



## Sample Information

**Patient Name:** 王本明  
**Gender:** Male  
**ID No.:** A120905169  
**History No.:** 15228634  
**Age:** 61

**Ordering Doctor:** DOC5394K 胡果正  
**Ordering REQ.:** 0BFDAWS  
**Signing in Date:** 2021/05/12

**Path No.:** S110-98768  
**MP No.:** TM21006  
**Assay:** Oncomine Tumor Mutation Load Assay  
**Sample Type:** FFPE  
**Block No.:** S110-15924A  
**Percentage of tumor cells:** 30%  
**Note:**

## Sample Cancer Type: Liver Cancer

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**Report Highlights**  
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1 Therapies Available  
26 Clinical Trials

## Relevant Liver Cancer Variants

Gene	Finding
NTRK1	Not detected
NTRK3	Not detected

## Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	TP53 p.(?) c.994-2A>T tumor protein p53 Allele Frequency: 39.21%	None	None	12

**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.

## Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
	<i>Tumor Mutational Burden</i> 4.17 Mut/Mb measured	pembrolizumab <sup>1</sup>	pembrolizumab	17

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.

## 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
TP53	p.(?)	c.994-2A>T	.	chr17:7574035	39.21%	NM_000546.5	unknown	1997
TRIM33	p.(I640V)	c.1918A>G	.	chr1:114964201	69.48%	NM_015906.3	missense	1822
PDE4DIP	p.(S1662N)	c.4985G>A	.	chr1:144873972	43.23%	NM_001198834.3	missense	1492
FH	p.(=)	c.447A>T	.	chr1:241675375	36.35%	NM_000143.3	synonymous	2000
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.5	nonframeshift Insertion	687
PIK3CB	p.(R896L)	c.2687G>T	.	chr3:138382857	52.60%	NM_006219.2	missense	1998
TNK2	p.(=)	c.1671C>T	.	chr3:195597046	42.38%	NM_001010938.1	synonymous	1017
PDGFRA	p.(S478fs)	c.1432delT	.	chr4:55139770	66.06%	NM_006206.5	frameshift Deletion	1989
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	100.00%	NM_006206.5	synonymous	1980
ADGRL3	p.(G1164E)	c.3491G>A	.	chr4:62903552	16.31%	NM_015236.5	missense	1772
PKHD1	p.(A313V)	c.938C>T	.	chr6:51929791	31.82%	NM_138694.3	missense	1999
SYNE1	p.(=)	c.22137C>T	.	chr6:152539446	47.55%	NM_182961.3	synonymous	1998
SYNE1	p.(=)	c.16038A>G	.	chr6:152642901	42.72%	NM_182961.3	synonymous	1999
SYNE1	p.(C4575F)	c.13724G>T	.	chr6:152652096	53.86%	NM_182961.3	missense	1994
SYNE1	p.(K4121S)	c.12362_12363delAG insGT	.	chr6:152658141	41.06%	NM_182961.3	missense	1990
SYNE1	p.(K4121R)	c.12362A>G	.	chr6:152658142	58.19%	NM_182961.3	missense	1990
SYNE1	p.(M3337K)	c.10010T>A	.	chr6:152686117	28.23%	NM_182961.3	missense	1998
NBN	p.(Q371L)	c.1112A>T	.	chr8:90970965	18.15%	NM_002485.4	missense	1543
TAF1L	p.(=)	c.456C>T	.	chr9:32635122	3.95%	NM_153809.2	synonymous	152
TAF1L	p.(?)	c.-20T>A	.	chr9:32635597	19.54%	NM_153809.2	unknown	1438
NUP214	p.(T1765A)	c.5293A>G	.	chr9:134074174	12.44%	NM_005085.3	missense	772
RET	p.(A472T)	c.1414G>A	.	chr10:43606805	5.45%	NM_020975.4	missense	55
ATM	p.(E1959A)	c.5876A>C	.	chr11:108181000	44.42%	NM_000051.3	missense	1909
ARID2	p.(=)	c.1806G>A	.	chr12:46243453	59.10%	NM_152641.3	synonymous	1951

**Disclaimer:** The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.05(003).

## 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
NKX2-1	p.(=)	c.906G>C	.	chr14:36986783	37.50%	NM_001079668.2	synonymous	760
NIN	p.(S1965C)	c.5894C>G	.	chr14:51196425	61.05%	NM_020921.3	missense	2000
NIN	p.(=)	c.399G>A	.	chr14:51259466	42.00%	NM_020921.3	synonymous	2000
KNL1	p.(G1540E)	c.4619G>A	.	chr15:40917081	58.77%	NM_144508.4	missense	1688
CDH5	p.(D301N)	c.901G>A	.	chr16:66424425	69.47%	NM_001795.4	missense	1261
CDH5	p.(I517T)	c.1550_1551delTCins CT	.	chr16:66432423	100.00%	NM_001795.4	missense	1963
PER1	p.(P867R)	c.2600C>G	.	chr17:8047056	78.27%	NM_002616.2	missense	612
ZNF521	p.(=)	c.2289C>T	.	chr18:22805593	55.53%	NM_015461.2	synonymous	1999
ZNF521	p.(L363V)	c.1087C>G	.	chr18:22806795	15.65%	NM_015461.2	missense	2000
ZNF521	p.(=)	c.630G>T	.	chr18:22807252	14.02%	NM_015461.2	synonymous	1997
DCC	p.(V772A)	c.2315T>C	.	chr18:50866233	41.50%	NM_005215.3	missense	2000
AMER1	p.(E1115K)	c.3343G>A	.	chrX:63409824	4.19%	NM_152424.3	missense	167
TAF1	p.(G804S)	c.2410G>A	.	chrX:70607234	7.84%	NM_004606.4	missense	51

## Biomarker Descriptions

### 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 potential<sup>1</sup>. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers<sup>2,3</sup>.

**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%)<sup>4,5,6,7,8,9</sup>. 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<sup>4,5</sup>. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes<sup>10,11,12,13</sup>.

**Potential relevance:** The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation<sup>14</sup>. The FDA has granted fast track designation (2019) to the p53 reactivator, APR-246 alone,<sup>15</sup> and breakthrough designation<sup>16</sup> (2020) in combination with azacitidine for myelodysplastic syndrome (MDS) and acute myeloid leukemia patients (AML) harboring a TP53 mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation<sup>17,18</sup>. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), chronic lymphocytic leukemia (CLL),<sup>19,20,21,22</sup>. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant<sup>23</sup>. 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 system<sup>24</sup>.

### 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

## Biomarker Descriptions (continued)

(mut/Mb) of DNA coding sequence<sup>25</sup>. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB<sup>26,27,28,29,30</sup>. 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<sup>31,32,33,34</sup>.

**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<sup>35</sup>. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb<sup>32,35</sup>. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb<sup>32,35</sup>. 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)<sup>32,35,36</sup>. 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<sup>35,37,38</sup>. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb<sup>39,40,41,42</sup>.

**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<sup>43</sup> 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<sup>40,44,45</sup>. 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<sup>46</sup>. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB<sup>47</sup>. 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<sup>48,49,50,51,52,53,54,55,56</sup>. 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<sup>57,58,59,60</sup>.

## Relevant Therapy Summary

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ No evidence

### TP53 p.(?) c.994-2A>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
atezolizumab	×	×	×	×	● (II)
niraparib	×	×	×	×	● (II)
olaparib	×	×	×	×	● (II)
talazoparib	×	×	×	×	● (II)
eprenetapopt, pembrolizumab	×	×	×	×	● (I/II)
xevinapant, nivolumab	×	×	×	×	● (I/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

### TP53 p.(?) c.994-2A>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BAY-1895344, niraparib	✕	✕	✕	✕	● (I)
HWH-340	✕	✕	✕	✕	● (I)
talazoparib, palbociclib, axitinib, crizotinib	✕	✕	✕	✕	● (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)
nivolumab	✕	✕	✕	✕	● (II)
pembrolizumab, ipilimumab + nivolumab	✕	✕	✕	✕	● (II)
chemotherapy, tremelimumab, durvalumab	✕	✕	✕	✕	● (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](http://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)  $\geq$  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®.

##### 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.<sup>1</sup>

##### 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)  $\geq$  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)  $\geq 10$ ] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.<sup>1</sup>
- 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,<sup>1</sup> or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.<sup>1</sup>
- 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)  $\geq 1$ ] 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.<sup>1</sup>

### 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  $\geq 10$ ) 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)  $\geq 1$ ] as determined by an FDA-approved test.<sup>1</sup>

### Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC who have been previously treated with sorafenib.<sup>1</sup>

### Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.<sup>1</sup>

### 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.<sup>1</sup>

### 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) [ $\geq 10$  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.<sup>1</sup>
- 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)  $\geq 10$ ] as determined by an FDA approved test.<sup>2</sup>

### 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.<sup>3</sup>

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>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](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](http://www.nccn.org).  
For NCCN International Adaptations & Translations, search [www.nccn.org/global/international\\_adaptations.aspx](http://www.nccn.org/global/international_adaptations.aspx).

## Tumor Mutational Burden

### ☒ 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]

### ☐ 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]

## 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 1.2021]

### ○ 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]

### ○ 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]

### ○ 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]

### ○ 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]

### ○ 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]

### ○ 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]

### ○ 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

### TP53 p.(?) c.994-2A>T

NCT ID	Title	Phase
NCT04122625	A Dose-optimization, Exploratory Phase Ib/II Study to Assess Safety and Efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) Mimetic Debio 1143, When Given in Combination With the Anti-PD-1 Antibody Nivolumab in Patients With Specific Solid Tumors Who Have Progressed During or Immediately After Anti-PD-1/PD-L1 Treatment	I/II
NCT04383938	Study of APR-246 in Combination With Pembrolizumab in Subjects With Solid Tumor Malignancies	I/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
NCT04042831	A Phase II Study of Olaparib in Patients With Advanced Biliary Tract Cancer With Aberrant DNA Repair Gene Mutations	II
NCT02401347	A Phase II Clinical Trial of the PARP Inhibitor Talazoparib in BRCA1 and BRCA2 Wild Type Patients With Advanced Triple Negative Breast Cancer and Homologous Recombination Deficiency or Advanced HER2 Negative Breast Cancer or Other Solid Tumors With a Mutation in Homologous Recombination Pathway Genes Talazoparib Beyond BRCA (TBB) Trial	II
NCT03415659	A Phase I, Open-label, Single-center, Single/Multiple-dose, Dose-escalation/Dose-expansion Clinical Study on Tolerance and Pharmacokinetics of HWH340 Tablet in Patients With Advanced Solid Tumors	I
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
NCT03207347	A Phase II Trial of the PARP Inhibitor, Niraparib, in BAP1 and Other DNA Damage Response (DDR) Pathway Deficient Neoplasms (UF-STO-ETI-001).	II
NCT03233204	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase 2 Subprotocol of Olaparib in Patients With Tumors Harboring Defects in DNA Damage Repair Genes	II
NCT04267939	An Open-label Phase Ib Study to Determine the Maximum Tolerated and/or Recommended Phase II Dose of the ATR Inhibitor BAY 1895344 in Combination With PARP Inhibitor Niraparib, in Patients With Recurrent Advanced Solid Tumors and Ovarian Cancer	I
NCT04693468	Modular Phase IB Hypothesis-Testing, Biomarker-Driven, Talazoparib Combination Trial (TalaCom)	I

## Clinical Trials Summary (continued)

### Tumor Mutational Burden

NCT ID	Title	Phase
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
No NCT ID	A Multicenter Phase II Study Of Nivolumab Monotherapy In Recurrent And/Or Metastatic Gastrointestinal Cancer Patients With High Tumor Mutation Burden (TMB-H)	II
No NCT ID	TR Accompanied with the Study Titled A Multicenter Phase II Study of Nivolumab Monotherapy in Recurrent and/or Metastatic Gastrointestinal Cancer Patients with High Tumor Mutation Burden (TMB-H).	II
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
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:

Laboratory Supervisor:

Pathologist:

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