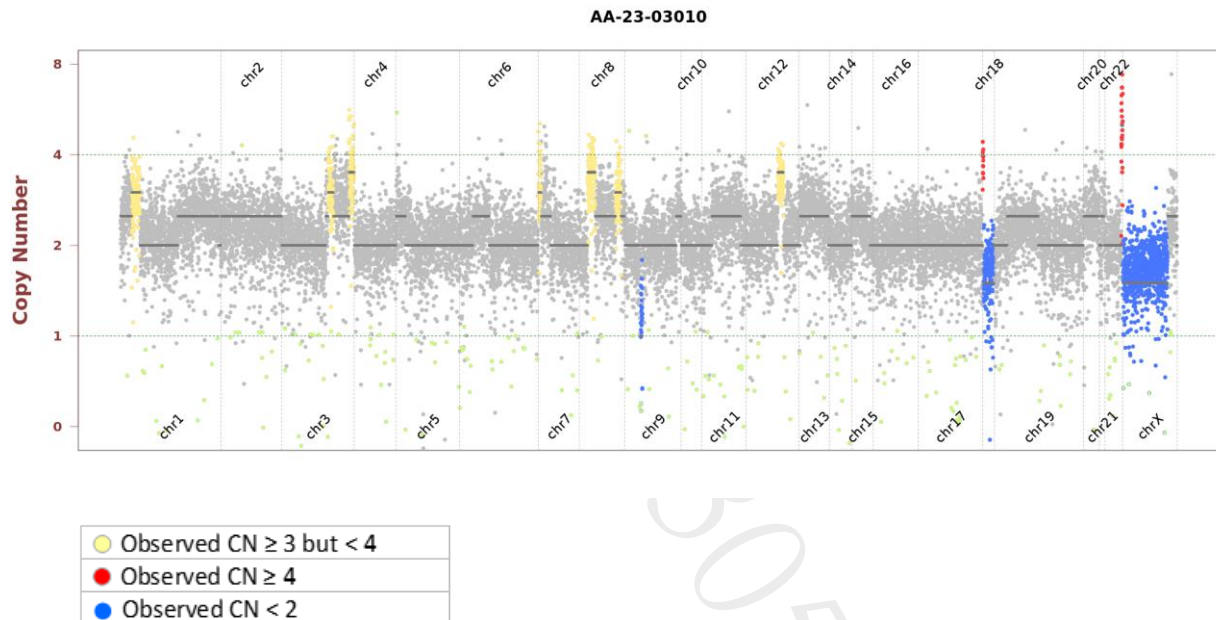
SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
KRAS	G12D	2	c.35G>A	NM_004985	COSM521	30.0%	2140
TP53	G245V	7	c.734G>T	NM_000546	COSM11196	39.5%	825

- 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
ERCC3	S764L	15	c.2291C>T	NM_000122	COSM3042186	38.3%	457
ESR1	S464N	7	c.1391G>A	NM_000125	-	18.1%	806
FAT1	E1292K	5	c.3874G>A	NM_005245	-	29.9%	782
FH	R101Q	3	c.302G>A	NM_000143	-	32.1%	2412
IL7R	T179M	4	c.536C>T	NM_002185	-	31.3%	511
NSD1	A487V	5	c.1460C>T	NM_022455	-	49.6%	786
TSC2	E1490G	34	c.4469A>G	NM_000548	-	46.3%	164

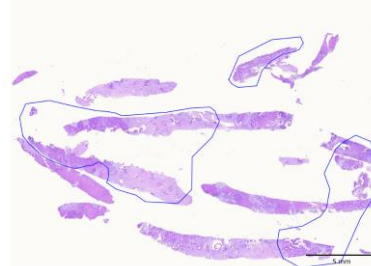
Note:

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

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TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Dec 12, 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11171944A
- Collection site: Liver
- Examined by: Dr. Chien-Ta Chiang
 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 (%): 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: 756x
- Target Base Coverage at 100x: 93%

RNA test

- Average unique RNA Start Sites per control GSP2: 150

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LIMITATIONS

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

NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

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

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

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

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

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

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

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

RNA test

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

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

DATABASE USED

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

Variant Analysis:

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Sign Off

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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*	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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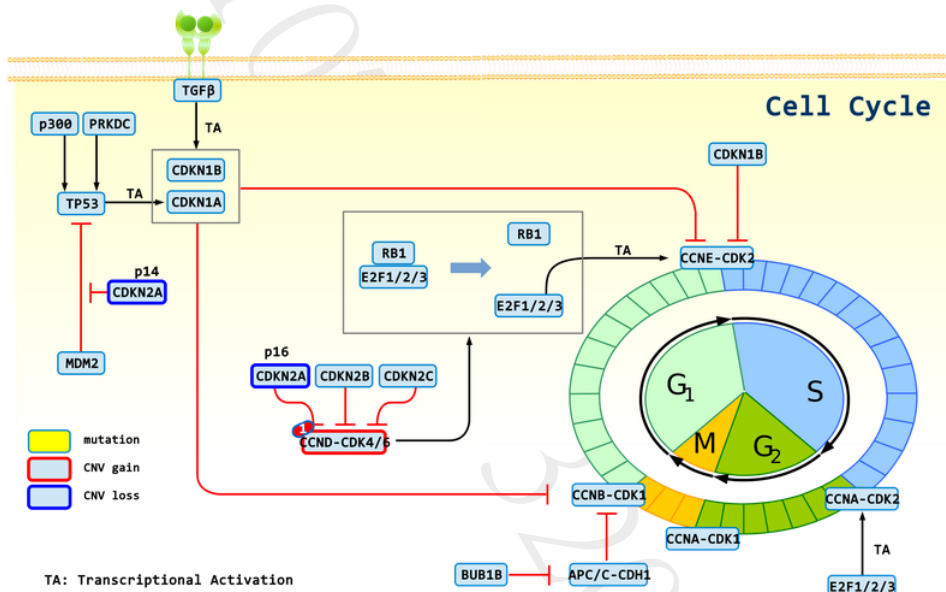
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APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Not Applicable.

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



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。

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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: 2453289; 1988, Cell;53(4):549-54
Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes.
2. PMID: 2114981; 1990, Eur J Clin Invest;20(3):225-35
ras oncogenes: their role in neoplasia.
3. PMID: 20617134; 2010, J Biomed Biotechnol;2010():150960
Clinical relevance of KRAS in human cancers.
4. PMID: 21993244; 2011, Nat Rev Cancer;11(11):761-74
RAS oncogenes: weaving a tumorigenic web.
5. PMID: 3047672; 1988, Nucleic Acids Res;16(16):7773-82
KRAS codon 12 mutations occur very frequently in pancreatic adenocarcinomas.
6. PMID: 3587348; 1987, Nature;327(6120):293-7
Prevalence of ras gene mutations in human colorectal cancers.
7. PMID: 1942608; 1991, Nihon Shokakibyo Gakkai Zasshi;88(8):1539-44
[Prevalence of K-ras gene mutations in human colorectal cancers].
8. PMID: 2252272; 1990, Am Rev Respir Dis;142(6 Pt 2):S27-30
The ras oncogenes in human lung cancer.
9. PMID: 1486840; 1992, Environ Health Perspect;98():13-24
Role of proto-oncogene activation in carcinogenesis.
10. PMID: 16474405; 2006, Nat Genet;38(3):331-6
Germline KRAS mutations cause Noonan syndrome.
11. PMID: 26037647; 2015, Mol Cancer Res;13(9):1325-35
Biochemical and Structural Analysis of Common Cancer-Associated KRAS Mutations.
12. PMID: 22871572; 2012, Mol Cancer Res;10(9):1228-39
KRAS(G12D)- and BRAF(V600E)-induced transformation of murine pancreatic epithelial cells requires MEK/ERK-stimulated IGF1R signaling.
13. PMID: 18349398; 2008, J Clin Oncol;26(9):1472-8
Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib.
14. PMID: 23401440; 2013, J Clin Oncol;31(8):1112-21
KRAS mutation: should we test for it, and does it matter?
15. PMID: 18024870; 2007, J Clin Oncol;25(33):5240-7
Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer.
16. PMID: 29946554; 2018, Gynecol Oncol Rep;25():41-44
Binimetinib (MEK162) in recurrent low-grade serous ovarian cancer resistant to chemotherapy and hormonal treatment.
17. PMID: 26075998; 2014, Gynecol Oncol Rep;10():28-9
Response to MEK inhibitor in small cell neuroendocrine carcinoma of the cervix with a KRAS mutation.
18. PMID: 25722381; 2015, Ann Oncol;26(5):894-901
A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC)†.
19. PMID: 24947927; 2014, Clin Cancer Res;20(16):4251-61

ACT Onco[®] + Report

Phase I expansion and pharmacodynamic study of the oral MEK inhibitor RO4987655 (CH4987655) in selected patients with advanced cancer with RAS-RAF mutations.

20. PMID: 27340376; 2016, Curr Colorectal Cancer Rep;12():141-150
Molecular Subtypes and Personalized Therapy in Metastatic Colorectal Cancer.
21. PMID: 22392911; 2012, Clin Cancer Res;18(9):2515-25
Inhibition of MEK and PI3K/mTOR suppresses tumor growth but does not cause tumor regression in patient-derived xenografts of RAS-mutant colorectal carcinomas.
22. PMID: 26369631; 2016, Clin Cancer Res;22(2):405-14
Sensitivity of KRAS-Mutant Colorectal Cancers to Combination Therapy That Cotargets MEK and CDK4/6.
23. PMID: 24407191; 2014, Br J Cancer;110(5):1148-54
Sorafenib and irinotecan (NEXIRI) as second- or later-line treatment for patients with metastatic colorectal cancer and KRAS-mutated tumours: a multicentre Phase I/II trial.
24. PMID: 23224737; 2013, Clin Cancer Res;19(3):743-51
A phase II study of sorafenib in patients with platinum-pretreated, advanced (Stage IIIB or IV) non-small cell lung cancer with a KRAS mutation.
25. PMID: 26307133; 2016, Clin Cancer Res;22(2):374-82
Copy Number Changes Are Associated with Response to Treatment with Carboplatin, Paclitaxel, and Sorafenib in Melanoma.
26. PMID: 15923428; 2005, Ann Oncol;16 Suppl 4():iv44-49
Prognostic and predictive factors in colorectal cancer: Kirsten Ras in CRC (RASCAL) and TP53CRC collaborative studies.
27. PMID: 26484411; 2015, Br J Cancer;113(9):1254-8
Impact of mutational status on survival in low-grade serous carcinoma of the ovary or peritoneum.
28. PMID: 24549645; 2013, J Pathol;231(4):449-56
KRAS (but not BRAF) mutations in ovarian serous borderline tumour are associated with recurrent low-grade serous carcinoma.
29. PMID: 24739573; 2014, Nat Rev Cancer;14(5):359-70
Unravelling mechanisms of p53-mediated tumour suppression.
30. PMID: 21125671; 2011, J Pathol;223(2):137-46
Haplo-insufficiency: a driving force in cancer.
31. PMID: 8001119; 1994, Cell;79(5):817-27
Transcriptional activation by p53 correlates with suppression of growth but not transformation.
32. 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.
33. PMID: 26646755; 2016, Ann Oncol;27(3):539-43
TP53 mutational status is predictive of pazopanib response in advanced sarcomas.
34. PMID: 25669829; 2015, Ann Oncol;26(5):1012-1018
Phase I study of pazopanib and vorinostat: a therapeutic approach for inhibiting mutant p53-mediated angiogenesis and facilitating mutant p53 degradation.
35. PMID: 27466356; 2016, Mol Cancer Ther;15(10):2475-2485
TP53 Alterations Correlate with Response to VEGF/VEGFR Inhibitors: Implications for Targeted Therapeutics.
36. 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.
37. PMID: 17145525; 2006, Semin Oncol;33(5 Suppl 10):S8-14

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Bevacizumab in combination with chemotherapy: first-line treatment of patients with metastatic colorectal cancer.

38. 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.
39. 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.
40. PMID: 10786679; 2000, Cancer Res;60(8):2155-62
Complete sequencing of TP53 predicts poor response to systemic therapy of advanced breast cancer.
41. 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.
42. PMID: 12432268; 2002, Cancer Biol Ther;1(3):226-31
Cycling to cancer with cyclin D1.
43. PMID: 8101826; 1993, Genes Dev;7(8):1572-83
Subunit rearrangement of the cyclin-dependent kinases is associated with cellular transformation.
44. PMID: 8221695; 1993, Cancer Res;53(22):5535-41
Coamplification of the CDK4 gene with MDM2 and GLI in human sarcomas.
45. PMID: 8586464; 1995, Glia;15(3):289-96
Gene amplification in human gliomas.
46. PMID: 9916925; 1999, Am J Pathol;154(1):113-8
Gene amplification and overexpression of CDK4 in sporadic breast carcinomas is associated with high tumor cell proliferation.
47. PMID: 24089445; 2013, Clin Cancer Res;19(19):5320-8
The cell-cycle regulator CDK4: an emerging therapeutic target in melanoma.
48. PMID: 23569312; 2013, J Clin Oncol;31(16):2024-8
Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma.
49. PMID: 27124835; 2016, JAMA Oncol;2(7):937-40
Progression-Free Survival Among Patients With Well-Differentiated or Dedifferentiated Liposarcoma Treated With CDK4 Inhibitor Palbociclib: A Phase 2 Clinical Trial.
50. PMID: 25501126; 2015, Clin Cancer Res;21(5):995-1001
CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment.
51. PMID: 27217383; 2016, Cancer Discov;6(7):740-53
Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non-Small Cell Lung Cancer, and Other Solid Tumors.
52. PMID: 31285369; 2019, Clin Cancer Res;25(19):5777-5786
A Phase 0 Trial of Ribociclib in Recurrent Glioblastoma Patients Incorporating a Tumor Pharmacodynamic- and Pharmacokinetic-Guided Expansion Cohort.
53. PMID: 17055429; 2006, Cell;127(2):265-75
The regulation of INK4/ARF in cancer and aging.
54. PMID: 8521522; 1995, Cell;83(6):993-1000
Alternative reading frames of the INK4a tumor suppressor gene encode two unrelated proteins capable of inducing cell cycle arrest.
55. PMID: 9529249; 1998, Cell;92(6):725-34
ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways.
56. PMID: 16115911; 2005, Clin Cancer Res;11(16):5740-7

ACT Onco[®] + Report

Comprehensive analysis of CDKN2A status in microdissected urothelial cell carcinoma reveals potential haploinsufficiency, a high frequency of homozygous co-deletion and associations with clinical phenotype.

57. PMID: 7550353; 1995, Nat Genet;11(2):210-2
Frequency of homozygous deletion at p16/CDKN2 in primary human tumours.
58. PMID: 27849562; 2017, Gut;66(7):1286-1296
Palbociclib (PD-0332991), a selective CDK4/6 inhibitor, restricts tumour growth in preclinical models of hepatocellular carcinoma.
59. PMID: 25524798; 2015, Lancet Oncol;16(1):25-35
The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.
60. PMID: 28283584; 2017, Oncologist;22(4):416-421
Clinical Benefit in Response to Palbociclib Treatment in Refractory Uterine Leiomyosarcomas with a Common CDKN2A Alteration.
61. PMID: 26715889; 2015, Curr Oncol;22(6):e498-501
Does CDKN2A loss predict palbociclib benefit?
62. PMID: 27542767; 2016, Clin Cancer Res;22(23):5696-5705
A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas.
63. PMID: 24797823; 2014, Oncologist;19(6):616-22
Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel.
64. PMID: 35050752; 2020, JCO Precis Oncol;4():757-766
Palbociclib in Patients With Non-Small-Cell Lung Cancer With CDKN2A Alterations: Results From the Targeted Agent and Profiling Utilization Registry Study.
65. PMID: 35100714; 2019, JCO Precis Oncol;3():1-8
Palbociclib in Patients With Pancreatic and Biliary Cancer With CDKN2A Alterations: Results From the Targeted Agent and Profiling Utilization Registry Study.
66. PMID: 27717303; 2016, N Engl J Med;375(18):1738-1748
Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer.
67. PMID: 28580882; 2017, J Clin Oncol;35(25):2875-2884
MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy.
68. PMID: 26728409; 2016, Clin Cancer Res;22(1):122-33
Coadministration of Trametinib and Palbociclib Radiosensitizes KRAS-Mutant Non-Small Cell Lung Cancers In Vitro and In Vivo.
69. PMID: 31401335; 2019, Transl Oncol;12(11):1425-1431
Concomitant Genetic Alterations are Associated with Worse Clinical Outcome in EGFR Mutant NSCLC Patients Treated with Tyrosine Kinase Inhibitors.
70. PMID: 19536107; 2009, Nat Rev Cancer;9(7):463-75
Novel anticancer targets: revisiting ERBB2 and discovering ERBB3.
71. PMID: 9130710; 1997, EMBO J;16(7):1647-55
ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling.
72. PMID: 22785351; 2012, Nat Rev Cancer;12(8):553-63
The ERBB network: at last, cancer therapy meets systems biology.
73. PMID: 7515147; 1994, Mol Cell Biol;14(6):3550-8
ErbB3 is involved in activation of phosphatidylinositol 3-kinase by epidermal growth factor.

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74. PMID: 12853564; 2003, Proc Natl Acad Sci U S A;100(15):8933-8
The ErbB2/ErbB3 heterodimer functions as an oncogenic unit: ErbB2 requires ErbB3 to drive breast tumor cell proliferation.
75. PMID: 19208461; 2009, Curr Opin Cell Biol;21(2):177-84
ErbB receptors and signaling pathways in cancer.
76. PMID: 23680147; 2013, Cancer Cell;23(5):603-17
Oncogenic ERBB3 mutations in human cancers.
77. PMID: 18698037; 2008, Clin Cancer Res;14(16):5188-97
HER3 is a determinant for poor prognosis in melanoma.
78. PMID: 20647770; 2010, Cancer Biol Ther;10(6):555-63
ErbB3 expression promotes tumorigenesis in pancreatic adenocarcinoma.
79. PMID: 30057690; 2018, Oncol Rev;12(1):355
HER3 signaling and targeted therapy in cancer.
80. PMID: 30109175; 2018, Acta Pharm Sin B;8(4):503-510
Understanding the biology of HER3 receptor as a therapeutic target in human cancer.
81. PMID: 25216528; 2014, Oncotarget;5(16):7138-48
HER3 as biomarker and therapeutic target in pancreatic cancer: new insights in pertuzumab therapy in preclinical models.
82. PMID: 27044931; 2016, J Clin Oncol;34(18):2165-71
Afatinib Activity in Platinum-Refractory Metastatic Urothelial Carcinoma in Patients With ERBB Alterations.
83. PMID: 29902295; 2018, JAMA Oncol;4(9):1189-1197
Association of ERBB Mutations With Clinical Outcomes of Afatinib- or Erlotinib-Treated Patients With Lung Squamous Cell Carcinoma: Secondary Analysis of the LUX-Lung 8 Randomized Clinical Trial.
84. PMID: 20485140; 2010, Ann Surg;251(6):1107-16
HER-3 overexpression is prognostic of reduced breast cancer survival: a study of 4046 patients.
85. PMID: 20816829; 2010, Semin Cell Dev Biol;21(9):944-50
The role of HER3, the unpretentious member of the HER family, in cancer biology and cancer therapeutics.
86. PMID: 24886126; 2014, Mol Cancer;13():105
Targeting of erbB3 receptor to overcome resistance in cancer treatment.
87. PMID: 16000581; 2005, Clin Cancer Res;11(13):4835-42
Can molecular markers predict when to implement treatment with aromatase inhibitors in invasive breast cancer?
88. PMID: 20064507; 2010, Exp Cell Res;316(7):1083-100
Mechanisms of resistance to HER family targeting antibodies.
89. PMID: 16818711; 2006, Clin Cancer Res;12(13):4103-11
Signaling via ErbB2 and ErbB3 associates with resistance and epidermal growth factor receptor (EGFR) amplification with sensitivity to EGFR inhibitor gefitinib in head and neck squamous cell carcinoma cells.
90. PMID: 31663373; 2019, Scand J Clin Lab Invest;79(8):601-612
Clinicopathological and prognostic values of ErbB receptor family amplification in primary osteosarcoma.
91. PMID: 33354548; 2020, South Asian J Cancer;9(2):74-79
Genomic Landscape and Targeted Treatment of Gallbladder Cancer: Results of a First Ongoing Prospective Study.
92. PMID: 17694082; 2007, Oncogene;26(37):5408-19
MOZ and MORF, two large MYSTic HATs in normal and cancer stem cells.
93. PMID: 27893709; 2017, Oncogene;36(20):2910-2918

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Identification of MYST3 as a novel epigenetic activator of ERα frequently amplified in breast cancer.

94. PMID: 25220592; 2014, Neoplasia;16(8):644-55
KAT6A, a chromatin modifier from the 8p11-p12 amplicon is a candidate oncogene in luminal breast cancer.
95. PMID: 29021135; 2017, Cancer Res;77(22):6190-6201
Histone Acetyltransferase KAT6A Upregulates PI3K/AKT Signaling through TRIM24 Binding.
96. PMID: 11502877; 2001, Mol Pharmacol;60(3):474-9
Inhibition of thymidylate synthase activity by antisense oligodeoxynucleotide and possible role in thymineless treatment.
97. PMID: 10482907; 1999, Br J Pharmacol;127(8):1777-86
Antisense down-regulation of thymidylate synthase to suppress growth and enhance cytotoxicity of 5-FUdR, 5-FU and Tomudex in HeLa cells.
98. PMID: 16818500; 2006, Mol Cancer Ther;5(6):1423-33
Therapeutic potential of antisense oligodeoxynucleotides to down-regulate thymidylate synthase in mesothelioma.
99. PMID: 29500934; 2018, J Clin Pharm Ther;43(4):507-512
Genotype and allele frequencies of TYMS rs2790 A > G polymorphism in a Chinese paediatric population with acute lymphoblastic leukaemia.
100. PMID: 28899623; 2018, Clin Breast Cancer;18(3):e301-e304
TYMS Gene Polymorphisms in Breast Cancer Patients Receiving 5-Fluorouracil-Based Chemotherapy.
101. PMID: 26220094; 2016, Clin Transl Oncol;18(1):107-12
Thymidylate synthase gene amplification predicts pemetrexed resistance in patients with advanced non-small cell lung cancer.
102. PMID: 21487406; 2011, Br J Cancer;104(10):1594-601
Thymidylate synthase as a determinant of pemetrexed sensitivity in non-small cell lung cancer.
103. PMID: 26502926; 2015, BMC Pulm Med;15():132
Thymidylate synthase expression as a predictive biomarker of pemetrexed sensitivity in advanced non-small cell lung cancer.
104. PMID: 23242435; 2013, J Thorac Oncol;8(1):19-30
Significance of folate receptor alpha and thymidylate synthase protein expression in patients with non-small-cell lung cancer treated with pemetrexed.
105. PMID: 20727737; 2010, Eur J Cancer;46(18):3358-64
Amplification of thymidylate synthetase in metastatic colorectal cancer patients pretreated with 5-fluorouracil-based chemotherapy.
106. PMID: 28968163; 2017, J Clin Oncol;35(32):3638-3646
MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer.
107. PMID: 28533223; 2017, Clin Cancer Res;23(17):5218-5224
MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer.
108. PMID: 27959613; 2016, N Engl J Med;375(20):1925-1936
Palbociclib and Letrozole in Advanced Breast Cancer.
109. PMID: 26030518; 2015, N Engl J Med;373(3):209-19
Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer.