Taipei Veterans General Hospital

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Sample Information

Patient Name: 王聖玉
Gender: Female
ID No.: A223119854
History No.: 25548270
Age: 57

Ordering Doctor: DOC1322F 趙毅
Ordering REQ.: D69DCEL
Signing in Date: 2021/06/25

Path No.: S110-98988
MP No.: TM21010
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S110-18643B
Percentage of tumor cells: 60%
Note:

Sample Cancer Type: Leiomyosarcoma

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*TET2 p.(F868L) c.2604T>G* tet methylcytosine dioxygenase 2 Allele Frequency: 81.35%	None	None	1
	Tumor Mutational Burden 3.34 Mut/Mb measured	**pembrolizumab** [1]	pembrolizumab	17

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
TET2	p.(F868L)	c.2604T>G	COSM87107	chr4:106157703	81.35%	NM_001127208.2	missense	976
DDR2	p.(R680C)	c.2038C>T	.	chr1:162745623	40.35%	NM_006182.4	missense	2000
RNASEL	p.(Q42=)	c.126G>A	.	chr1:182555816	41.64%	NM_021133.4	synonymous	1998
PIK3C2B	p.(K837N)	c.2511G>C	.	chr1:204415251	43.80%	NM_002646.4	missense	2000
EML4	p.(?)	c.-72C>T	.	chr2:42396680	73.28%	NM_019063.5	unknown	116
MSH6	p.(M662K)	c.1985T>A	.	chr2:48027107	70.05%	NM_000179.3	missense	828
LRP1B	p.(N2626S)	c.7877A>G	.	chr2:141283562	70.10%	NM_018557.3	missense	1716
LRP1B	p.(S2462=)	c.7386C>T	.	chr2:141299349	71.21%	NM_018557.3	synonymous	667
STK36	p.(Q49K)	c.145C>A	.	chr2:219538408	68.32%	NM_015690.5	missense	1998
LTF	p.(V274I)	c.820G>A	.	chr3:46492047	41.37%	NM_002343.6	missense	1999
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	99.77%	NM_002343.6	nonframeshift Insertion	1326
PDGFRA	p.(S478Pfs*11)	c.1432delT	.	chr4:55139770	77.74%	NM_006206.6	frameshift Deletion	1833
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	99.86%	NM_006206.6	synonymous	1475
NSD1	p.(L2425=)	c.7275A>G	.	chr5:176721644	39.18%	NM_022455.4	synonymous	1996
DST	p.(P4497S)	c.13489C>T	.	chr6:56365928	45.97%	NM_001144769.5	missense	1999
EPHB4	p.(P983=)	c.2949G>A	.	chr7:100401098	39.69%	NM_004444.5	synonymous	194
KMT2C	p.(P2012S)	c.6034C>T	.	chr7:151878911	40.72%	NM_170606.3	missense	1999
CDKN2B	p.(G42R)	c.124G>A	.	chr9:22008829	4.84%	NM_004936.4	missense	62
FANCG	p.(P590A)	c.1768C>G	.	chr9:35074206	38.83%	NM_004629.2	missense	1996
TLR4	p.(A121S)	c.361G>T	.	chr9:120474767	83.46%	NM_138554.5	missense	1481
TET1	p.(A1530=)	c.4590C>T	.	chr10:70426930	42.13%	NM_030625.3	synonymous	1830
KAT6B	p.(E1100Rfs*36)	c.3298_3299delGA	.	chr10:76781913	99.50%	NM_012330.4	frameshift Deletion	605
KAT6B	p.(P2020S)	c.6058C>T	.	chr10:76790640	57.76%	NM_012330.4	missense	1960
ATM	p.(S2797=)	c.8391T>C	.	chr11:108214071	54.32%	NM_000051.3	synonymous	937
ZNF384	p.(Q501Hfs*48)	c.1503delG	.	chr12:6777110	100.00%	NM_001135734.2	frameshift Deletion	357
ARID2	p.(P10T)	c.28C>A	.	chr12:46123647	55.46%	NM_152641.4	missense	1996
KMT2D	p.(P2349L)	c.7046C>T	.	chr12:49434507	40.37%	NM_003482.4	missense	1999
LAMP1	p.(D315E)	c.945C>A	.	chr13:113975873	17.28%	NM_005561.4	missense	1997
NIN	p.(M1804T)	c.5411T>C	.	chr14:51208337	44.95%	NM_020921.3	missense	1179
BLM	p.(G441V)	c.1322G>T	.	chr15:91303925	7.70%	NM_000057.4	missense	1999
MYH11	p.(S100=)	c.300C>T	.	chr16:15931810	16.15%	NM_001040114.1	synonymous	1777

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
NLRP1	p.(R536Q)	c.1607G>A	.	chr17:5462409	81.40%	NM_033004.4	missense	1301
NF1	p.(T1648A)	c.4942A>G	.	chr17:29652944	58.84%	NM_001042492.3	missense	1222
ERBB2	p.(R1230P)	c.3689G>C	.	chr17:37884218	37.77%	NM_004448.3	missense	871
TCF3	p.(G431S)	c.1291_1293delGGCinsAGT	.	chr19:1619348	50.84%	NM_001136139.4	missense	596
KEAP1	p.(S146C)	c.437C>G	.	chr19:10610273	37.64%	NM_203500.2	missense	1998
SMARCA4	p.(N519=)	c.1557C>T	.	chr19:11105641	49.80%	NM_001128849.3	synonymous	1998
AKT2	p.(R176=)	c.528C>T	.	chr19:40747890	4.69%	NM_001626.6	synonymous	64
MIR8085			.	chr19:45261477	37.78%	NR_107052.1		945
TOP1	p.(I482=)	c.1446C>T	.	chr20:39741559	50.48%	NM_003286.4	synonymous	1997
ITGB2	p.(Q440H)	c.1320G>C	.	chr21:46311816	42.58%	NM_000211.5	missense	1677
MYH9	p.(E488=)	c.1464G>A	.	chr22:36710280	4.12%	NM_002473.6	synonymous	170
SSX1	p.(Q173=)	c.519G>A	.	chrX:48125774	3.80%	NM_005635.4	synonymous	79

Biomarker Descriptions

TET2 (tet methylcytosine dioxygenase 2)

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to a family of ten-eleven translocation (TET) proteins that also includes TET1 and TET3[1]. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[2,3]. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded ß-helix domain (DSBH)[4]. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[1,2,3]

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40%-60% chronic myelomonocytic leukemia (CMML)[5]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[2,6]. TET2 mutations are also observed in 9% of uterine, 8% of melanoma and acute myeloid leukemia (AML), as well as 6% of diffuse large B-cell lymphoma (DLBCL).

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[7,8]. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia[8,9]

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[10]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[11,12,13,14,15]. 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[16,17,18,19].

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[20]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[17,20]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[17,20]. 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)[17,20,21]. There is

Biomarker Descriptions (continued)

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[20,22,23]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[24,25,26,27].

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[28] was expanded to include TMB-H (>/= 10 mut/Mb) solid tumors that have progressed on prior therapy. Indications have been expanded for these ICIs to include several other cancer types including NSCLC, advanced renal cell carcinoma, classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability (MSI)-High or mismatch repair deficient (dMMR) colorectal cancer, and hepatocellular carcinoma. Atezolizumab (2016), avelumab (2017), and durvalumab (2017), that target programmed death-ligand 1 (PD-L1), were subsequently approved by the FDA. However, the predictive biomarkers that underlie the clinical benefits of these approved immunotherapies, including TMB, are under active investigation. Several published studies including the CheckMate 586 and CheckMate 817 clinical trials have concluded that high TMB was associated with improved response to FDA approved checkpoint inhibitors[25,29,30]. 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[31]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[32]. 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[33,34,35,36,37,38,39,40,41]. 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[42,43,44,45].

Relevant Therapy Summary

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

TET2 p.(F868L) c.2604T>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ATSP-7041	✖	✖	✖	✖	● (I)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	○	✖	✖	● (II)
atezolizumab	✖	✖	✖	✖	● (II)
atezolizumab + chemotherapy	✖	✖	✖	✖	● (II)
atezolizumab, nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (II)

* 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

Tumor Mutational Burden (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
chemotherapy, tremelimumab, durvalumab	✖	✖	✖	✖	● (I/II)
cobimetinib, atezolizumab	✖	✖	✖	✖	● (I/II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BAY1905254	✖	✖	✖	✖	● (I)
nivolumab, ipilimumab	✖	✖	✖	✖	● (I)
pembrolizumab, targinine	✖	✖	✖	✖	● (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 2021-04-14. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2021-03-22 **Variant class:** Tumor Mutational Burden

Indications and usage:

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

Melanoma

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

Non-Small Cell Lung Cancer (NSCLC)

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

Small Cell Lung Cancer (SCLC)

- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[1]

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 cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[1]
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

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

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

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

Gastric Cancer

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

Esophageal Cancer

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

Cervical Cancer

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

Hepatocellular Carcinoma (HCC)

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

Merkel Cell Carcinoma (MCC)

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

Renal Cell Carcinoma (RCC)

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

Endometrial Carcinoma

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

Tumor Mutational Burden-High (TMB-H) Cancer

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

Cutaneous Squamous Cell Carcinoma (cSCC)

Tumor Mutational Burden (continued)

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

Triple-Negative Breast Cancer (TNBC)

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

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

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

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

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

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf

Current NCCN Information

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

NCCN information is current as of 2021-04-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

Tumor Mutational Burden

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

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

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

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

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

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

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 1.2021]

Tumor Mutational Burden (continued)

pembrolizumab

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

NCCN Recommendation category: 2A

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

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

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pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2021]

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pembrolizumab

Cancer type: Cholangiocarcinoma, Liver Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Gallbladder Cancer, Intrahepatic, Extrahepatic; Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 1.2021]

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pembrolizumab

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

NCCN Recommendation category: 2A

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

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

Tumor Mutational Burden (continued)

pembrolizumab

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

NCCN Recommendation category: 2A

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

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

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pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2021]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Ewing Sarcoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2B

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

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

Clinical Trials Summary

TET2 p.(F868L) c.2604T>G

NCT ID	Title	Phase
NCT03654716	Phase I Study of the Dual MDM2/MDMX Inhibitor ALRN-6924 in Pediatric Cancer	I

Tumor Mutational Burden

NCT ID	Title	Phase
NCT03241745	Phase II Trial of Single-Agent Nivolumab in Patients With Microsatellite Unstable/Mismatch Repair Deficient/Hypermutated Uterine Cancer	II
NCT04216953	A Multicentre, Open-label, Phase I-II Study Evaluating the Combination of a MEK Inhibitor and a PDL1 Inhibitor in Pediatric and Adult Patients With Locally Advanced and/or Metastatic Soft Tissue Sarcoma.	I/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
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
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	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 MOST: My own specific treatment	II
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT03668119	A Randomized, Open-Label, Phase II Study of Nivolumab in Combination With Ipilimumab or Nivolumab Monotherapy in Participants With Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)	II
NCT02628067	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)	II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II

Clinical Trials Summary (continued)

Tumor Mutational Burden (continued)

NCT ID	Title	Phase
NCT03518606	A Phase I/II Basket Trial Evaluating A Combination Of Metronomic Oral Vinorelbine Plus Anti-PD-L1/ Anti-CTLA4 ImmunothErapy In Patients With Advanced Solid Tumour	I/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
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
NCT04500548	3CI Study: Childhood Cancer Combination Immunotherapy. Phase Ib and Expansion Study of Nivolumab Combination Immunotherapy in Children, Adolescent, and Young Adult (CAYA) Patients With Relapsed/Refractory Hypermutant Cancers	I
NCT03236935	Phase Ib Trial of L-NMMA in Combination With Pembrolizumab in Patients With Melanoma, Non-Small Cell Lung Cancer, Head and Neck Squamous Cell Carcinoma, Classical Hodgkin Lymphoma, Urothelial Carcinoma, Cervical Cancer, Esophageal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Primary Mediastinal Large B-cell Lymphoma, Renal Cell Carcinoma, Small Cell Lung Cancer, Microsatellite Instability-High/Mismatch Repair Deficient Cancer, or for the Treatment of Adult Patients With Unresectable or Metastatic Tumor Mutational Burden-High Solid Tumors	I

Signatures

Testing Personnel:

2021.06.25
12:16:06 +08'00'

Laboratory Supervisor:

2021.06.25
12:16:16 +08'00'

Pathologist:

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