Taipei Veterans General Hospital

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Sample Information

Patient Name: 何再添
Gender: Male
ID No.: Q121002937
History No.: 17345389
Age: 61

Ordering Doctor: DOC1885G 楊慕華
Ordering REQ.: D5K38MJ
Signing in Date: 2020/12/10

Path No.: S109-96819
MP No.: TM20010
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S109-78724C
Percentage of tumor cells: 90%
Note:

Sample Cancer Type: Melanoma

Table of Contents

	Page
Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)	2
Biomarker Descriptions	3
Relevant Therapy Summary	5
Relevant Therapy Details	7
Clinical Trials Summary	11

Report Highlights

3 Relevant Biomarkers
3 Therapies Available
27 Clinical Trials

Relevant Melanoma Findings

Gene	Finding
BRAF	Not detected
KIT	Not detected
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	*GNA11 p.(Q209L) c.626A>T* G protein subunit alpha 11 Allele Fraction: 0.375	None	None	12
IIC	*BAP1 p.(N89fs) c.264delC* BRCA1 associated protein 1 Allele Fraction: 0.879	None	None	6
	Tumor Mutational Burden 3.34 Mut/Mb measured	**pembrolizumab** [1]	ipilimumab + nivolumab nivolumab pembrolizumab	10

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.
Although no fusion transcript can be detected, there is high imbalance of the number of 3' reads and 5' reads in the RET gene (3'/5' imbalance value: 25.86). A high 3'/5' imbalance value is suggestive of the presence of gene fusion. The possibility of RET fusion involving partners other than those targeted by the panel cannot be excluded. Further confirmation with other methodologies is suggested.

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

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
BAP1	p.(N89fs)	c.264delC	.	chr3:52442084	0.879	NM_004656.3	frameshift Deletion	1993
GNA11	p.(Q209L)	c.626A>T	COSM52969	chr19:3118942	0.375	NM_002067.4	missense	1083
MTR	p.(=)	c.2686C>T	.	chr1:237048430	0.424	NM_000254.2	synonymous	1009
LRP1B	p.(=)	c.2679C>T	.	chr2:141747192	0.505	NM_018557.2	synonymous	1643
STK36	p.(L672P)	c.2015T>C	.	chr2:219557405	0.503	NM_015690.4	missense	1996
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	0.998	NM_002343.5	nonframeshift Insertion	424
FGFR3	p.(L164V)	c.490C>G	.	chr4:1803138	0.504	NM_000142.4	missense	912
FGFR3	p.(=)	c.1371C>T	.	chr4:1806655	0.481	NM_000142.4	synonymous	1450
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	1.000	NM_006206.5	synonymous	1820
APC	p.(R976T)	c.2927G>C	.	chr5:112174218	0.481	NM_000038.5	missense	811
PKHD1	p.(=)	c.7906C>T	.	chr6:51720696	0.630	NM_138694.3	synonymous	1944
PKHD1	p.(Y617H)	c.1849T>C	.	chr6:51918951	0.386	NM_138694.3	missense	2000
SYNE1	p.(M5634T)	c.16901T>C	.	chr6:152631649	0.788	NM_182961.3	missense	584
SYNE1	p.(L5015M)	c.15043T>A	.	chr6:152647681	1.000	NM_182961.3	missense	772
EGFR	p.(=)	c.2457G>A	.	chr7:55249159	0.482	NM_005228.4	synonymous	1999

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

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
SAMD9	p.(M57T)	c.170T>C	.	chr7:92735241	0.523	NM_001193307.1	missense	1137
MET	p.(=)	c.2622T>C	.	chr7:116403307	0.523	NM_001127500.2	synonymous	1067
EPHB6	p.(S324A)	c.970T>G	.	chr7:142563253	0.494	NM_004445.5	missense	1998
EPHB6	p.(=)	c.1770G>A	.	chr7:142565385	0.511	NM_004445.5	synonymous	370
EPHB6	p.(=)	c.1887G>A	.	chr7:142565776	0.492	NM_004445.5	synonymous	1742
SYK	p.(R627H)	c.1880G>A	.	chr9:93657854	0.493	NM_003177.6	missense	1852
NUP214	p.(R741L)	c.2222G>T	.	chr9:134026097	0.484	NM_005085.3	missense	1257
KMT2A	p.(=)	c.8454C>G	.	chr11:118375061	0.500	NM_001197104.1	synonymous	1131
ERBB3	p.(=)	c.1780C>T	.	chr12:56488261	0.481	NM_001982.3	synonymous	1542
FLT1	p.(R275K)	c.824G>A	.	chr13:29005437	0.519	NM_002019.4	missense	1234
NKX2-1	p.(=)	c.1161C>T	.	chr14:36986528	0.493	NM_001079668.2	synonymous	1441
TSHR	p.(=)	c.1758T>C	.	chr14:81610160	0.519	NM_000369.2	synonymous	1042
DICER1	p.(G1575R)	c.4723G>A	.	chr14:95562534	0.482	NM_030621.4	missense	1868
THBS1	p.(N601S)	c.1802A>G	.	chr15:39881431	0.498	NM_003246.3	missense	1551
HLF	p.(?)	c.-47T>TCTTTT	.	chr17:53342799	0.052	NM_002126.4	unknown	959
TCF3	p.(G431S)	c.1291_1293delGGCinsAGT	.	chr19:1619348	1.000	NM_001136139.3	missense	511
ITGB2	p.(=)	c.123C>T	.	chr21:46330223	0.515	NM_000211.4	synonymous	1170

Biomarker Descriptions

BAP1 (BRCA1 associated protein 1)

Background: The BAP1 gene encodes the BRCA1 associated protein 1 that belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes[1]. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation[2]. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure[2]. Germline mutations in BAP1 are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a heritable condition which confers an elevated risk of developing uveal melanoma, malignant mesothelioma, and renal cell carcinoma[3,4,5,6,7,8].

Alterations and prevalence: Recurrent somatic mutations in BAP1 are observed in 21% of mesothelioma, 19% of cholangiocarcinoma, 16% of uveal melanoma, and 7% of kidney renal clear cell carcinoma[9,10]. BAP1 biallelic deletions are observed in 11% of mesothelioma[9,10].

Potential relevance: Currently, no therapies are approved for BAP1 aberrations.

Biomarker Descriptions (continued)

GNA11 (G protein subunit alpha 11)

Background: The GNA11 gene encodes an alpha subunit of heterotrimeric guanine nucleotide-binding proteins (G-proteins). G-protein alpha subunits bind guanine nucleotide, hydrolyze GTP, and interact with specific receptor and effector molecules. GNA11 is closely related to GNAQ, another G-protein alpha subunit.

Alterations and prevalence: Somatic activating mutations in GNA11 and GNAQ at amino acids R183 and Q209 are common in uveal melanoma and are mutually exclusive. These mutations render the G protein constitutively active leading to the stimulation of MAP kinases, PI3K/AKT, and protein kinase C, which promote tumor growth and proliferation[11,12,13]. Approximately 45% of uveal melanoma cases contain activating mutations in GNA11 and up to 50% of cases contain activating mutations in GNAQ[9,10,14]. By contrast, GNA11 and GNAQ mutations are infrequent in cutaneous melanoma, with a combined prevalence of approximately 1%, and are infrequently observed in other cancers[9,10].

Potential relevance: Currently, no therapies are approved for GNA11 aberrations. In a randomized phase II clinical trial of MEK inhibitor selumetinib versus chemotherapy, GNA11 and GNAQ positive uveal melanoma patients demonstrated a median progression-free survival (PFS) of 15.9 weeks versus 7 weeks, respectively[15]. However, no statistically significant improvement in overall survival (OS) was observed and the improvement in outcomes was associated with a high rate of adverse events[15].

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[16]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[17,18,19,20,21]. 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[22,23,24,25].

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[26]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[23,26]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[23,26]. 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)[23,26,27]. 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[26,28,29]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[30,31,32,33].

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, and pembrolizumab also for advanced esophageal squamous cell carcinoma. In 2020, the indication for pembrolizumab[34] 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 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[31,35,36]. In contrast, several previously promising trials have 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[37]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[38]. TMB score estimation is affected by the utilized assays, therefore efforts are underway to develop a standardized approach to calculate with the aim to support consistent reporting of TMB values across laboratories[39,40,41,42].

Relevant Therapy Summary

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

GNA11 p.(Q209L) c.626A>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selumetinib, ulixertinib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
HH-2710	✖	✖	✖	✖	● (I/II)
LXS-196, binimetinib	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
BGB-3245	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
LXH254	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
MLN-2480	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	✖	✖	● (I)

BAP1 p.(N89fs) c.264delC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
atezolizumab	✖	✖	✖	✖	● (II)
niraparib	✖	✖	✖	✖	● (II)
nivolumab, talazoparib	✖	✖	✖	✖	● (II)
olaparib	✖	✖	✖	✖	● (II)
BAY-1895344, niraparib	✖	✖	✖	✖	● (I)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	○	✖	✖	● (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*
ipilimumab + nivolumab	✖	○	✖	✖	● (II)
nivolumab	✖	○	✖	✖	● (I/II)
atezolizumab	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BAY1905254	✖	✖	✖	✖	● (I)
zimberelimab	✖	✖	✖	✖	● (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 2020-10-14. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2020-10-14 **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.

Tumor Mutational Burden (continued)

- Limitations of Use: KEYTRUDA® is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

- 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 Cancer 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

Tumor Mutational Burden (continued)

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

Cutaneous Squamous Cell Carcinoma (cSCC)

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

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

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.[2]

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

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s085lbl.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 2020-10-01. 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

○ ipilimumab + nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging biomarker in metastatic disease (Not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2020]

○ nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging biomarker in metastatic disease (Not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2020]

○ pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent or Metastatic Cervical Cancer; Progressed on prior treatment and does not have satisfactory alternative treatment options; Tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] as determined by an FDA-approved test (Second-line therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 2.2020]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Thyroid Gland Anaplastic Carcinoma, Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Medullary Carcinoma, Thyroid Gland Papillary Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; Unresectable locoregional recurrent/persistent disease not amenable to RAI therapy (Not specified)
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; CNS or soft tissue or bone metastases not amenable to RAI therapy (Not specified)
- Thyroid Gland Medullary Carcinoma; Locoregional recurrent/persistent disease (Not specified) (Useful in Certain Circumstances)
- Thyroid Gland Medullary Carcinoma; Recurrent or persistent disease; Distant metastases; Asymptomatic, symptomatic or progression of disease (Not specified) (Useful in Certain Circumstances)
- Thyroid Gland Anaplastic Carcinoma; Metastatic (Not specified) (Useful in Certain Circumstances)

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

pembrolizumab

Cancer type: Endometrial Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Unresectable or Metastatic Endometrial Carcinoma or Uterine Sarcoma; Progressed on prior treatment and does not have satisfactory alternative treatment options; Tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] as determined by an FDA-approved test (Not specified) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 2.2020]

Clinical Trials Summary

GNA11 p.(Q209L) c.626A>T

NCT ID	Title	Phase
NCT03947385	A Phase I/II Study of IDE196 in Patients With Solid Tumors Harboring GNAQ/11 Mutations or PRKC Fusions	I/II
NCT03905148	A Phase Ib, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of a RAF Dimer Inhibitor BGB-283 in Combination With MEK Inhibitor PD-0325901 in Patients With Advanced or Refractory Solid Tumors	I/II
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II

Clinical Trials Summary (continued)

GNA11 p.(Q209L) c.626A>T (continued)

NCT ID	Title	Phase
NCT04198818	A First-in-Human, Open Label, Phase I/II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HH2710 in Patients With Advanced Tumors	I/II
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT04418167	A Phase I Study of ERK1/2 Inhibitor JSI-1187 Administered as Monotherapy and in Combination With Dabrafenib for the Treatment of Advanced Solid Tumors With MAPK Pathway Mutations	I
NCT03429803	A Phase I Study of TAK-580 (MLN2480) for Children With Low-Grade Gliomas and Other RAS/RAF/MEK/ERK Pathway Activated Tumors	I
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	I
NCT02407509	A Phase I Trial of RO5126766 (a Dual RAF/MEK Inhibitor) Exploring Intermittent, Oral Dosing Regimens in Patients With Solid Tumours or Multiple Myeloma, With an Expansion to Explore Intermittent Dosing in Combination With Everolimus	I
NCT04249843	A First-in-Human, Phase Ia/Ib, Open Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor BGB-3245 in Patients With Advanced or Refractory Tumors	I
NCT02607813	A Phase I Dose Finding Study of Oral LXH254 in Adult Patients With Advanced Solid Tumors Harboring MAPK Pathway Alterations	I
NCT02857270	A Phase I Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	I

BAP1 p.(N89fs) c.264delC

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
NCT03925350	A Phase II Study of Niraparib in Patients With Advanced Melanoma With Genetic Homologous Recombination (HR) Mutation / Alteration	II
NCT04187833	Phase II Trial of Nivolumab in Combination with Talazoparib in Patients with Unresectable or Metastatic Melanoma and Mutations in BRCA or BRCA-ness Genes.	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
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

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
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
NCT03838042	INFORM2 Exploratory Multinational Phase I/II Combination Study of Nivolumab and Entinostat in Children and Adolescents with Refractory High-risk Malignancies	I/II
NCT02992964	Pilot Study of Nivolumab in Pediatric Patients With Hypermutant Cancers	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
NCT04087018	A Phase Ib Study to Evaluate the Safety and Clinical Activity of AB122 in Biomarker-Selected Participants With Advanced Solid Tumors	I

Signatures

Testing Personnel:

2020.12.11
13:43:14 +08'00'

Laboratory Supervisor:

2020.12.11
13:43:29 +08'00'

Pathologist:

2020.12.11
13:43:48 +08'00'

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