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Sample Information

Patient Name: 羅敬輝
Gender: Male
ID No.: Q121689729
History No.: 45669009
Age: 50

Ordering Doctor: DOC1225B 陳明晃
Ordering REQ.: 0AXFDCE
Signing in Date: 2020/10/09

Path No.: S109-89737
MP No.: TM20004
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S108-42927FSC
Percentage of tumor cells: 50%
Note:

Sample Cancer Type: Cholangiocarcinoma

Table of Contents

Report Highlights

4 Relevant Biomarkers
3 Therapies Available
34 Clinical Trials

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*KRAS p.(G12V) c.35G>T* KRAS proto-oncogene, GTPase Allele Frequency: 16.40%	None	cabozantinib	18
IIC	*PTPN11 p.(G60S) c.178G>A* protein tyrosine phosphatase, non-receptor type 11 Allele Frequency: 5.13%	None	None	7
IIC	*STK11 p.(Y272fs) c.815_816delAC* serine/threonine kinase 11 Allele Frequency: 28.41%	None	None	6
	Tumor Mutational Burden 7.62 Mut/Mb measured	None	ipilimumab + nivolumab nivolumab	12

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.06(005).The content of this report has not been evaluated or approved by the FDA or other regulatory agencies.

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
KRAS	p.(G12V)	c.35G>T	COSM520	chr12:25398284	16.40%	NM_033360.3	missense	1579
PTPN11	p.(G60S)	c.178G>A	.	chr12:112888162	5.13%	NM_002834.4	missense	39
STK11	p.(Y272fs)	c.815_816delAC	.	chr19:1221291	28.41%	NM_000455.4	frameshift Deletion	968
ARID1A	p.(R1906P)	c.5717G>C	.	chr1:27106106	60.60%	NM_006015.5	missense	1713
TAL1	p.(=)	c.933A>G	.	chr1:47685455	100.00%	NM_003189.5	synonymous	386
TAL1	p.(P50S)	c.148C>T	.	chr1:47691413	4.58%	NM_003189.5	missense	131
BCL9	p.(P663S)	c.1987C>T	.	chr1:147091948	5.34%	NM_004326.3	missense	131
NTRK1	p.(?)	c.-10C>T	.	chr1:156830717	3.49%	NM_002529.3	unknown	86
ABL2	p.(G721E)	c.2162G>A	.	chr1:179078195	5.83%	NM_005158.4	missense	103
ABL2	p.(G720S)	c.2158G>A	.	chr1:179078199	10.00%	NM_005158.4	missense	100
ABL2	p.(A464T)	c.1390G>A	.	chr1:179084139	4.40%	NM_005158.4	missense	91
PIK3C2B	p.(=)	c.288C>A	.	chr1:204438643	100.00%	NM_002646.3	synonymous	1949
ALK	p.(G924D)	c.2771G>A	.	chr2:29451794	4.72%	NM_004304.4	missense	106
FN1	p.(=)	c.741C>T	.	chr2:216293006	4.44%	NM_212482.2	synonymous	135
FN1	p.(=)	c.732C>T	.	chr2:216293015	3.70%	NM_212482.2	synonymous	135
PAX3	p.(=)	c.807C>T	.	chr2:223086092	46.05%	NM_181459.3	synonymous	2000
FANCD2	p.(Q65H)	c.195G>C	.	chr3:10074646	40.01%	NM_033084.4	missense	1657
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.5	nonframeshift Insertion	122
BAP1	p.(?)	c.-46G>A	.	chr3:52443940	4.23%	NM_004656.3	unknown	71
PHF7	p.(?)	c.-2956C>T	.	chr3:52443940	4.23%	NM_016483.6	unknown	71
NSD2	p.(=)	c.2493G>A	.	chr4:1957042	3.75%	NM_001042424.2	synonymous	80
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	100.00%	NM_006206.5	synonymous	1845
KDR	p.(=)	c.1029G>A	.	chr4:55976883	61.19%	NM_002253.2	synonymous	1193
CSF1R	p.(=)	c.2457G>A	.	chr5:149435686	7.33%	NM_005211.3	synonymous	232
CSF1R	p.(P818S)	c.2452C>T	.	chr5:149435691	10.64%	NM_005211.3	missense	94
MAP3K7	p.(?)	c.-10G>A	.	chr6:91296612	4.46%	NM_145331.2	unknown	112
MAP3K7	p.(?)	c.-41G>A	.	chr6:91296643	11.11%	NM_145331.2	unknown	108
ROS1	p.(G421R)	c.1261G>A	.	chr6:117714388	4.29%	NM_002944.2	missense	70

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Variants (Exclude variant in Taiwan BioBank with >1% allele frequency) (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
WRN	p.(V641I)	c.1921G>A	.	chr8:30954306	21.09%	NM_000553.4	missense	460
ADGRA2	p.(S1079L)	c.3236C>T	.	chr8:37699092	4.05%	NM_032777.9	missense	74
KAT6A	p.(E1109del)	c.3326_3328delAAG	.	chr8:41794797	50.33%	NM_006766.4	nonframeshift Deletion	1504
PRKDC	p.(T1345R)	c.4036C>G	.	chr8:48802852	3.96%	NM_006904.6	missense	1566
NCOA2	p.(=)	c.549G>A	.	chr8:71078982	3.92%	NM_006540.3	synonymous	51
NBN	p.(=)	c.1035C>T	.	chr8:90971042	47.92%	NM_002485.4	synonymous	1488
CSMD3	p.(?)	c.6256-1G>A	.	chr8:113363474	3.70%	NM_198123.1	unknown	108
RECQL4	p.(P820L)	c.2459C>T	.	chr8:145738605	3.81%	NM_004260.3	missense	105
JAK2	p.(V392M)	c.1174G>A	.	chr9:5065000	48.70%	NM_004972.3	missense	1998
TAF1L	p.(A1540T)	c.4618G>A	.	chr9:32630960	49.95%	NM_153809.2	missense	2000
TAF1L	p.(A1513V)	c.4538C>T	.	chr9:32631040	5.26%	NM_153809.2	missense	95
TAF1L	p.(P638S)	c.1912C>T	.	chr9:32633666	7.63%	NM_153809.2	missense	118
TAF1L	p.(=)	c.459G>A	.	chr9:32635119	7.94%	NM_153809.2	synonymous	63
TAF1L	p.(=)	c.456C>T	.	chr9:32635122	12.70%	NM_153809.2	synonymous	63
TAF1L	p.(C152Y)	c.455G>A	.	chr9:32635123	9.52%	NM_153809.2	missense	63
TAF1L	p.(D151N)	c.451G>A	.	chr9:32635127	20.63%	NM_153809.2	missense	63
PAX5	p.(=)	c.700C>T	.	chr9:36966626	62.89%	NM_016734.2	synonymous	1334
ABL1	p.(H1053Y)	c.3157C>T	.	chr9:133760834	5.66%	NM_005157.5	missense	212
RET	p.(G211S)	c.631G>A	.	chr10:43600405	4.60%	NM_020975.4	missense	326
RET	p.(V292M)	c.874G>A	.	chr10:43601830	46.77%	NM_020975.4	missense	635
KAT6B	p.(=)	c.5148G>A	.	chr10:76789730	13.41%	NM_012330.3	synonymous	82
NFKB2	p.(=)	c.1254G>A	.	chr10:104159181	3.45%	NM_001077494.3	synonymous	116
NUP98	p.(Q1142E)	c.3424C>G	.	chr11:3723781	51.39%	NM_016320.4	missense	1905
NUP98	p.(=)	c.2637G>A	.	chr11:3733899	50.06%	NM_016320.4	synonymous	841
NUP98	p.(=)	c.1624A>C	.	chr11:3752727	50.65%	NM_016320.4	synonymous	1548
IRS2	p.(P1232L)	c.3695C>T	.	chr13:110434706	3.41%	NM_003749.2	missense	88
IRS2	p.(=)	c.1020C>T	.	chr13:110437381	4.35%	NM_003749.2	synonymous	69
HIF1A	p.(=)	c.1731C>T	.	chr14:62207544	56.06%	NM_001530.3	synonymous	1616
HSP90AA1	p.(A149T)	c.445G>A	.	chr14:102552637	3.70%	NM_001017963.2	missense	54

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Variants (Exclude variant in Taiwan BioBank with >1% allele frequency) (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
HSP90AA1	p.(E147K)	c.439G>A	.	chr14:102552643	9.26%	NM_001017963.2	missense	54
CREBBP	p.(P1943L)	c.5828C>T	.	chr16:3779220	3.45%	NM_004380.2	missense	87
CREBBP	p.(M626I)	c.1878G>A	.	chr16:3828764	4.48%	NM_004380.2	missense	67
MALT1	p.(=)	c.57G>A	.	chr18:56338932	4.29%	NM_006785.3	synonymous	70
MAP2K2	p.(G393D)	c.1178G>A	.	chr19:4090621	4.04%	NM_030662.3	missense	99
AKT2	p.(M180I)	c.540G>A	.	chr19:40747878	8.33%	NM_001626.5	missense	72
AKT2	p.(=)	c.537C>T	.	chr19:40747881	8.22%	NM_001626.5	synonymous	73
AKT2	p.(=)	c.531C>T	.	chr19:40747887	6.00%	NM_001626.5	synonymous	50
ERCC1	p.(P3S)	c.7C>T	.	chr19:45926626	4.29%	NM_001983.3	missense	70
PLCG1	p.(=)	c.2517G>A	.	chr20:39797752	47.82%	NM_002660.2	synonymous	1999
ERG	p.(=)	c.462C>T	.	chr21:39775558	50.00%	NM_182918.3	synonymous	826
MN1	p.(R943Q)	c.2828G>A	.	chr22:28193704	4.11%	NM_002430.2	missense	73
MYH9	p.(=)	c.1449C>T	.	chr22:36710295	6.82%	NM_002473.5	synonymous	88
MYH9	p.(T483I)	c.1448C>T	.	chr22:36710296	5.68%	NM_002473.5	missense	88
CYP2D6	p.(V342A)	c.1025T>C	.	chr22:42523597	7.56%	NM_000106.5	missense	1998
CYP2D6	p.(C161Y)	c.482G>A	.	chr22:42525058	3.95%	NM_000106.5	missense	76
TFE3	p.(=)	c.762G>A	.	chrX:48895740	4.96%	NM_006521.5	synonymous	121
TAF1	p.(A871T)	c.2611G>A	.	chrX:70608210	7.45%	NM_004606.4	missense	94

Biomarker Descriptions

KRAS (KRAS proto-oncogene, GTPase)

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[1,2,3].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[4]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[4,5,6]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,8].

Potential relevance: Currently, no therapies are approved for KRAS aberrations. However, the KRAS G12C inhibitor, sotorasib (AMG 510)[9], was granted fast track designation (2019) for previously treated non-small cell lung cancer (NSCLC) patients with KRAS G12C mutations. The EGFR antagonists, cetuximab[10] and panitumumab[11], are contraindicated for treatment of colorectal cancer patients

Biomarker Descriptions (continued)

with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[8]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[12].

PTPN11 (protein tyrosine phosphatase, non-receptor type 11)

Background: The PTPN11 gene encodes a tyrosine phosphatase non-receptor type 11 protein, and is also known as Src homology region 2 domain-containing phosphatase-2 (SHP-2)[13]. PTPN11 is a member of the protein tyrosine phosphatase (PTP) family that is ubiquitously expressed and regulates cellular growth, differentiation, mitotic cycle, and oncogenic transformation. PTPN11 contains two tandem N-terminal Src homology-2 domains (N-SH2 and C-SH2), a PTP catalytic domain, and uncharacterized C-terminal domain[14]. PTPN11 regulates various signaling processes including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, and JAK/STAT pathways[15,16]. Germline mutations in PTPN11 are associated with LEOPARD syndrome and Noonan syndrome with a predisposition to juvenile myelomonocytic leukemia (JMML) or myeloproliferative neoplasms (MPN)[17,18]. Somatic mutations in PTPN11 are associated with JMML[19,20] and solid tumors such as lung, colon, and thyroid[14,21]

Alterations and prevalence: Somatic alterations in PTPN11 include mutations and amplification[17,22]. PTPN11 mutations occur in 6% of uterine carcinoma and 5% of acute myeloid leukemia (AML) cases[7]. Mutations including E76K and D61Y result in PTPN11 activation and are associated with 30% of JMML[16].

Potential relevance: Currently, no therapies are approved for PTPN11 aberrations. Somatic mutations in PTPN11 confer drug resistance to venetoclax and azacitidine in AML[23,24].

STK11 (serine/threonine kinase 11)

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and tumor suppression[25]. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development[26,27].

Alterations and prevalence: Somatic mutations in STK11 have been reported in 10% of lung cancer, 4% of cervical cancer, and up to 3% of cholangiocarcinoma and uterine cancer[4,7,28,29]. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer[4,7]. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others[4,7,26,29,30].

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, the presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors[31]. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)[32].

Tumor Mutational Burden

Background: Tumor mutational burden (TMB), also known as tumor mutational load (TML), is the count of somatic mutations in the DNA of cancer cells. TMB is determined by next-generation sequencing and is expressed as the number of mutations per megabase (mut/Mb) of DNA coding sequence[33]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[34,35,36,37,38]. High TMB is associated with increased neo-antigen burden and has been linked to response to immune checkpoint inhibitors (ICIs) that target the cytotoxic T lymphocyte antigen-4 (CTLA4), programmed death protein 1 (PD1), and programmed death-ligand 1 (PD-L1) inhibitors[39,40,41,42].

Alterations and prevalence: In one study of over 100,000 tumor samples, the median TMB value was 3.6 mut/Mb although TMB values vary widely across cancers[43]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[40,43]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[40,43]. For example, within non-small cell lung cancer (NSCLC), higher TMB was observed in former/current smokers (10.5 mut/Mb) relative to never smokers (0.6 mut/Mb)[40,43,44]. There is no consensus around the definition of high and low TMB that could be applied universally to all tumor types, instead multiple sources

Biomarker Descriptions (continued)

suggest that TMB status is a cancer type specific attribute[43,45,46]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[47,48,49,50].

Potential relevance: ICIs stimulate a patient's own T-cells to kill tumors and have exhibited benefits in some patients. The first ICI to be approved by the FDA was ipilimumab (2011), an anti-CTLA4 antibody indicated for the treatment of metastatic melanoma. In 2014, anti-PD-1 antibodies nivolumab (2014) and pembrolizumab (2014) were subsequently approved, for the treatment of metastatic melanoma, and pembrolizumab also for advanced esophageal squamous cell carcinoma. Indications have been expanded for these ICIs to include several other cancer types including NSCLC, advanced renal cell carcinoma, classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability (MSI)-High or mismatch repair deficient colorectal cancer, and hepatocellular carcinoma. Atezolizumab (2016), avelumab (2017), and durvalumab (2017), that target programmed death-ligand 1 (PD-L1) were subsequently approved by the FDA. However, the predictive biomarkers that underlie the clinical benefits of these approved immunotherapies, including TMB, are under active investigation. Several published studies including the CheckMate 586 and CheckMate 817 clinical trials have concluded that high TMB was associated with improved response to FDA approved checkpoint inhibitors[48,51,52]. In contrast, several previously promising trials have failed to show an improvement in survival outcomes between high and low TMB including CheckMate 227 (ipilimumab + nivolumab vs. chemotherapy), CheckMate 026 (nivolumab vs. chemotherapy), KEYNOTE 189 (pembroluzimab vs. chemotherapy), KEYNOTE 021 (pembroluzimab vs. pembroluzimab + chemotherapy), and Lung-MAP (nivolumab + ipilimumab vs. nivolumab). In response, suggestions to combine TMB score with PD-L1 expression as a way to increase the predictive power for patient stratification have been reported[53]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[54]. TMB score estimation is affected by the utilized assays, therefore efforts are underway to develop a standardized approach to calculate with the aim to support consistent reporting of TMB values across laboratories[55,56,57,58].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

KRAS p.(G12V) c.35G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cetuximab	⊘	⊘	⊘	⊘	✖
panitumumab	⊘	⊘	✖	⊘	✖
cetuximab + oxaliplatin	✖	✖	⊘	✖	✖
panitumumab + oxaliplatin	✖	✖	⊘	✖	✖
cabozantinib	✖	✖	✖	○	✖
cetuximab + chemotherapy	✖	✖	✖	⊘	✖
panitumumab + chemotherapy	✖	✖	✖	⊘	✖
selumetinib, ulixertinib	✖	✖	✖	✖	● (II)
anti-KRAS G12V mTCR	✖	✖	✖	✖	● (I/II)
ASTX029	✖	✖	✖	✖	● (I/II)
avelumab, binimetinib, talazoparib	✖	✖	✖	✖	● (I/II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

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Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

KRAS p.(G12V) c.35G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	✖	✖	● (I/II)
neratinib, valproic acid	✖	✖	✖	✖	● (I/II)
RMC-4630, cobimetinib	✖	✖	✖	✖	● (I/II)
zotatifin	✖	✖	✖	✖	● (I/II)
BGB-3245	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
LXH254	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
neratinib, trametinib	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
TAK 659, chemotherapy	✖	✖	✖	✖	● (I)
ulixertinib, antimalarial	✖	✖	✖	✖	● (I)

PTPN11 p.(G60S) c.178G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selumetinib, ulixertinib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
BGB-3245	✖	✖	✖	✖	● (I)
LXH254	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

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Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

STK11 p.(Y272fs) c.815_816delAC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
paxalisib	✖	✖	✖	✖	● (II)
samotolisib	✖	✖	✖	✖	● (II)
telaglenastat	✖	✖	✖	✖	● (II)
temsirolimus	✖	✖	✖	✖	● (II)
gedatolisib + palbociclib	✖	✖	✖	✖	● (I)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ipilimumab + nivolumab	✖	○	✖	○	✖
nivolumab	✖	○	✖	✖	● (II)
atezolizumab	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BAY1905254	✖	✖	✖	✖	● (I)
zimberelimab	✖	✖	✖	✖	● (I)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.06(005).

Relevant Therapy Details

Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⛔ Not recommended 🛡 Resistance

FDA information is current as of 2020-05-26. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12V) c.35G>T

⊘ cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2019-04-23 **Variant class:** KRAS G12 mutation

Indications and usage:

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved test

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: Erbitux® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125084s273lbl.pdf

KRAS p.(G12V) c.35G>T (continued)

⊘ panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2017-06-29 **Variant class:** KRAS G12 mutation

Indications and usage:

VECTIBIX® is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC):

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.
- Limitation of Use: VECTIBIX® is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125147s207lbl.pdf

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Current NCCN Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

NCCN information is current as of 2020-05-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

KRAS p.(G12V) c.35G>T

cetuximab

Cancer type: Colon Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2020]

cetuximab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2020]

panitumumab

Cancer type: Colon Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2020]

panitumumab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2020]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.06(005).

KRAS p.(G12V) c.35G>T (continued)

EGFR tyrosine kinase inhibitor

Cancer type: Non-Small Cell Lung Cancer **Variant class:** KRAS mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Non-responsiveness to EGFR TKI therapy is associated with KRAS and BRAF mutations and ALK or ROS1 gene fusions."
- "KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR TKIs."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

Tumor Mutational Burden

ipilimumab + nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging biomarker in metastatic disease (Not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging biomarker in metastatic disease (Not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.06(005).

Current EMA Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

EMA information is current as of 2020-05-26. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12V) c.35G>T

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-30 **Variant class:** KRAS exon 2 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf

panitumumab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-24 **Variant class:** KRAS exon 2 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.06(005).

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⛔ Not recommended ⛊ Resistance

ESMO information is current as of 2020-05-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12V) c.35G>T

○ cabozantinib

Cancer type: Thyroid Gland Medullary Carcinoma **Variant class:** RAS mutation

ESMO Level of Evidence/Grade of Recommendation: II / C

Population segment (Line of therapy):
- Metastatic Thyroid Gland Medullary Carcinoma (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Annals of Oncology 30: 1856–1883, 2019 doi:10.1093/annonc/mdz400]

⊘ cetuximab

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:
- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.06(005).

KRAS p.(G12V) c.35G>T (continued)

⊘ cetuximab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."
- "Thus, the activity of the anti-EGFR antibodies is confined to RAS WT tumours (and not only KRAS WT tumours). This is true for the combinations of cetuximab or panitumumab alone or with irinotecan- and oxaliplatin-based regimens. Treatment with anti-EGFR antibodies may even harm patients with a RAS mutation, especially when combined with oxaliplatin [I/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

⊘ panitumumab

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

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KRAS p.(G12V) c.35G>T (continued)

⊘ panitumumab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."
- "Thus, the activity of the anti-EGFR antibodies is confined to RAS WT tumours (and not only KRAS WT tumours). This is true for the combinations of cetuximab or panitumumab alone or with irinotecan- and oxaliplatin-based regimens. Treatment with anti-EGFR antibodies may even harm patients with a RAS mutation, especially when combined with oxaliplatin [I/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

Tumor Mutational Burden

○ ipilimumab + nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

- Stage IV Squamous and Non-squamous (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.06(005).

Signatures

Testing Personnel:

Shu-Ying Wang 2020.10.16 11:38:50 +08'00'

Laboratory Supervisor:

2020.10.16 11:39:06 +08'00'

Pathologist:

Yi-Chu Yeh 2020.10.16 11:39:19 +08'00'

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