Taipei Veterans General Hospital

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Sample Information

Patient Name: 林嘉慶
Gender: Male
ID No.: F120846697
History No.: 46646382
Age: 48

Ordering Doctor: DOC1885G 楊慕華
Ordering REQ.: 0BBETRT
Signing in Date: 2021/01/21

Path No.: S110-98098
MP No.: TM21002
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S109-51351C
Percentage of tumor cells: 40%
Note:

Sample Cancer Type: Head and Neck Cancer

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Relevant Head and Neck Cancer Variants

Gene	Finding
ERBB2	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
	Tumor Mutational Burden 1.67 Mut/Mb measured	**pembrolizumab** [1]	ipilimumab + nivolumab nivolumab pembrolizumab	11

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO

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
TAL1	p.(G62R)	c.184G>C	.	chr1:47691377	38.13%	NM_003189.5	missense	674
ITGA10	p.(L1100M)	c.3298C>A	.	chr1:145541510	47.70%	NM_003637.4	missense	1998
TPR	p.(L793F)	c.2379G>T	.	chr1:186321198	44.80%	NM_003292.2	missense	587
ALK	p.(S78W)	c.233C>G	.	chr2:30143293	50.60%	NM_004304.4	missense	1990
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.5	nonframeshift Insertion	702
FGFR3	p.(=)	c.1371C>T	.	chr4:1806655	49.27%	NM_000142.4	synonymous	1642
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.73%	NM_006206.5	synonymous	1131
KDR	p.(=)	c.3456G>A	.	chr4:55955089	48.08%	NM_002253.2	synonymous	965
CSF1R	p.(=)	c.1929C>T	.	chr5:149440465	49.41%	NM_005211.3	synonymous	1014
FGFR4	p.(I197T)	c.590T>C	.	chr5:176518092	47.57%	NM_213647.2	missense	1999
SYNE1	p.(Q7798P)	c.23393A>C	.	chr6:152501338	46.07%	NM_182961.3	missense	1437
SAMD9	p.(F222L)	c.664T>C	.	chr7:92734747	52.18%	NM_001193307.1	missense	1148
CSMD3	p.(I1468K)	c.4403T>A	.	chr8:113563061	22.22%	NM_198123.1	missense	108
WT1	p.(=)	c.681C>T	.	chr11:32450131	52.10%	NM_024426.4	synonymous	689
TCF12	p.(=)	c.1692A>G	.	chr15:57555419	48.57%	NM_207037.1	synonymous	1999
BLM	p.(I947V)	c.2839A>G	.	chr15:91333894	51.25%	NM_000057.3	missense	1565
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	51.47%	NM_001795.4	missense	1226
PLCG1	p.(=)	c.2973C>T	.	chr20:39801128	49.12%	NM_002660.2	synonymous	682
ITGB2	p.(=)	c.1590C>T	.	chr21:46309960	54.07%	NM_000211.4	synonymous	479
EP300	p.(=)	c.6582A>G	.	chr22:41574297	46.00%	NM_001429.3	synonymous	926

Biomarker Descriptions

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[1]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[2,3,4,5,6]. 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[7,8,9,10].

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[11]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[8,11]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[8,11]. 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)[8,11,12]. There is no consensus around the definition of high and low TMB that could be applied universally to all tumor types, instead multiple sources

Biomarker Descriptions (continued)

suggest that TMB status is a cancer type specific attribute[11,13,14]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[15,16,17,18].

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[19] 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[16,20,21]. 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[22]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[23]. 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[24,25,26,27].

Relevant Therapy Summary

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

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)
chemotherapy, tremelimumab, durvalumab	✖	✖	✖	✖	● (I/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 2020-11-18. 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 2020-11-02. 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 1.2021]

○ pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- 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: Thyroid Gland Medullary Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- 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)

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

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):
- 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)

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 (Second-line therapy) (Useful in Certain Circumstances)

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

Clinical Trials Summary

Tumor Mutational Burden

NCT ID	Title	Phase
NCT03518606	A Phase I/II Basket Trial Evaluating A Combination Of Metronomic Oral Vinorelbine Plus Anti-PD-L1/ Anti-CTLA4 ImmunothErapy In Patients With Advanced Solid Tumour	I/II

Clinical Trials Summary (continued)

Tumor Mutational Burden (continued)

NCT ID	Title	Phase
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
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
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
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:

2021.01.22
14:21:22 +08'00'

Laboratory Supervisor:

2021.01.22
14:21:36 +08'00'

Pathologist:

2021.01.22
14:21:48 +08'00'

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