Taipei Veterans General Hospital

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Sample Information

Patient Name: 陳祈炊
Gender: Male
ID No.: C100932297
History No.: 46342658
Age: 75

Ordering Doctor: DOC1324H 李沛璋
Ordering REQ.: 0BKBRDT
Signing in Date: 2021/08/19

Path No.: S110-99321
MP No.: TM21011
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S109-23427G
Percentage of tumor cells: 50%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Other Solid Tumor

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*KRAS p.(G12D) c.35G>A* KRAS proto-oncogene, GTPase Allele Frequency: 18.63%	None	cabozantinib	2
	Tumor Mutational Burden 5.01 Mut/Mb measured	None	**pembrolizumab** [1]	3

Public data sources included in relevant therapies: FDA[1], 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.

Prevalent cancer biomarkers without relevant evidence based on included data sources
CDKN2B p.(Q32) c.94C>T*

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
CDKN2B	p.(Q32*)	c.94C>T	.	chr9:22008859	5.66%	NM_004936.4	nonsense	53
KRAS	p.(G12D)	c.35G>A	COSM521	chr12:25398284	18.63%	NM_033360.4	missense	1991
LCK	p.(D496Y)	c.1486G>T	.	chr1:32751273	14.19%	NM_001042771.2	missense	1720
TAL1	p.(G271R)	c.811G>A	.	chr1:47685577	5.56%	NM_003189.5	missense	72
TAL1	p.(G270=)	c.810G>A	.	chr1:47685578	4.17%	NM_003189.5	synonymous	72
JAK1	p.(V310I)	c.928G>A	.	chr1:65332611	49.82%	NM_002227.4	missense	1999
PDE4DIP	p.(R295C)	c.883C>T	.	chr1:144922524	22.96%	NM_001198834.4	missense	1999
ITGA10	p.(P964=)	c.2892T>C	.	chr1:145538781	51.25%	NM_003637.5	synonymous	1994
DDR2	p.(T681I)	c.2042C>T	.	chr1:162745627	50.00%	NM_006182.4	missense	2000
ABL2	p.(G729=)	c.2187G>A	.	chr1:179078170	5.17%	NM_005158.5	synonymous	116
ABL2	p.(G721E)	c.2162G>A	.	chr1:179078195	4.85%	NM_005158.5	missense	103
ABL2	p.(G720S)	c.2158G>A	.	chr1:179078199	3.85%	NM_005158.5	missense	104
ALK	p.(G924S)	c.2770G>A	.	chr2:29451795	5.41%	NM_004304.5	missense	111
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	99.79%	NM_002343.6	nonframeshift Insertion	1861
BAP1	p.(?)	c.-39G>A	.	chr3:52443933	3.77%	NM_004656.4	unknown	53
PHF7	p.(?)	c.-2963C>T	.	chr3:52443933	3.77%	NM_016483.7	unknown	53
EPHB1	p.(R905C)	c.2713C>T	.	chr3:134968200	50.43%	NM_004441.5	missense	1999
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	99.74%	NM_006206.6	synonymous	1954
IL2	p.(Q42=)	c.126G>A	.	chr4:123377470	51.91%	NM_000586.4	synonymous	994
PIK3R1	p.(H25=)	c.75C>T	.	chr5:67522578	47.70%	NM_181523.3	synonymous	1998
RAD50	p.(L1264F)	c.3790C>T	.	chr5:131977907	47.67%	NM_005732.4	missense	1999
CSF1R	p.(R83H)	c.248G>A	.	chr5:149460389	50.33%	NM_005211.3	missense	1999
NOTCH4	p.(C598Y)	c.1793G>A	.	chr6:32184790	6.00%	NM_004557.4	missense	50
NOTCH4	p.(L13_L16del)	c.36_47delGCTGCTGCTGCT	.	chr6:32191658	39.41%	NM_004557.4	nonframeshift Deletion	
PRDM1	p.(R286C)	c.856C>T	.	chr6:106552891	57.51%	NM_001198.4	missense	1998
ROS1	p.(E1605Q)	c.4813G>C	.	chr6:117662652	53.26%	NM_002944.2	missense	1992
SYNE1	p.(A3140=)	c.9420G>A	.	chr6:152694259	45.77%	NM_182961.4	synonymous	1997
CARD11	p.(W1125*)	c.3375G>A	.	chr7:2946362	4.76%	NM_032415.6	nonsense	84
AKAP9	p.(T3899I)	c.11696C>T	.	chr7:91739445	51.05%	NM_005751.4	missense	1998

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
EPHB4	p.(R535Q)	c.1604G>A	.	chr7:100411628	49.87%	NM_004444.5	missense	1999
TRIM24	p.(G863=)	c.2589A>G	.	chr7:138265310	50.21%	NM_015905.3	synonymous	1219
KMT2C	p.(L901P)	c.2702T>C	.	chr7:151932969	47.70%	NM_170606.3	missense	587
CDKN2A	p.(D92N)	c.274G>A	.	chr9:21971084	4.63%	NM_001195132.1	missense	108
CDKN2B	p.(R45C)	c.133C>T	.	chr9:22008820	13.46%	NM_004936.4	missense	52
CDKN2B	p.(G42R)	c.124G>A	.	chr9:22008829	3.77%	NM_004936.4	missense	53
CDKN2B	p.(A38V)	c.113C>T	.	chr9:22008840	7.55%	NM_004936.4	missense	53
TAF1L	p.(C805Y)	c.2414G>A	.	chr9:32633164	4.00%	NM_153809.2	missense	100
TAF1L	p.(P638L)	c.1913C>T	.	chr9:32633665	5.68%	NM_153809.2	missense	176
RALGDS	p.(F884=)	c.2652C>T	.	chr9:135974064	4.81%	NM_001271775.2	synonymous	104
RALGDS	p.(T883I)	c.2648C>T	.	chr9:135974068	4.81%	NM_001271775.2	missense	104
KAT6B	p.(S1717N)	c.5150G>A	.	chr10:76789732	4.72%	NM_012330.4	missense	127
ZNF384	p.(Q501Hfs*48)	c.1503delG	.	chr12:6777110	100.00%	NM_001135734.2	frameshift Deletion	532
ARID2	p.(M1?)	c.1A>G	.	chr12:46123620	11.27%	NM_152641.4	missense	1996
CDK4	p.(R139Q)	c.416G>A	.	chr12:58144812	10.71%	NM_000075.4	missense	1999
DICER1	p.(?)	c.4204_4206+19delinsTGTAAGTT	.	chr14:95566098	73.83%	NM_030621.4	unknown	749
DICER1	p.(?)	c.4206+9G>T	.	chr14:95566108	21.23%	NM_030621.4	unknown	749
CREBBP	p.(L2139=)	c.6417G>A	.	chr16:3778631	3.70%	NM_004380.3	synonymous	54
CREBBP	p.(P2137=)	c.6411C>T	.	chr16:3778637	3.70%	NM_004380.3	synonymous	54
IL21R	p.(R139C)	c.415C>T	.	chr16:27454345	49.15%	NM_021798.4	missense	2000
ZNF521	p.(P87=)	c.261A>G	.	chr18:22807621	42.49%	NM_015461.3	synonymous	1998
SMAD4	p.(F339Afs*39)	c.1014_1033delATTTAAGGTTCCTTCAAGCTinsG	.	chr18:48591851	14.62%	NM_005359.6	frameshift Block Substitution	1956
TCF3	p.(G431S)	c.1291_1293delGGCinsAGT	.	chr19:1619348	51.06%	NM_001136139.4	missense	709
AKT2	p.(K181=)	c.543G>A	.	chr19:40747875	4.38%	NM_001626.6	synonymous	160
AKT2	p.(Y178=)	c.534C>T	.	chr19:40747884	12.58%	NM_001626.6	synonymous	151
AKT2	p.(Y177=)	c.531C>T	.	chr19:40747887	6.96%	NM_001626.6	synonymous	115
AKT2	p.(R176=)	c.528C>T	.	chr19:40747890	4.67%	NM_001626.6	synonymous	107
PTPRT	p.(S139=)	c.417C>T	.	chr20:41419904	48.19%	NM_133170.4	synonymous	1880
MN1	p.(S1113L)	c.3338C>T	.	chr22:28193194	3.67%	NM_002430.3	missense	109
MN1	p.(S1111F)	c.3332C>T	.	chr22:28193200	4.50%	NM_002430.3	missense	111

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
MYH9	p.(I486=)	c.1458C>T	.	chr22:36710286	4.13%	NM_002473.6	synonymous	121
MYH9	p.(F485=)	c.1455C>T	.	chr22:36710289	4.96%	NM_002473.6	synonymous	121
EP300	p.(N1717S)	c.5150A>G	.	chr22:41572865	57.00%	NM_001429.4	missense	2000
EP300	p.(G2387S)	c.7159G>A	.	chr22:41574874	54.61%	NM_001429.4	missense	1996
TAF1	p.(V783I)	c.2347G>A	.	chrX:70607231	5.26%	NM_004606.5	missense	57
TAF1	p.(D1427N)	c.4279G>A	.	chrX:70627896	8.18%	NM_004606.5	missense	110

Biomarker Descriptions

CDKN2B (cyclin dependent kinase inhibitor 2B)

Background: CDKN2B encodes the cyclin-dependent kinase inhibitor 2B protein, a cell cycle regulator that controls G1/S progression[1]. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[2,3,4]. CDK2NB is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,5,6].

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 56% of esophageal squamous cell carcinoma, 54% of glioblastoma, 42% of pleural mesothelioma, 31% of bladder urothelial carcinoma, 28% of head and neck squamous cell carcinoma, and 27% of pancreatic adenocarcinoma[7].

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations.

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[8,9,10].

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[11]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[11,12,13]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,14].

Potential relevance: The KRAS inhibitor, sotorasib[15], is approved (2021) for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The small molecular inhibitor, RO-5126766, was granted breakthrough designation (2021) alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer[16]. Additionally, onvansertib[17] was granted fast track designation (2020) for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab[18] and panitumumab[19], are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[14]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[20].

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[21]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[22,23,24,25,26]. 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[27,28,29,30].

Biomarker Descriptions (continued)

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[31]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[28,31]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[28,31]. 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)[28,31,32]. There is no consensus around the definition of high and low TMB that could be applied universally to all tumor types, instead multiple sources suggest that TMB status is a cancer type specific attribute[31,33,34]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[35,36,37,38].

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. Pembrolizumab was also approved (2014) for advanced esophageal squamous cell carcinoma. In 2020, the indication for pembrolizumab[39] was expanded to include TMB-H (>/= 10 mut/Mb) solid tumors that have progressed on prior therapy. 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 (dMMR) 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[36,40,41]. In contrast, several promising previous trials 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 (pembrolizumab vs. chemotherapy), KEYNOTE 021 (pembrolizumab vs. pembrolizumab + 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[42]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[43]. Pembrolizumab is indicated for use in various cancer types with evidence of metastasis including Ewing sarcoma, salivary gland neoplasms, cervical cancer, uterine sarcoma, endometrial carcinoma, thyroid cancer, ovarian cancer, esophageal cancer, esophagogastric junction cancer, breast cancer, and germ cell tumors with high TMB[44,45,46,47,48,49,50,51,52]. TMB score estimation is affected by the utilized assays, therefore efforts are underway to develop a standardized approach for score calculation with the aim to support consistent reporting of TMB values across laboratories[53,54,55,56].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

KRAS p.(G12D) c.35G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	✖	✖	○	✖
RMC-4630, pembrolizumab	✖	✖	✖	✖	● (I)
mRNA-5671, pembrolizumab	✖	✖	✖	✖	○ (I)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	○	○	✖	✖	● (II)
atezolizumab	✖	✖	✖	✖	● (II)
pembrolizumab, quavonlimab, favezelimab, lenvatinib	✖	✖	✖	✖	○ (II)

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

Relevant Therapy Details

Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

FDA information is current as of 2021-07-14. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

○ pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2021-07-01 **Variant class:** Tumor Mutational Burden

Indications and usage:

KEYTRUDA® is a programmed death receptor-1 (PD-1)-blocking antibody indicated:

Melanoma

- for the treatment of patients with unresectable or metastatic melanoma.
- for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

Non-Small Cell Lung Cancer (NSCLC)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥ 1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic.
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA®.

Head and Neck Squamous Cell Cancer (HNSCC)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult patients with relapsed or refractory cHL.
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.
- Limitations of Use: KEYTRUDA® is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[1]

Tumor Mutational Burden (continued)

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options,[1] or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1]
- Limitations of Use: The safety and effectiveness of KEYTRUDA® in pediatric patients with MSI-H central nervous system cancers have not been established.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

- for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma[1]
- as a single agent for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1]

Esophageal Cancer

- for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

Cervical Cancer

- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test.[1]

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC who have been previously treated with sorafenib.[1]

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1]

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of patients with advanced RCC.

Endometrial Carcinoma

- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.[1]

Tumor Mutational Burden-High (TMB-H) Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1]
- Limitations of Use: The safety and effectiveness of KEYTRUDA® in pediatric patients with TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma (cSCC)

Tumor Mutational Burden (continued)

- for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

Triple-Negative Breast Cancer (TNBC)

- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.[2]

Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.[3]

[1]This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

[2]This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

[3]This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s100lbl.pdf

Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2021-07-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

Tumor Mutational Burden

○ pembrolizumab

Cancer type: Chondrosarcoma, Osteosarcoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 1.2021]

○ pembrolizumab

Cancer type: Breast Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IV; Recurrent, Invasive, Unresectable, Local (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 5.2021]

○ pembrolizumab

Cancer type: Cervical Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Metastatic, Progression (Second-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2021]

○ pembrolizumab

Cancer type: Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Squamous Cell; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2021]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Gastric Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 3.2021]

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pembrolizumab

Cancer type: Head and Neck Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Nasopharyngeal; Recurrent, Unresectable, Metastatic (Subsequent therapy); Useful in certain circumstances
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

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pembrolizumab

Cancer type: Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 3.2021]

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pembrolizumab

Cancer type: Ovarian Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2021]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Testicular Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Germ Cell Tumor; Metastatic (Third-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Testicular Cancer [Version 2.2021]

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pembrolizumab

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Locally Recurrent, Advanced, Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 1.2021]

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pembrolizumab

Cancer type: Thyroid Gland Medullary Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Persistent, Local, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 1.2021]

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pembrolizumab

Cancer type: Thyroid Gland Anaplastic Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVC; Metastatic (Second-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 1.2021]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Endometrial Carcinoma, Uterine Sarcoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Metastatic (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 3.2021]

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pembrolizumab

Cancer type: Ewing Sarcoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 1.2021]

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2021-07-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12D) c.35G>A

○ 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 (First-line therapy)

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

Clinical Trials in Taiwan region:

Clinical Trials Summary

KRAS p.(G12D) c.35G>A

NCT ID	Title	Phase
NCT04418661	A Phase I, Open-label, Multicenter, Safety Study of SAR442720 in Combination With Pembrolizumab in Patients With Advanced Malignancies	I
NCT03948763	A Phase I, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma	I

Tumor Mutational Burden

NCT ID	Title	Phase
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT02628067	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)	II
NCT03516981	A Phase II Precision Oncology Study of Biomarker-Directed, Pembrolizumab-(MK-3475, SCH 900475) Based Combination Therapy for Advanced Non-Small Cell Lung Cancer (KEYNOTE-495; KeyImPaCT)	II

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-07-14. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12D) c.35G>A

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2021-04-06 **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/2021/125084s277s280lbl.pdf

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

KRAS p.(G12D) c.35G>A (continued)

defactinib + RO-5126766

Cancer type: Endometrial Carcinoma **Variant class:** KRAS mutation

Supporting Statement:
The FDA has granted Breakthrough Designation to the small molecule inhibitor, RO-5126766 alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer.

Reference:

https://investor.verastem.com//news-releases/news-release-details/verastem-oncology-receives-breakthrough-therapy-designation-vs

bevacizumab + onvansertib + FOLFIRI

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

Supporting Statement:
The FDA has granted Fast Track Designation to the Polo-like Kinase 1 (PLK1) inhibitor, onvansertib, in combination with FOLFIRI and bevacizumab, for KRAS mutations in metastatic colorectal cancer in the second line.

Reference:

https://cardiffoncology.investorroom.com/2020-05-28-Cardiff-Oncology-Announces-Fast-Track-Designation-Granted-by-the-FDA-to-Onvansertib-for-Second-Line-Treatment-of-KRAS-Mutated-Colorectal-Cancer

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-07-01. 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.(G12D) c.35G>A

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 2.2021]

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 1.2021]

KRAS p.(G12D) c.35G>A (continued)

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 2.2021]

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 1.2021]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2021-07-14. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12D) c.35G>A

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

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2021-07-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12D) c.35G>A

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)]

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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)]

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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)]

KRAS p.(G12D) c.35G>A (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)]

Signatures

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