Taipei Veterans General Hospital

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Sample Information

Patient Name: 曾光星
Gender: Male
ID No.: E100322971
History No.: 41674059
Age: 69

Ordering Doctor: DOC6238J 李君陽
Ordering REQ.: 0CBVJQN
Signing in Date: 2022/11/03

Path No.: S111-97972
MP No.: TM22014
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S110-07523B
Percentage of tumor cells: 20%

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

Note:

Sample Cancer Type: Pancreatic Cancer

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Relevant Pancreatic Cancer Variants

Gene	Finding
NTRK1	None detected
NTRK3	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*Tumor Mutational Burden* 12.09 Mut/Mb measured	**pembrolizumab** [1]	pembrolizumab	19
IIC	*KRAS p.(G13D) c.38G>A* KRAS proto-oncogene, GTPase Allele Frequency: 5.41%	None	None	29

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.

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.(G13D)	c.38G>A	COSM532	chr12:25398281	5.41%	NM_033360.4	missense	1738
PAX7	p.(L213=)	c.639G>A	.	chr1:19018300	50.43%	NM_002584.3	synonymous	1616
DPYD	p.(N120=)	c.360C>T	.	chr1:98187189	4.05%	NM_000110.4	synonymous	74
ITGA10	p.(V591D)	c.1772T>A	.	chr1:145534267	4.85%	NM_003637.5	missense	2000
ITGA10	p.(R822W)	c.2464C>T	.	chr1:145537454	4.95%	NM_003637.5	missense	2000
ITGA10	p.(P964=)	c.2892T>C	.	chr1:145538781	47.77%	NM_003637.5	synonymous	1997
TPR	p.(R446H)	c.1337G>A	.	chr1:186328983	4.95%	NM_003292.3	missense	546
MSH2	p.(A573T)	c.1717G>A	.	chr2:47698159	39.33%	NM_000251.3	missense	684
MSH6	p.(R791H)	c.2372G>A	.	chr2:48027494	10.17%	NM_000179.3	missense	59
XPC	p.(T591S)	c.1771A>T	.	chr3:14199612	52.73%	NM_004628.5	missense	1997
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.6	nonframeshift Insertion	76
LTF	p.(L16=)	c.46C>T	.	chr3:46501307	3.80%	NM_002343.6	synonymous	79
EPHA3	p.(G388=)	c.1164A>G	.	chr3:89391098	5.80%	NM_005233.6	synonymous	1999
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	100.00%	NM_006206.6	synonymous	1980
PDGFRB	p.(A1096V)	c.3287C>T	.	chr5:149495360	6.28%	NM_002609.4	missense	1751
CILK1	p.(N176S)	c.527A>G	.	chr6:52883264	50.48%	NM_014920.5	missense	1999
EPHA7	p.(R488Q)	c.1463G>A	.	chr6:93979365	5.00%	NM_004440.4	missense	2000
ROS1	p.(R2269=)	c.6807A>G	.	chr6:117609892	5.70%	NM_002944.2	synonymous	2000
SYNE1	p.(S6263L)	c.18788C>T	.	chr6:152589218	49.43%	NM_182961.4	missense	352
TRRAP	p.(A3854T)	c.11560G>A	.	chr7:98609958	45.70%	NM_001244580.1	missense	1998
BRAF	p.(L721M)	c.2161T>A	.	chr7:140434537	6.70%	NM_004333.6	missense	2000
BRAF	p.(A718V)	c.2153C>T	.	chr7:140434545	6.46%	NM_004333.6	missense	1998
KMT2C	p.(N4807=)	c.14421C>T	.	chr7:151836799	50.60%	NM_170606.3	synonymous	2000

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
KAT6A	p.(P224L)	c.671C>T	.	chr8:41845011	5.26%	NM_006766.5	missense	95
CSMD3	p.(R3025C)	c.9073C>T	.	chr8:113301669	5.15%	NM_198123.2	missense	2000
CSMD3	p.(P2397L)	c.7190C>T	.	chr8:113332186	4.20%	NM_198123.2	missense	119
PTPRD	p.(T342=)	c.1026G>A	.	chr9:8518365	46.84%	NM_002839.4	synonymous	158
TAF1L	p.(M1444I)	c.4332G>A	.	chr9:32631246	5.65%	NM_153809.2	missense	177
TAF1L	p.(R1442Q)	c.4325G>A	.	chr9:32631253	10.45%	NM_153809.2	missense	134
TAF1L	p.(R1442W)	c.4324C>T	.	chr9:32631254	5.97%	NM_153809.2	missense	134
TAF1L	p.(I1440=)	c.4320C>T	.	chr9:32631258	8.99%	NM_153809.2	synonymous	89
TAF1L	p.(I1439=)	c.4317C>T	.	chr9:32631261	3.33%	NM_153809.2	synonymous	90
TAF1L	p.(S557N)	c.1670G>A	.	chr9:32633908	4.18%	NM_153809.2	missense	263
TAF1L	p.(S375=)	c.1125C>T	.	chr9:32634453	6.01%	NM_153809.2	synonymous	1998
XPA	p.(R258C)	c.772C>T	.	chr9:100437771	50.53%	NM_000380.4	missense	1999
RET	p.(R417C)	c.1249C>T	.	chr10:43604664	7.02%	NM_020975.6	missense	242
TET1	p.(A337E)	c.1010C>A	.	chr10:70333105	50.48%	NM_030625.3	missense	1999
BMPR1A	p.(A259=)	c.777G>A	.	chr10:88676992	49.64%	NM_004329.3	synonymous	1944
FGFR2	p.(R330W)	c.988C>T	.	chr10:123276929	5.21%	NM_000141.5	missense	96
FANCF	p.(L62=)	c.184C>T	.	chr11:22647173	6.96%	NM_022725.4	synonymous	1953
ZNF384	p.(Q501Hfs*48)	c.1503delG	.	chr12:6777110	99.69%	NM_001135734.2	frameshift Deletion	968
ARID2	p.(W266*)	c.798G>A	.	chr12:46230549	6.58%	NM_152641.4	nonsense	1428
ARID2	p.(S564P)	c.1690T>C	.	chr12:46242728	5.40%	NM_152641.4	missense	556
ERBB3	p.(R453H)	c.1358G>A	.	chr12:56487212	48.10%	NM_001982.4	missense	2000
DDIT3	p.(R179H)	c.536G>A	.	chr12:57910635	45.92%	NM_001195055.1	missense	1570
EP400	p.(H1156=)	c.3468C>T	.	chr12:132497580	6.55%	NM_015409.5	synonymous	2000
BIVM-ERCC5	p.(I746M)	c.2238A>G	.	chr13:103514060	47.78%	NM_001204425.2	missense	1986
ERCC5	p.(I292M)	c.876A>G	.	chr13:103514060	47.78%	NM_000123.4	missense	1986
LTK	p.(S356N)	c.1067G>A	.	chr15:41801258	6.05%	NM_002344.6	missense	2000
BLM	p.(G692*)	c.2074G>T	.	chr15:91306387	5.30%	NM_000057.4	nonsense	1999
IGF1R	p.(M588V)	c.1762A>G	.	chr15:99456445	51.15%	NM_000875.5	missense	2000
RNF213	p.(A3576T)	c.10726G>A	.	chr17:78327966	50.33%	NM_001256071.3	missense	1999
CDH2	p.(G513S)	c.1537G>A	.	chr18:25570122	51.45%	NM_001792.5	missense	2000
AKT2	p.(R176=)	c.528C>T	.	chr19:40747890	10.26%	NM_001626.6	synonymous	78
AKT2	p.(R176H)	c.527G>A	.	chr19:40747891	6.41%	NM_001626.6	missense	78

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
AURKC	p.(?)	c.-169G>A	.	chr19:57742448	17.35%	NM_001015878.2	unknown	392
TOP1	p.(?)	c.-45C>A	.	chr20:39657663	7.45%	NM_003286.4	unknown	2000
ERG	p.(S473=)	c.1419T>C	.	chr21:39755346	3.96%	NM_182918.4	synonymous	101
MYH9	p.(T1539=)	c.4617G>A	.	chr22:36684926	5.85%	NM_002473.6	synonymous	2000
KDM6A	p.(T1345A)	c.4033A>G	.	chrX:44969351	11.50%	NM_021140.3	missense	513

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: The KRAS inhibitor, sotorasib[9], is approved (2021) for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The FDA has granted breakthrough therapy designation (2021) to the small molecule inhibitor, adagrasib, for KRAS G12C positive in non-small cell lung cancer following prior systemic therapy[10].The small molecular inhibitor, RO-5126766, was also 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[11]. Additionally, onvansertib[12] was granted fast track designation (2020) for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab[13] and panitumumab[14], 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)[8]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[15].

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[16]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[17,18,19,20,21]. 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[22,23,24,25].

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[26]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[23,26]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[23,26]. 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)[23,26,27]. 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[26,28,29]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[30,31,32,33].

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[34] was expanded to include TMB-H (>/= 10 mut/Mb) solid tumors that have progressed on prior therapy. Indications

Biomarker Descriptions (continued)

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[31,35,36]. 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[37]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[38]. 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[39,40,41,42,43,44,45,46,47]. 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[48,49,50,51].

Relevant Therapy Summary

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

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	◑	✖	○	● (II)
atezolizumab	✖	✖	✖	✖	● (II)
atezolizumab + chemotherapy, atezolizumab + tiragolumab	✖	✖	✖	✖	● (II)
atezolizumab, nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
envafolimab	✖	✖	✖	✖	● (II)
ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
nivolumab	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
PRJ1-3024	✖	✖	✖	✖	● (I/II)
bapotulimab	✖	✖	✖	✖	● (I)
FT538, avelumab, nivolumab, pembrolizumab, atezolizumab	✖	✖	✖	✖	● (I)
PD-1 Inhibitor, natural killer cell therapy	✖	✖	✖	✖	● (I)
YBL-006	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

KRAS p.(G13D) c.38G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
atezolizumab + cobimetinib	✖	✖	✖	✖	● (II)
onvansertib, chemotherapy	✖	✖	✖	✖	● (II)
selumetinib, durvalumab	✖	✖	✖	✖	● (II)
ulixertinib, antimalarial	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
cobimetinib, atezolizumab, antimalarial	✖	✖	✖	✖	● (I/II)
DCC-3116, trametinib	✖	✖	✖	✖	● (I/II)
HH-2710	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	✖	✖	● (I/II)
neratinib, valproic acid	✖	✖	✖	✖	● (I/II)
OKI-179, binimetinib	✖	✖	✖	✖	● (I/II)
RMC-4630, pembrolizumab	✖	✖	✖	✖	● (I/II)
AZD-0364	✖	✖	✖	✖	● (I)
BBP-398	✖	✖	✖	✖	● (I)
CDK 4/6 inhibitor, MEK inhibitor	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
GGTI-2418, bortezomib	✖	✖	✖	✖	● (I)
GH35	✖	✖	✖	✖	● (I)
HBI 2376	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
neratinib, trametinib	✖	✖	✖	✖	● (I)
palbociclib, binimetinib	✖	✖	✖	✖	● (I)
PF-07284892, binimetinib	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RMC-4630, temuterkib	✖	✖	✖	✖	● (I)
trametinib, ruxolitinib	✖	✖	✖	✖	● (I)
ZEN-3694, binimetinib	✖	✖	✖	✖	● (I)

* 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 2022-08-17. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2022-08-05 **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 adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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

Tumor Mutational Burden (continued)

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - 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, 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 MSI-H central nervous system cancers have not been established.

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

- for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test.

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]

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

- in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

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 adult patients with advanced RCC.
- in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
- for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
- as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Tumor Mutational Burden-High (TMB-H) Cancer

Tumor Mutational Burden (continued)

- 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)

- for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.

Triple-Negative Breast Cancer (TNBC)

- for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test.

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.[2]

[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 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/2022/125514s133lbl.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 2022-08-01. 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: Pancreatic Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma; Metastatic (First-line therapy); Useful in certain circumstances
- Adenocarcinoma; Locally Advanced, Metastatic, Recurrent (Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 1.2022]

○ pembrolizumab

Cancer type: Chondrosarcoma, Ewing Sarcoma, 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 2.2022]

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

○ pembrolizumab

Cancer type: Cervical Small Cell Neuroendocrine Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2022]

Tumor Mutational Burden (continued)

pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2022]

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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 3.2022]

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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 2.2022]

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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 2.2022]

Tumor Mutational Burden (continued)

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 2.2022]

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pembrolizumab

Cancer type: Large Cell Neuroendocrine Carcinoma, Mixed Neuroendocrine Non-Neuroendocrine Neoplasm, Small Cell Neuroendocrine Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Poorly Differentiated; Advanced, Progression (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 1.2022]

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pembrolizumab

Cancer type: Neuroendocrine Tumor

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Well Differentiated; G3; Locally Advanced, Metastatic, Progression, Unresectable (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 1.2022]

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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 3.2022]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Castration-Resistant Prostate Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2022]

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pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 2.2022]

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pembrolizumab

Cancer type: Myxofibrosarcoma, Undifferentiated Pleomorphic Sarcoma, Undifferentiated Sarcoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 2.2022]

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pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Testicular Cancer [Version 2.2022]

Tumor Mutational Burden (continued)

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); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2022]

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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, Regional (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2022]

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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, Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2022]

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pembrolizumab

Cancer type: Endometrial Carcinoma, Endometrial Clear Cell Adenocarcinoma, Endometrial Serous Adenocarcinoma, Undifferentiated and Dedifferentiated Carcinomas of the Uterine Corpus, Uterine Corpus Carcinosarcoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2022]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Uterine Sarcoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2022]

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pembrolizumab

Cancer type: Castration-Resistant Prostate Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Adenocarcinoma; Visceral Metastases, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2022]

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 2022-08-01. For the most up-to-date information, search www.esmo.org.

Tumor Mutational Burden

○ pembrolizumab

Cancer type: Endometrial Carcinoma **Variant class:** Tumor Mutational Burden

ESMO Level of Evidence/Grade of Recommendation: III / B

Population segment (Line of therapy):
- Progression (Line of therapy not specified); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Endometrial Cancer [Annals of Oncology (2022), doi: https://doi.org/10.1016/j.annonc.2022.05.009.]

Clinical Trials in Taiwan region:

Clinical Trials Summary

Tumor Mutational Burden

NCT ID	Title	Phase
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	II
No NCT ID	A Multicenter Phase II Study Of Nivolumab Monotherapy In Recurrent And/Or Metastatic Gastrointestinal Cancer Patients With High Tumor Mutation Burden (TMB-H)	II
No NCT ID	TR Accompanied with the Study Titled A Multicenter Phase II Study of Nivolumab Monotherapy in Recurrent and/or Metastatic Gastrointestinal Cancer Patients with High Tumor Mutation Burden (TMB-H).	II
NCT03767075	Basket of Baskets: A Modular, Open-label, Phase II, Multicentre Study To Evaluate Targeted Agents in Molecularly Selected Populations With Advanced Solid Tumours	II
NCT04185831	MEGALiT - a Multicenter, Basket and Umbrella Explorative Trial on the Efficacy and Safety of Molecular Profile Selected Commercially Available Targeted Anti-cancer Drugs in Patients With Advanced Cancers Progressive on Standard Therapy	II
NCT04551521	Continuous ReAssessment With Flexible ExTension in Rare Malignancies - CRAFT: The NCT-PMO-1602 Phase II Trial	II
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT04632992	MyTACTIC: An Open-Label Phase II Study Evaluating Targeted Therapies in Patients Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response	II
NCT02029001	A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients with Progressive Locally-advanced or Metastatic Solid Tumors.	II
NCT04891198	An Open, Single-arm, Multi-center Phase II Clinical Study of ENVAFOLIMAB Single-agent Treatment in Patients With Advanced Solid Tumors	II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT02628067	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158).	II
NCT03838042	INFORM2 Exploratory Multinational Phase I/II Combination Study of Nivolumab and Entinostat in Children and Adolescents with Refractory High-risk Malignancies	I/II
NCT05315167	A Phase I/II, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Prime Efficacy of PRJ1-3024 in Subjects With Advanced Solid Tumors	I/II
NCT03666273	An Open-label, Phase I, First-in-human, Dose Escalation and Expansion Study to Evaluate the Safety, Tolerability, Maximum Tolerated or Administered Dose, Pharmacokinetics, Pharmacodynamics and Tumor Response Profile of the ILDR2 Function-blocking Antibody BAY1905254 in Patients With Advanced Solid Tumors	I
NCT05069935	A Phase I, Open-Label, Multicenter Study of FT538 in Combination With Monoclonal Antibodies in Subjects With Advanced Solid Tumors	I
No NCT ID	An Exploratory Study Of PD-1 Inhibitor Combined With NK Cells In The Treatment Of Advanced Malignant Solid Tumors	I

Clinical Trials Summary (continued)

Tumor Mutational Burden (continued)

NCT ID	Title	Phase
NCT04450901	A Phase I, Open-Label, Multicenter, Single Arm, Dose Escalation/Dose Expansion Study of YBL-006 in Patients With Advanced Solid Tumors	I

KRAS p.(G13D) c.38G>A

NCT ID	Title	Phase
NCT04214418	Phase I/II Open-label Study of Combination Therapy With The MEK Inhibitor, Cobimetinib, Immune Checkpoint Blockade, Atezolizumab, And The AUTOphagy Inhibitor, Hydroxychloroquine In KRAS-mutated Advanced Malignancies	I/II
NCT04752696	A Phase II Study of Onvansertib in Combination With Nanoliposomal Irinotecan, Leucovorin, and Fluorouracil for Second-Line Treatment of Patients With Metastatic Pancreatic Ductal Adenocarcinoma	II
NCT04348045	MAZEPPA: Phase II PRODIGE-GERCOR Study to Evaluate MAintenance Therapy With Olaparib or Selumetinib Plus Durvalumab According to BRCAness and KRAS Somatic Status Personalized in Metastatic Pancreatic Adenocarcinoma Patients	II
NCT05221320	A Phase II Basket Trial of Ulixertinib (BVD-523) in Combination With Hydroxychloroquine in Patients With Advanced GI Malignancies Harboring Mitogen-activated Protein Kinase (MAPK) Pathway Mutations (BVD-523-HCQ)	II
NCT04892017	A Phase 1/2, First-in-Human Study of DCC-3116 as Monotherapy and in Combination With RAS/MAPK Pathway Inhibitors in Patients With Advanced or Metastatic Solid Tumors With RAS/MAPK Pathway Mutations	I/II
NCT03919292	Phase 1/2 Study of Neratinib and Divalproex Sodium (Valproate) in Advanced Solid Tumors, With an Expansion Cohort in Ras-Mutated Cancers	I/II
NCT04615312	Phase I Clinical Study on the Safety and Tolerability of a CDK4 / 6 Inhibitor and a MEK Inhibitor in the Treatment of Metastatic Digestive System Tumors	I
NCT03284502	A Phase Ib, Open-label, Multicenter, Dose Escalation Study of the Safety, Tolerability, and Pharmacokinetics of HM95573 in Combination With Either Cobimetinib or Cetuximab in Patients With Locally Advanced or Metastatic Solid Tumors	I
NCT04870034	Perioperative Analysis of Binimetinib and Palbociclib in RAS-Driven Tumors	I
NCT04916236	Phase I/Ib Study With the Combination of RMC-4630 (SHP2 Inhibitor) and LY3214996 (ERK Inhibitor) in Metastatic KRAS Mutant CRC, PDAC and NSCLC	I
NCT04303403	Phase Ib Study Evaluating Safety and Tolerability of Combination Trametinib and Ruxolitinib in Patients with Advanced RAS Mutant Colorectal Cancer and Pancreatic Adenocarcinoma	I
NCT04145297	A Phase I Trial of Ulixertinib (BVD-523) and Hydroxychloroquine in Patients With Advanced MAPK-Mutated Gastrointestinal Adenocarcinomas	I
NCT03905148	A Phase Ib, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of a RAF Dimer Inhibitor BGB-283 in Combination With MEK Inhibitor PD-0325901 in Patients With Advanced or Refractory Solid Tumors	I/II
NCT03900442	Phase Ib Pharmacodynamic and Pharmacokinetic Study of the Geranylgeranyltransferase I Inhibitor PTX-100 (GGTI-2418) in Patients With Advanced Malignancies	I
NCT02079740	An Open Label, Two-Part, Phase Ib/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor Trametinib and the BCL2-Family Inhibitor Navitoclax (ABT-263) in Combination in Subjects With KRAS or NRAS Mutation-Positive Advanced Solid Tumors	I/II

Clinical Trials Summary (continued)

KRAS p.(G13D) c.38G>A (continued)

NCT ID	Title	Phase
NCT05111561	A Phase I Study of ZEN003694 in Combination With Binimetinib in Solid Tumors With RAS Pathway Alterations and Triple Negative Breast Cancer	I
NCT04418661	A Phase 1/2, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of SAR442720 in Combination With Pembrolizumab in Patients With Advanced Malignancies	I/II
NCT05010694	A Phase I Study Evaluating the Safety, Tolerability, Pharmacokinetic Characteristics, and Primary Antitumor Activity of GH35 in Patients With Advanced Solid Tumors With KRAS Mutation	I
NCT05163028	A Phase I, Open-Label, Dose Escalation of HBI-2376 in Patients With Advanced Malignant Solid Tumors Harboring KRAS or EGFR Mutations	I
NCT04418167	A Phase I Study of ERK1/2 Inhibitor JSI-1187 Administered as Monotherapy and in Combination With Dabrafenib for the Treatment of Advanced Solid Tumors With MAPK Pathway Mutations	I
NCT03065387	Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib, or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/ Amplification, or HER3/4 Mutation or KRAS Mutation	I
NCT05340621	A Phase Ib/II Study of OKI-179 Plus Binimetinib in Patients With Advanced Solid Tumors and Activating Mutations in the RAS Pathway (Phase 1b) and in Patients With Advanced NRAS-Mutated Melanoma (Phase II)	I/II
NCT04800822	A Phase I Open-Label, Multi-Center, Dose Escalation and Dose Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Evidence of Antitumor Activity of PF-07284892 (ARRY-558) as a Single Agent and in Combination Therapy in Participants With Advanced Solid Tumors	I
NCT04198818	A First-in-Human, Open Label, Phase I/II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HH2710 in Patients With Advanced Tumors	I/II
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	I
NCT04551521	Continuous ReAssessment With Flexible ExTension in Rare Malignancies - CRAFT: The NCT-PMO-1602 Phase II Trial	II
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT04305249	A Phase I, Open-Label, Multi-Center Dose Finding Study to Investigate the Safety, Pharmacokinetics, and Preliminary Efficacy of ATG-017 Monotherapy in Patients With Advanced Solid Tumors and Hematological Malignancies	I
NCT04528836	A Phase I/IB First-in-Human Study of the SHP2 Inhibitor BBP-398 (Formerly Known as IACS-15509) in Patients With Advanced Solid Tumors	I

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2022-08-17. For the most up-to-date information, search www.fda.gov.

KRAS p.(G13D) c.38G>A

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2021-09-24 **Variant class:** KRAS G13 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.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

- in combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf

panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2021-08-25 **Variant class:** KRAS G13 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/2021/125147s210lbl.pdf

KRAS p.(G13D) c.38G>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 2022-08-01. 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: Giant Cell Tumor of Soft Tissue **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "NCCN does not recommend this systemic treatment for GCTB since it is not technically a malignant tumor."

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2022]

KRAS p.(G13D) c.38G>A

cetuximab

Cancer type: Colon Cancer **Variant class:** KRAS G13D mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2022]

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cetuximab

Cancer type: Rectal Cancer **Variant class:** KRAS G13D mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2022]

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panitumumab

Cancer type: Colon Cancer **Variant class:** KRAS G13D mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2022]

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panitumumab

Cancer type: Rectal Cancer **Variant class:** KRAS G13D mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "The panel believes that patients with any known KRAS mutation, including G13D, should not be treated with cetuximab or panitumumab."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2022]

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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 1.2022]

KRAS p.(G13D) c.38G>A (continued)

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 1.2022]

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 1.2022]

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 1.2022]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2022-08-17. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G13D) c.38G>A

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2022-05-25 **Variant class:** KRAS exon 2 mutation

Reference:

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

KRAS p.(G13D) c.38G>A (continued)

panitumumab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2022-07-06 **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 2022-08-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G13D) c.38G>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)]

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)]

KRAS p.(G13D) c.38G>A (continued)

⊘ 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)]

⊘ 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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