Taipei Veterans General Hospital

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Sample Information

Patient Name: 曹光昇
Gender: Male
ID No.: J121326884
History No.: 46840782
Age: 54

Ordering Doctor: DOC6300K 吳宜鴻
Ordering REQ.: 0BFFJBS
Signing in Date: 2021/04/28

Path No.: S110-98698
MP No.: TM21005
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S110-13078A+B
Percentage of tumor cells: 40%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents

Report Highlights

3 Relevant Biomarkers
1 Therapies Available
33 Clinical Trials

Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	Not detected	MET	Not detected
BRAF	Not detected	NTRK1	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected

Genomic Alteration	Finding
Tumor Mutational Burden	***14.23 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*TP53 p.(R273L) c.818G>T* tumor protein p53 Allele Frequency: 29.75%	None	None	12
IIC	*ARID1A p.(T783fs) c.2348_2351delCAGGinsGA* AT-rich interaction domain 1A Allele Frequency: 33.10%	None	None	5
	Tumor Mutational Burden 14.23 Mut/Mb measured	**pembrolizumab** [1]	pembrolizumab	19

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
ARID1A	p.(T783fs)	c.2348_2351delCAGGinsGA	.	chr1:27088739	33.10%	NM_006015.5	frameshift Block Substitution	1979
TP53	p.(R273L)	c.818G>T	COSM10779	chr17:7577120	29.75%	NM_000546.5	missense	2000
PAX7	p.(=)	c.609G>A	.	chr1:19018270	40.81%	NM_002584.2	synonymous	1529
PAX7	p.(=)	c.654A>C	.	chr1:19018315	36.47%	NM_002584.2	synonymous	1999
PAX7	p.(=)	c.777G>A	.	chr1:19018438	33.37%	NM_002584.2	synonymous	1999
DDR2	p.(D81Y)	c.241G>T	.	chr1:162724469	25.18%	NM_006182.2	missense	1998
PBX1	p.(=)	c.843A>G	.	chr1:164781232	26.69%	NM_002585.3	synonymous	1004
SOX11	p.(A174E)	c.521C>A	.	chr2:5833374	36.00%	NM_003108.3	missense	1814
PAX3	p.(I96L)	c.286A>T	.	chr2:223161732	28.19%	NM_181459.3	missense	1926
XPC	p.(R617S)	c.1851G>T	.	chr3:14199532	36.47%	NM_004628.4	missense	1999
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.5	nonframeshift Insertion	1844
MITF	p.(M212L)	c.634A>T	.	chr3:69988300	11.01%	NM_198159.2	missense	1999
EPHA3	p.(=)	c.666C>T	.	chr3:89259522	39.90%	NM_005233.5	synonymous	2000
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.95%	NM_006206.5	synonymous	1985
AFF1	p.(P798L)	c.2393C>T	.	chr4:88036378	44.40%	NM_001166693.2	missense	2000
PKHD1	p.(=)	c.3846T>G	.	chr6:51890762	31.17%	NM_138694.3	synonymous	1986
RPS6KA2	p.(=)	c.1794G>A	.	chr6:166833420	34.90%	NM_001006932.2	synonymous	1954
EGFR	p.(P20R)	c.59C>G	.	chr7:55087029	8.11%	NM_005228.4	missense	1998
EPHB6	p.(E45G)	c.134A>G	.	chr7:142561422	31.70%	NM_004445.5	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
EPHB6	p.(A266V)	c.797C>T	.	chr7:142562355	13.12%	NM_004445.5	missense	983
KMT2C	p.(A4748P)	c.14242G>C	.	chr7:151841899	28.79%	NM_170606.2	missense	1997
KMT2C	p.(=)	c.5958G>T	.	chr7:151878987	18.00%	NM_170606.2	synonymous	2000
ADGRA2	p.(T1315I)	c.3944C>T	.	chr8:37699800	56.38%	NM_032777.9	missense	1999
HOOK3	p.(=)	c.1716C>G	.	chr8:42863050	44.17%	NM_032410.3	synonymous	1997
PRKDC	p.(P473T)	c.1417C>A	.	chr8:48848322	10.45%	NM_006904.6	missense	1991
CSMD3	p.(G1104V)	c.3311G>T	.	chr8:113651140	8.59%	NM_198123.1	missense	1223
PTPRD	p.(P126L)	c.377C>T	.	chr9:8528755	29.26%	NM_002839.3	missense	1999
CYP2C19	p.(E318V)	c.953A>T	.	chr10:96580386	12.27%	NM_000769.2	missense	1996
NUP98	p.(=)	c.3774A>G	.	chr11:3720547	33.27%	NM_016320.4	synonymous	1999
NUMA1	p.(=)	c.3985T>C	.	chr11:71724564	3.53%	NM_006185.3	synonymous	170
ARID2	p.(S1137*)	c.3410C>A	.	chr12:46245316	41.48%	NM_152641.3	nonsense	1996
KMT2D	p.(G794E)	c.2381G>A	.	chr12:49445085	3.70%	NM_003482.3	missense	135
KMT2D	p.(A792T)	c.2374G>A	.	chr12:49445092	4.51%	NM_003482.3	missense	133
ERBB3	p.(?)	c.-10C>T	.	chr12:56474075	16.76%	NM_001982.3	unknown	1999
HNF1A	p.(I618M)	c.1854C>G	.	chr12:121438953	72.70%	NM_000545.6	missense	2000
EP400	p.(H1765P)	c.5294A>C	.	chr12:132512746	14.96%	NM_015409.4	missense	1999
FLT1	p.(F135*)	c.404_405delTCinsAA	.	chr13:29012466	21.82%	NM_002019.4	nonsense	1517
BCL11B	p.(=)	c.885G>C	.	chr14:99642288	70.27%	NM_138576.3	synonymous	713
TCF12	p.(P279L)	c.836C>T	.	chr15:57524920	20.38%	NM_207037.1	missense	947
TSC2	p.(=)	c.2055C>T	.	chr16:2121893	3.85%	NM_000548.4	synonymous	52
MYH11	p.(=)	c.1131G>A	.	chr16:15857672	67.33%	NM_001040114.1	synonymous	1999
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	68.65%	NM_001795.4	missense	1968
PER1	p.(=)	c.738G>T	.	chr17:8052895	66.83%	NM_002616.2	synonymous	1999
CDH2	p.(=)	c.2085C>A	.	chr18:25565088	14.91%	NM_001792.4	synonymous	1998
CDH20	p.(=)	c.1662G>T	.	chr18:59217224	18.03%	NM_031891.3	synonymous	1048
CDH20	p.(V569I)	c.1705G>A	.	chr18:59217267	54.60%	NM_031891.3	missense	1066
BCL2	p.(P40fs)	c.119_127delCGGGGGCCGinsGGGGCCA	.	chr18:60985773	100.00%	NM_000633.2	frameshift Block Substitution	707
BCL2	p.(?)	c.-32C>A	.	chr18:60985931	16.77%	NM_000633.2	unknown	1998
TCF3	p.(=)	c.759C>T	.	chr19:1622116	59.85%	NM_001136139.3	synonymous	1995
KEAP1	p.(G558V)	c.1673G>T	.	chr19:10599903	38.99%	NM_203500.1	missense	913

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
PTPRT	p.(W146L)	c.437G>T	.	chr20:41419884	36.45%	NM_133170.3	missense	2000
MYH9	p.(=)	c.2061C>T	.	chr22:36702074	53.13%	NM_002473.5	synonymous	1999
MYH9	p.(=)	c.1455C>T	.	chr22:36710289	5.00%	NM_002473.5	synonymous	100

Biomarker Descriptions

ARID1A (AT-rich interaction domain 1A)

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[1]. ARID1A (also known as BAF250A) belongs to the ARID1 subfamily that also includes AR1D1B. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[2,3]. The SWI/SNF core complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1, and SMARCA2/BRM[3]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[3,4]. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription[2]. Recurrent inactivating mutations in SWI/SNF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[2].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[4]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[2]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[3,5,6].

Potential relevance: Currently, no therapies are approved for ARID1A aberrations.

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[7]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[8,9].

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%)[5,6,10,11,12,13]. 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[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[14,15,16,17].

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[18]. The FDA has granted fast track designation (2019) to the p53 reactivator, APR-246 alone,[19] and breakthrough designation[20] (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[21,22]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), chronic lymphocytic leukemia (CLL),[23,24,25,26]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[27]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[28].

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[29]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[30,31,32,33,34]. High TMB is associated with increased neo-antigen burden and has been linked to

Biomarker Descriptions (continued)

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[35,36,37,38].

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[39]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[36,39]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[36,39]. 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)[36,39,40]. 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[39,41,42]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[43,44,45,46].

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[47] 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[44,48,49]. 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 (pembroluzimab vs. chemotherapy), KEYNOTE 021 (pembroluzimab vs. pembroluzimab + 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[50]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[51]. 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, and germ cell tumors with high TMB[52,53,54,55,56,57]. 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[58,59,60,61].

Relevant Therapy Summary

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

TP53 p.(R273L) c.818G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
atezolizumab	✖	✖	✖	✖	● (II)
durvalumab + olaparib	✖	✖	✖	✖	● (II)
niraparib	✖	✖	✖	✖	● (II)
olaparib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
eprenetapopt, pembrolizumab	✖	✖	✖	✖	● (I/II)
sintilimab	✖	✖	✖	✖	● (I/II)
BAY-1895344, niraparib	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

TP53 p.(R273L) c.818G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
HWH-340	✖	✖	✖	✖	● (I)
talazoparib, palbociclib, axitinib, crizotinib	✖	✖	✖	✖	● (I)

ARID1A p.(T783fs) c.2348_2351delCAGGinsGA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
niraparib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
PLX-2853	✖	✖	✖	✖	● (I/II)
copanlisib, olaparib, durvalumab	✖	✖	✖	✖	● (I)
VX-803	✖	✖	✖	✖	● (I)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	○	✖	✖	● (II)
pembrolizumab, chemotherapy	✖	✖	✖	✖	● (III)
atezolizumab	✖	✖	✖	✖	● (II)
atezolizumab + chemotherapy	✖	✖	✖	✖	● (II)
atezolizumab, bevacizumab	✖	✖	✖	✖	● (II)
atezolizumab, nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, quavonlimab, MK-4280, lenvatinib	✖	✖	✖	✖	● (II)
sintilimab	✖	✖	✖	✖	● (II)
sintilimab, bevacizumab	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
anti-PD-1	✖	✖	✖	✖	● (I)
BAY1905254	✖	✖	✖	✖	● (I)
KN046	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

Tumor Mutational Burden (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
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 2021-02-17. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2020-11-13 **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 recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

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)

- 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)

Tumor Mutational Burden (continued)

- 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/2020/125514s088lbl.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 2021-02-01. 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: 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 (Line of therapy not specified); Useful in certain circumstances

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

○ 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: 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 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 2.2020]

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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, Locally Recurrent, Unresectable, Symptomatic, Progression, Distant Metastases, Asymptomatic (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2020]

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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 2.2020]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Endometrial Cancer **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
- Uterine Sarcoma; Recurrent, Metastatic (Line of therapy not specified); Useful in certain circumstances

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

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.(R273L) c.818G>T

NCT ID	Title	Phase
NCT04383938	Study of APR-246 in Combination With Pembrolizumab in Subjects With Solid Tumor Malignancies	I/II
No NCT ID	Single-arm Exploratory Study for Sintilimab Second-line or Later-line Treatment of Advanced Non-small Cell Lung Cancer with DDR Pathway Gene Mutation	I/II
NCT03334617	An Open-Label, Multi-Drug, Biomarker-Directed, Multi-Centre Phase II Umbrella Study in Patients with Non-Small Cell Lung Cancer, who Progressed on an anti-PD-1/PD-L1 Containing Therapy (HUDSON)	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
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
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
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

Clinical Trials Summary (continued)

TP53 p.(R273L) c.818G>T (continued)

NCT ID	Title	Phase
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

ARID1A p.(T783fs) c.2348_2351delCAGGinsGA

NCT ID	Title	Phase
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
NCT02286687	Phase II Study of the PARP Inhibitor Talazoparib in Advanced Cancer Patients With Somatic Alterations in BRCA1/2, Mutations/Deletions in Other BRCA Pathway Genes and Germline Mutation in BRCA1/2 (Not Breast or Ovarian Cancer)	II
NCT03297424	A Phase Ib/IIa Dose-escalation Study to Assess Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of PLX2853 in Subjects With Advanced Malignancies	I/II
NCT03842228	A Phase Ib Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors	I
NCT02278250	An Open-Label Study of the Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Profile of M4344 (Formerly VX-803) as a Single Agent and in Combination With Cytotoxic Chemotherapy in Participants With Advanced Solid Tumors	I

Tumor Mutational Burden

NCT ID	Title	Phase
No NCT ID	Pembrolizumab Alone Versus Pembrolizumab-Chemotherapy in First line NSCLC	III
NCT03836066	A Phase II Open Label Study of Atezolizumab in Combination With Bevacizumab as First Line Treatment for Locally Advanced or Metastasic High-intermediate Tumor Mutation Burden Selected Non-squamous Non-small Cell Lung Cancer (NSCLC) Patients.	II
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	II
NCT03516981	A Phase II Precision Oncology Study of Biomarker-Directed, Pembrolizumab-(MK-3475, SCH 900475) Based Combination Therapy for Advanced Non-Small Cell Lung Cancer (KEYNOTE-495; KeyImPaCT)	II
NCT03574402	An Open-label, Multi-center, Phase II Umbrella Study to Assess Efficacy of Targeted Therapy or Immunotherapy Directed by Next Generation Sequencing (NGS) in Chinese Patients With Advanced NSCLC (TRUMP)	II
NCT04213170	Prospective Phase II Clinical Study of Sintilimab Combined With Bevacizumab for Driving Gene-negative, Asymptomatic Brain Metastases From Non-small Cell Lung Cancer	II
No NCT ID	A Multicenter, Open and Prospective Study on the Effect of Immunotherapy on T Cell Surface Receptors and Cytokines in non-small-cell lung carcinoma	I

Clinical Trials Summary (continued)

Tumor Mutational Burden (continued)

NCT ID	Title	Phase
NCT03733951	An Open-Label, Multicenter, Dose-Escalation and Expansion Phase Ia/Ib Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of KN046 Monotherapy in Subjects With Advanced Solid Tumors and Lymphoma	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
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
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
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
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:

2021.04.29
14:22:34 +08'00'

Laboratory Supervisor:

2021.04.29
14:22:50 +08'00'

Pathologist:

2021.04.29
14:23:22 +08'00'

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