



Sample Information

Patient Name: 潘思穎
Gender: Female
ID No.: A223080376
History No.: 29515977
Age: 54

Ordering Doctor: DOC1337C 洪逸平
Ordering REQ.: 0BYRPMZ
Signing in Date: 2022/08/18

Path No.: S111-97850
MP No.: TM22008
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S111-71107A
Percentage of tumor cells: 30%

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

Note:

Sample Cancer Type: Pancreatic Cancer

Table of Contents	Page
Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)	2
Biomarker Descriptions	3
Relevant Therapy Summary	5
Relevant Therapy Details	6
Clinical Trials Summary	16
Alert Details	16

Report Highlights
2 Relevant Biomarkers
4 Therapies Available
2 Clinical Trials

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	<i>Tumor Mutational Burden</i> 5.88 Mut/Mb measured	pembrolizumab ¹	pembrolizumab	2
IIC	<i>BRAF p.(T599dup) c.1796_1797insTAC</i> B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 12.06%	None	dabrafenib ipilimumab + nivolumab vemurafenib	1

Public data sources included in relevant therapies: FDA¹, NCCN, EMA², 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

*TP53 p.(E224Rfs*23) c.669delT*

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
BRAF	p.(T599dup)	c.1796_1797insTAC	.	chr7:140453138	12.06%	NM_004333.6	nonframeshift Insertion	1816
TP53	p.(E224Rfs*23)	c.669delT	.	chr17:7578179	13.30%	NM_000546.5	frameshift Deletion	902
PIK3CD	p.(R188W)	c.562C>T	.	chr1:9776098	15.51%	NM_005026.5	missense	316
MSH6	p.(H918=)	c.2754T>C	.	chr2:48027876	36.54%	NM_000179.3	synonymous	1998
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.6	nonframeshift Insertion	105
SETD2	p.(T254S)	c.761C>G	.	chr3:47165365	59.33%	NM_014159.6	missense	1704
BAP1	p.(?)	c.-56G>A	.	chr3:52443950	3.51%	NM_004656.4	unknown	57
PHF7	p.(?)	c.-2946C>T	.	chr3:52443950	3.51%	NM_016483.7	unknown	57
MAGI1	p.(R77Q)	c.230G>A	.	chr3:66023754	41.88%	NM_001033057.2	missense	1459
TNK2	p.(L364=)	c.1092G>A	.	chr3:195605458	56.17%	NM_001010938.2	synonymous	1994
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	99.80%	NM_006206.6	synonymous	1524
AFF1	p.(P451A)	c.1351C>G	.	chr4:88026972	48.35%	NM_001166693.2	missense	2000
ADGRB3	p.(G614=)	c.1842C>T	.	chr6:69703767	50.96%	NM_001704.3	synonymous	1452
SYNE1	p.(N3672=)	c.11016C>T	.	chr6:152674790	50.08%	NM_182961.4	synonymous	1999
AKAP9	p.(L1150F)	c.3448C>T	.	chr7:91641872	54.33%	NM_005751.4	missense	1999
BRAF	p.(D22N)	c.64G>A	.	chr7:140624440	43.95%	NM_004333.6	missense	794
ADGRA2	p.(D1313V)	c.3938A>T	.	chr8:37699794	49.90%	NM_032777.10	missense	1455
JAK2	p.(Q34R)	c.101A>G	.	chr9:5022088	63.90%	NM_004972.4	missense	2000
MLLT10	p.(A395T)	c.1183G>A	.	chr10:21962410	56.02%	NM_001195626.3	missense	980

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.07(002).

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
NUMA1	p.(R1070C)	c.3208C>T	.	chr11:71725341	50.42%	NM_006185.4	missense	1077
KMT2D	p.(A1841=)	c.5523C>T	.	chr12:49437156	48.20%	NM_003482.4	synonymous	2000
NLRP1	p.(V876M)	c.2626G>A	.	chr17:5445250	14.68%	NM_033004.4	missense	1349
NLRP1	p.(S113_T114dup)	c.331_332insCCACC T	.	chr17:5486106	48.96%	NM_033004.4	nonframeshift Insertion	1971
PGAP3	p.(S111=)	c.333G>T	.	chr17:37840949	44.47%	NM_033419.5	synonymous	1997
TCF3	p.(G431S)	c.1291_1293delGGC nsAGT	.	chr19:1619348	53.75%	NM_001136139.4	missense	240
SMARCA4	p.(Q201L)	c.602A>T	.	chr19:11097111	47.93%	NM_001128849.3	missense	459
AKT2	p.(M180I)	c.540G>A	.	chr19:40747878	13.51%	NM_001626.6	missense	74
AKT2	p.(R176=)	c.528C>T	.	chr19:40747890	7.55%	NM_001626.6	synonymous	53

Biomarker Descriptions

BRAF (B-Raf proto-oncogene, serine/threonine kinase)

Background: The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1 (CRAF). BRAF is among the most commonly mutated kinases in cancer. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, dedifferentiation, and survival^{1,2}. BRAF mutations are categorized into three distinct functional classes namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF³. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead^{3,4,5}.

Alterations and prevalence: Recurrent somatic mutations in BRAF are observed in 40-60% of melanoma and thyroid cancer, approximately 10% of colorectal cancer, and about 2% of non-small cell lung cancer (NSCLC)^{6,7,8,9,10}. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types^{4,11}. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R/, G464V/E/, and BRAF fusions⁴. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I⁴. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer, and prevalent in histiocytic neoplasms^{12,13,14}. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11 as well as additional codons flanking V600 in the activation loop¹¹. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer^{7,10}. BRAF fusions are mutually exclusive to BRAF V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types^{15,16,17,18,19}. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain leading to constitutive kinase activation^{5,15,17}.

Potential relevance: Vemurafenib²⁰ (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive⁴. BRAF kinase inhibitors including dabrafenib²¹ (2013) and encorafenib²² (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib²² is approved in combination with cetuximab²³ (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations⁴. Trametinib²⁴ (2013) and binimetinib²⁵ (2018) were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC. The combinations of dabrafenib/trametinib (2015) and vemurafenib/cobimetinib²⁶ (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017) with a BRAF V600E mutation. The PD-L1 antibody, atezolizumab²⁷, has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. In 2018, binimetinib²⁸ was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The pan-RAF kinase inhibitor, tovorafenib (DAY-101), was granted breakthrough therapy designation (2020) by the FDA for pediatric

Biomarker Descriptions (continued)

patients with advanced low-grade glioma harboring activating RAF alterations²⁹. The ERK inhibitor ulixertinib³⁰ was also granted a fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma³¹. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification and alternative splice transcripts as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)^{32,33,34,35,36,37,38}. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported¹⁹.

TP53 (tumor protein p53)

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential³⁹. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers^{40,41}.

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)^{7,10,42,43,44,45}. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282^{7,10}. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes^{46,47,48,49}.

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation⁵⁰. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,⁵¹ and breakthrough designation⁵² (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation^{53,54}. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL)^{55,56,57,58}. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant⁵⁹. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system⁶⁰.

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 sequence⁶¹. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB^{62,63,64,65,66}. 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^{67,68,69,70}.

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 cancers⁷¹. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb^{68,71}. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb^{68,71}. 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)^{68,71,72}. 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^{71,73,74}. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb^{75,76,77,78}.

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 pembrolizumab⁷⁹ 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

Biomarker Descriptions (continued)

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^{76,80,81}. 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 reported⁸². Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB⁸³. 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^{84,85,86,87,88,89,90,91,92}. 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^{93,94,95,96}.

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)

BRAF p.(T599dup) c.1796_1797insTAC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
dabrafenib	✕	○	✕	✕	✕
vemurafenib	✕	○	✕	✕	✕
ipilimumab + nivolumab	✕	✕	✕	○	✕
belvarafenib	✕	✕	✕	✕	● (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 2022-06-15. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor

Label as of: 2022-05-20

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) $\geq 1\%$] 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 $\geq 1\%$) 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 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).

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 not MSI-H or dMMR, 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

- 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

Tumor Mutational Burden (continued)

- 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/2022/125514s123lbl.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 2022-06-01. 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 3.2022]

☐ 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]

○ 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 2.2022]

○ 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]

○ 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 1.2022]

○ 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]

○ 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]

○ 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 1.2022]

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]

○ 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]

○ 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]

○ 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]

○ 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]

○ 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]

○ 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]

○ 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]

BRAF p.(T599dup) c.1796_1797insTAC

○ dabrafenib

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma Variant class: BRAF mutation

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]

○ vemurafenib

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma Variant class: BRAF mutation

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]

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 2022-06-01. For the most up-to-date information, search www.esmo.org.

BRAF p.(T599dup) c.1796_1797insTAC

☐ ipilimumab + nivolumab

Cancer type: Melanoma

Variant class: BRAF mutation

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

Population segment (Line of therapy):

- Asymptomatic, Brain Metastases (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-EANO-ESMO Brain Metastasis from Solid Tumours [Ann Oncol (2021), <https://doi.org/10.1016/j.annonc.2021.07.016>]

Clinical Trials in Taiwan region:

Clinical Trials Summary

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

BRAF p.(T599dup) c.1796_1797insTAC

NCT ID	Title	Phase
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II

Alerts Informed By Public Data Sources

Current NCCN Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

NCCN information is current as of 2022-06-01. 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]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

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