Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 曾姿綺
Gender: Female
ID No.: T226310000
History No.: 49010131
Age: 5

Ordering Doctor: DOC6633K 王緯歆
Ordering REQ.: D72LLJ9
Signing in Date: 2022/10/27

Path No.: S111-97947
MP No.: TM22013
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S111-40746A
Percentage of tumor cells: 80%

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

Note:

Sample Cancer Type: Other Solid Tumor

Table of Contents

Report Highlights

1 Relevant Biomarkers
1 Therapies Available
2 Clinical Trials

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*Tumor Mutational Burden* 2.55 Mut/Mb measured	None	**pembrolizumab** [1]	2

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.

Prevalent cancer biomarkers without relevant evidence based on included data sources

GNAS p.(R201C) c.601C>T

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

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
GNAS	p.(R201C)	c.601C>T	COSM27887	chr20:57484420	32.73%	NM_000516.6	missense	385
NRAS	p.(L53=)	c.159G>A	.	chr1:115256552	44.40%	NM_002524.5	synonymous	2000
PIK3C2B	p.(A866=)	c.2598T>G	.	chr1:204415164	48.92%	NM_002646.4	synonymous	1999
PIK3C2B	p.(P311=)	c.933G>T	.	chr1:204437998	50.54%	NM_002646.4	synonymous	1102
FANCD2	p.(Q65H)	c.195G>C	.	chr3:10074646	50.38%	NM_033084.6	missense	1999
RAF1	p.(V21M)	c.61G>A	.	chr3:12660160	49.87%	NM_002880.3	missense	1997
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	99.90%	NM_002343.6	nonframeshift Insertion	1974
GATA2	p.(T477=)	c.1431C>T	.	chr3:128199874	48.99%	NM_032638.5	synonymous	1478
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	99.90%	NM_006206.6	synonymous	1985
NOTCH4	p.([P271=;D272G])	c.813_815delAGAinsGGG	.	chr6:32188640	50.73%	NM_004557.4	synonymous, missense	1995
NOTCH4	p.(L106I)	c.316C>A	.	chr6:32190423	50.83%	NM_004557.4	missense	1999
PKHD1	p.(G2648S)	c.7942G>A	.	chr6:51712738	54.31%	NM_138694.4	missense	1994
SYNE1	p.(K4121S)	c.12362_12363delAGinsGT	.	chr6:152658141	50.63%	NM_182961.4	missense	1995
SYNE1	p.(K4121R)	c.12362A>G	.	chr6:152658142	48.62%	NM_182961.4	missense	1995
RPS6KA2	p.(R730H)	c.2189G>A	.	chr6:166826287	51.24%	NM_001006932.3	missense	1089
KAT6A	p.(E1109del)	c.3326_3328delAAG	.	chr8:41794797	49.20%	NM_006766.5	nonframeshift Deletion	1988
TAF1L	p.(I396L)	c.1186A>T	.	chr9:32634392	51.43%	NM_153809.2	missense	1999
KAT6B	p.(E1099Kfs*14)	c.3294_3297delAGAA	.	chr10:76781909	99.80%	NM_012330.4	frameshift Deletion	1955
CYP2C19	p.(R261W)	c.781C>T	.	chr10:96541716	47.13%	NM_000769.4	missense	1950
KMT2A	p.(N3797=)	c.11391T>C	.	chr11:118390741	52.51%	NM_001197104.2	synonymous	179
ZNF384	p.(Q501Hfs*48)	c.1503delG	.	chr12:6777110	99.54%	NM_001135734.2	frameshift Deletion	1311
ARID2	p.(T938S)	c.2813C>G	.	chr12:46244719	51.15%	NM_152641.4	missense	2000
PTPN11	p.(T330=)	c.990A>C	.	chr12:112915717	49.26%	NM_002834.5	synonymous	743
FLT1	p.(A967=)	c.2901G>A	.	chr13:28896979	47.75%	NM_002019.4	synonymous	1996
IRS2	p.(Q1269P)	c.3806A>C	.	chr13:110434595	32.32%	NM_003749.3	missense	625
TRIP11	p.(I1747V)	c.5239A>G	.	chr14:92454649	46.57%	NM_004239.4	missense	1604
IDH2	p.(P23R)	c.68C>G	.	chr15:90645555	53.51%	NM_002168.4	missense	370
CREBBP	p.(Q2333=)	c.6999G>A	.	chr16:3778049	40.05%	NM_004380.3	synonymous	1151
RNF213	p.(E2191K)	c.6571G>A	.	chr17:78318706	47.40%	NM_001256071.3	missense	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
BCL2	p.(A42Pfs*54)	c.124delG	.	chr18:60985775	56.01%	NM_000633.2	frameshift Deletion	1132
BCL2	p.(P40Rfs*112)	c.119_127delCGGGGGCCGinsGGGGCCA	.	chr18:60985773	41.25%	NM_000633.2	frameshift Block Substitution	1132
BCL3	p.(P383=)	c.1149C>T	.	chr19:45262070	49.95%	NM_005178.5	synonymous	1998
TAF1	p.(R1182H)	c.3545G>A	.	chrX:70617241	5.36%	NM_004606.5	missense	112

Biomarker Descriptions

GNAS (GNAS complex locus)

Background: GNAS encodes the stimulatory alpha subunit of the guanine nucleotide-binding protein (G-protein). G-protein alpha subunits bind guanine nucleotide, hydrolyze GTP, and interact with specific receptor and effector molecules. GNAS links receptor-ligand interactions with the activation of adenylyl cyclase and a variety of cellular responses.

Alterations and prevalence: Recurrent somatic mutations at amino acid positions R201 and Q227 lead to constitutive activation of GNAS and are observed in pancreatic cancer (3%) as well as lung adenocarcinoma, colorectal, and gastric cancers (approximately 1%)[1,2,3,4]. In colorectal cancer, GNAS mutations were enriched in right-sided tumors[5]. In lung adenocarcinoma, GNAS mutations were enriched in female patients with invasive mucinous adenocarcinoma[4]. Specifically, GNAS mutations in these patients were exclusively observed at R201C/H, along with concurrent mutations in KRAS or BRAF.[4].

Potential relevance: Currently, no therapies are approved for GNAS aberrations. A case study of a patient with appendiceal adenocarcinoma harboring a GNAS R201H mutation reported a progression-free survival (PFS) of 4 months when treated with the MEK inhibitor trametinib[6].

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[7]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[8,9,10,11,12]. 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[13,14,15,16].

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[17]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[14,17]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[14,17]. 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)[14,17,18]. 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[17,19,20]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[21,22,23,24].

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[25] 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.

Biomarker Descriptions (continued)

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[22,26,27]. 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[28]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[29]. 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[30,31,32,33,34,35,36,37,38]. 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[39,40,41,42].

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)

* 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: 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]

○ 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]

Tumor Mutational Burden (continued)

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]

---

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]

---

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]

Tumor Mutational Burden (continued)

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 3.2022]

---

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]

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]

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
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

Alerts Informed By Public Data Sources

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]

Signatures

Testing Personnel:

2022.10.28
17:00:14 +08'00'

Laboratory Supervisor:

2022.10.28
17:00:29 +08'00'

Pathologist:

2022.10.28
17:00:42 +08'00'

References

1. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
2. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
3. Landis et al. GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenylyl cyclase in human pituitary tumours. Nature. 1989 Aug 31;340(6236):692-6. PMID: 2549426
4. Ritterhouse et al. GNAS mutations in primary mucinous and non-mucinous lung adenocarcinomas. Mod. Pathol. 2017 Dec;30(12):1720-1727. PMID: 28776576
5. Loree et al. Classifying Colorectal Cancer by Tumor Location Rather than Sidedness Highlights a Continuum in Mutation Profiles and Consensus Molecular Subtypes. Clin. Cancer Res. 2018 Mar 1;24(5):1062-1072. PMID: 29180604
6. Ang et al. Clinical Benefit from Trametinib in a Patient with Appendiceal Adenocarcinoma with a GNAS R201H Mutation. Case Rep Oncol. 2017 Jun 22;10(2):548-552. doi: 10.1159/000477562. eCollection 2017 May-Aug. PMID: 28868010
7. Yuan et al. Novel technologies and emerging biomarkers for personalized cancer immunotherapy. 4:3. PMID: 26788324
8. Temko et al. Somatic POLE exonuclease domain mutations are early events in sporadic endometrial and colorectal carcinogenesis, determining driver mutational landscape, clonal neoantigen burden and immune response. J. Pathol. 2018 Jul;245(3):283-296. PMID: 29604063
9. Mehnert et al. Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer. 126(6):2334-40. PMID: 27159395
10. Bouffet et al. Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency. J. Clin. Oncol. 2016 Jul 1;34(19):2206-11. PMID: 27001570
11. Humphris et al. Hypermutation In Pancreatic Cancer. Gastroenterology. 2017 Jan;152(1):68-74.e2. PMID: 27856273
12. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
13. Snyder et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N. Engl. J. Med. 2014 Dec 4;371(23):2189-2199. PMID: 25409260
14. Alexandrov et al. Signatures of mutational processes in human cancer. Nature. 2013 Aug 22;500(7463):415-21. PMID: 23945592
15. Rizvi et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015 Apr 3;348(6230):124-8. PMID: 25765070
16. Van et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science. 2015 Oct 9;350(6257):207-211. PMID: 26359337
17. Chalmers et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. 9:34. PMID: 28420421
18. Govindan et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell. 2012 Sep 14;150(6):1121-34. PMID:22980976
19. Endris et al. Measurement of tumor mutational burden (TMB) in routine molecular diagnostics: in silico and real-life analysis of three larger gene panels. Int. J. Cancer. 2019 May 1;144(9):2303-2312. PMID: 30446996
20. Meléndez et al. Methods of measurement for tumor mutational burden in tumor tissue. Transl Lung Cancer Res. 2018 Dec;7(6):661-667. PMID: 30505710
21. Hellmann et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N. Engl. J. Med. 2018 May 31;378(22):2093-2104. PMID: 29658845
22. Ready et al. First-Line Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers. J. Clin. Oncol. 2019 Apr 20;37(12):992-1000. PMID: 30785829
23. Alborelli et al. Tumor mutational burden assessed by targeted NGS predicts clinical benefit from immune checkpoint inhibitors in non-small cell lung cancer. J. Pathol. 2020 Jan;250(1):19-29. PMID: 31471895
24. Heeke et al. In-house Implementation of Tumor Mutational Burden Testing to Predict Durable Clinical Benefit in Non-small Cell Lung Cancer and Melanoma Patients. Cancers (Basel). 2019 Aug 29;11(9). PMID: 31470674
25. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s133lbl.pdf
26. F. et al. CheckMate 817: First-Line Nivolumab + Ipilimumab in Patients with ECOG PS 2 and Other Special Populations with Advanced NSCLC. Volume 14, Issue 10, Supplement, Pages S214–S215. Abstract OA04.02
27. Zhu et al. Association Between Tumor Mutation Burden (TMB) and Outcomes of Cancer Patients Treated With PD-1/PD-L1 Inhibitions: A Meta-Analysis. Front Oncol, 9:1161, 04 Nov 2019. PMID: 31258479

References (continued)

28. Castellanos et al. Tumor mutational burden (TMB) and PD-L1 expression as predictors of response to immunotherapy (IO) in NSCLC. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 2630-2630. Abstract 2630
29. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]
30. NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2022]
31. NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2022]
32. NCCN Guidelines® - NCCN-Testicular Cancer [Version 2.2022]
33. NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2022]
34. NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2022]
35. NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2022]
36. NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]
37. NCCN Guidelines® - NCCN-Ovarian Cancer [Version 3.2022]
38. NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]
39. https://www.focr.org/tmb
40. http://www.iqnpath.org/category/tmb
41. Stenzinger et al. Tumor mutational burden standardization initiatives: Recommendations for consistent tumor mutational burden assessment in clinical samples to guide immunotherapy treatment decisions. Genes Chromosomes Cancer. 2019 Aug;58(8):578-588. PMID: 30664300
42. Merino et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. J Immunother Cancer. 2020 Mar;8(1). PMID: 32217756