Taipei Veterans General Hospital

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Sample Information

Patient Name: 江世榮
Gender: Male
ID No.: A104282189
History No.: 18898130
Age: 64

Ordering Doctor: DOC3016D 江起陸
Ordering REQ.: 0AYRLUE
Signing in Date: 2020/11/14

Path No.: S109-89849
MP No.: TM20007
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S109-76220A
Percentage of tumor cells: 90%
Note:

Sample Cancer Type: Small Cell Lung Cancer

Report Highlights

3 Relevant Biomarkers
4 Therapies Available
18 Clinical Trials

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*TP53 p.(Q167*) c.499C>T* tumor protein p53 Allele Fraction: 0.844	None	olaparib	7
IIC	*RB1 p.(G865*) c.2593G>T* RB transcriptional corepressor 1 Allele Fraction: 0.778	None	None	1
	Tumor Mutational Burden 7.51 Mut/Mb measured	**pembrolizumab** [1]	ipilimumab + nivolumab nivolumab pembrolizumab	11

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
RB1	p.(G865*)	c.2593G>T	.	chr13:49050909	0.778	NM_000321.2	nonsense	1304
TP53	p.(Q167*)	c.499C>T	.	chr17:7578431	0.844	NM_000546.5	nonsense	1559
PLEKHG5	p.(P989del)	c.2965_2967delCCT	.	chr1:6528135	0.491	NM_001265593.1	nonframeshift Deletion	1543
PDE4DIP	p.(R870W)	c.2608C>T	.	chr1:144904704	0.536	NM_001198834.3	missense	1999
DDR2	p.(T681I)	c.2042C>T	.	chr1:162745627	0.505	NM_006182.2	missense	1999
ABL2	p.(=)	c.3450C>G	.	chr1:179076907	0.467	NM_005158.4	synonymous	1992
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	1.000	NM_002343.5	nonframeshift Insertion	343
FOXL2	p.(A179G)	c.536C>G	.	chr3:138665029	0.464	NM_023067.3	missense	645
FOXL2	p.(=)	c.501C>T	.	chr3:138665064	0.477	NM_023067.3	synonymous	633
ATR	p.(L1781F)	c.5343G>T	.	chr3:142218506	0.373	NM_001184.3	missense	1994
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	0.998	NM_006206.5	synonymous	1939
CSF1R	p.(A245T)	c.733G>A	.	chr5:149456995	0.888	NM_005211.3	missense	2000
NOTCH4	p.(D272G)	c.813_815delAGAinsGGG	.	chr6:32188640	0.507	NM_004557.3	synonymous, missense	1989
DAXX	p.(?)	c.1976+1G>C	.	chr6:33287156	0.448	NM_001141970.1	unknown	1996
PKHD1	p.(=)	c.6267G>A	.	chr6:51777229	0.461	NM_138694.3	synonymous	2000
SYNE1	p.(L5015M)	c.15043T>A	.	chr6:152647681	1.000	NM_182961.3	missense	1994
SYNE1	p.(=)	c.10866T>C	.	chr6:152675854	0.545	NM_182961.3	synonymous	1992
SMO	p.(T179M)	c.536C>T	.	chr7:128843429	0.656	NM_005631.4	missense	2000
WRN	p.(=)	c.87A>G	.	chr8:30916050	0.031	NM_000553.4	synonymous	64
WRN	p.(R685S)	c.2055G>C	.	chr8:30958438	0.867	NM_000553.4	missense	917
KAT6A	p.(E1109del)	c.3326_3328delAAG	.	chr8:41794797	0.756	NM_006766.4	nonframeshift Deletion	1960
TAF1L	p.(A1540T)	c.4618G>A	.	chr9:32630960	0.509	NM_153809.2	missense	1999
TAF1L	p.(D151N)	c.451G>A	.	chr9:32635127	0.050	NM_153809.2	missense	140
XPA	p.(L191V)	c.571C>G	.	chr9:100447307	0.902	NM_000380.3	missense	1511
RALGDS	p.(T883I)	c.2648C>T	.	chr9:135974068	0.042	NM_001271775.1	missense	95
KAT6B	p.(=)	c.369C>T	.	chr10:76602984	0.130	NM_012330.3	synonymous	54
KAT6B	p.(=)	c.372C>T	.	chr10:76602987	0.074	NM_012330.3	synonymous	54
KAT6B	p.(=)	c.5148G>A	.	chr10:76789730	0.043	NM_012330.3	synonymous	115

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
MEN1	p.(=)	c.369T>C	.	chr11:64577213	0.507	NM_000244.3	synonymous	1668
NUMA1	p.(R72Q)	c.215G>A	.	chr11:71734187	0.057	NM_006185.3	missense	88
BIRC3	p.(=)	c.798C>T	.	chr11:102196038	0.807	NM_182962.2	synonymous	1999
KMT2A	p.(C1476del)	c.4426_4428delTGT	.	chr11:118359419	0.133	NM_001197104.1	nonframeshift Deletion	1973
EP400	p.(=)	c.9240G>A	.	chr12:132562086	0.647	NM_015409.4	synonymous	1669
TSHR	p.(L552H)	c.1655T>A	.	chr14:81610057	0.223	NM_000369.2	missense	2000
KNL1	p.(A1212T)	c.3634G>A	.	chr15:40916096	0.092	NM_144508.4	missense	273
CDH11	p.(=)	c.945G>A	.	chr16:65022114	0.974	NM_001797.3	synonymous	1993
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	0.998	NM_001795.4	missense	1967
TCF3	p.(G431S)	c.1291_1293delGGCinsAGT	.	chr19:1619348	0.931	NM_001136139.3	missense	520
KEAP1	p.(R272fs)	c.812_813insT	.	chr19:10602765	0.858	NM_203500.1	frameshift Insertion	1991
AKT2	p.(=)	c.531C>T	.	chr19:40747887	0.096	NM_001626.5	synonymous	94
CHEK2	p.(=)	c.1428G>A	.	chr22:29090053	0.182	NM_007194.3	synonymous	55
ATRX	p.(D861N)	c.2581G>A	.	chrX:76938167	0.998	NM_000489.4	missense	823
BTK	p.(I276T)	c.827T>C	.	chrX:100615088	0.886	NM_000061.2	missense	1613

Biomarker Descriptions

RB1 (RB transcriptional corepressor 1)

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[1,2]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[3]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[1,2,4]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[5].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)[6]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[6]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[7,8,9].

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

Biomarker Descriptions (continued)

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[10]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[11,12].

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%)[6,13,14,15,16,17]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, R248, R273, and R282[6,13]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[18,19,20,21].

Potential relevance: The FDA has granted fast track designation (2019) for APR-246 alone[22] and breakthrough designation[23] (2020) in combination with azacitidine for myelodysplastic syndrome (MDS) patients harboring a TP53 mutation. Similar to APR-246, other investigational therapies aimed at restoring wild-type TP53 activity, as well as compounds that induce synthetic lethality are under clinical evaluation[24,25]. TP53 mutations confer poor prognosis in multiple blood cancers including acute myeloid leukemia (AML), MDS, myeloproliferative neoplasms (MPN), chronic lymphocytic leukemia (CLL),[26,27,28,29]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[30]. 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, high-risk disease presentation, and predicted death and leukemic transformation independently of the IPSS-R staging system[31].

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[32]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[33,34,35,36,37]. 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[38,39,40,41].

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[42]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[39,42]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[39,42]. 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)[39,42,43]. 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[42,44,45]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[46,47,48,49].

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[50] 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[47,51,52]. 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),

Biomarker Descriptions (continued)

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[53]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[54]. 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[55,56,57,58].

Relevant Therapy Summary

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

TP53 p.(Q167*) c.499C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✖	○	✖	✖	● (II)
berzosertib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
eprenetapopt, pembrolizumab	✖	✖	✖	✖	● (I/II)
HWH-340	✖	✖	✖	✖	● (I)

RB1 p.(G865*) c.2593G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	○	✖	✖	● (II)
ipilimumab + nivolumab	✖	○	✖	✖	● (II)
nivolumab	✖	○	✖	✖	● (I/II)
atezolizumab	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
entinostat, 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

Tumor Mutational Burden (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
anti-PD-1	✖	✖	✖	✖	● (I)
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.

TP53 p.(Q167*) c.499C>T

○ olaparib

Cancer type: Prostate Cancer **Variant class:** HRR mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Castration Resistant Prostate Adenocarcinoma; M1; Prior therapy of abiraterone/enzalutamide (Second-line therapy) (Useful in certain circumstances)
- Castration Resistant Prostate Adenocarcinoma; M1 (Subsequent therapy) (Useful in certain circumstances)

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

○ olaparib

Cancer type: Prostate Cancer **Variant class:** HRR mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Castration Resistant Prostate Adenocarcinoma; M1; Prior therapy of docetaxel (Second-line therapy) (Useful in certain circumstances)

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

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]

Tumor Mutational Burden (continued)

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]

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]

Tumor Mutational Burden (continued)

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

TP53 p.(Q167*) c.499C>T

NCT ID	Title	Phase
NCT03009682	Phase II, Single-arm Study of Olaparib Monotherapy in Relapsed Small Cell Lung Cancer Patients With HR Pathway Gene Mutations Not Limited to BRCA 1/2 Mutations, ATM Deficiency or MRE11A Mutations(SUKSES-B)	II
NCT03718091	A Phase II Study of M6620 (VX-970) in Selected Solid Tumors	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
NCT04383938	Study of APR-246 in Combination With Pembrolizumab in Subjects With Solid Tumor Malignancies	I/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

RB1 p.(G865*) c.2593G>T

NCT ID	Title	Phase
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II

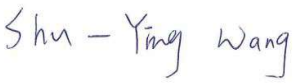
Clinical Trials Summary (continued)

Tumor Mutational Burden

NCT ID	Title	Phase
NCT03083691	A Phase II Trial of Nivolumab in Combination with Ipilimumab to Evaluate Efficacy and Safety Relapsed in Lung Cancer and to Evaluate Biomarkers Predictive for Response to Immune Checkpoint Inhibition	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
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
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:



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Laboratory Supervisor:

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Pathologist:

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