Taipei Veterans General Hospital

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Sample Information

Patient Name: 楊素珏
Gender: Female
ID No.: A210404031
History No.: 40989353
Age: 63

Ordering Doctor: DOC3016D 江起陸
Ordering REQ.: C21LME7
Signing in Date: 2020/09/25

Path No.: S109-89668
MP No.: TM20003
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S109-29671A
Percentage of tumor cells: 90%
Note:

Sample Cancer Type: Small Cell Lung Cancer

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*NFE2L2 p.(D29Y) c.85G>T* nuclear factor, erythroid 2 like 2 Allele Frequency: 51.28%	None	None	2
	Tumor Mutational Burden 3.34 Mut/Mb measured	None	ipilimumab + nivolumab nivolumab	11

Public data sources included in relevant therapies: FDA[1], 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
NFE2L2	p.(D29Y)	c.85G>T	COSM132845	chr2:178098960	51.28%	NM_006164.4	missense	1999
PIK3CD	p.(=)	c.2085G>A	.	chr1:9782062	32.65%	NM_005026.4	synonymous	1421
PAX8	p.(K221M)	c.662A>T	.	chr2:113999243	5.00%	NM_003466.3	missense	1219
NFE2L2	p.(R449H)	c.1346G>A	.	chr2:178095985	46.01%	NM_006164.4	missense	576
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.5	nonframeshift Insertion	319
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	100.00%	NM_006206.5	synonymous	1986
KIT	p.(T304A)	c.910A>G	.	chr4:55570043	50.80%	NM_000222.2	missense	1996
TET2	p.(=)	c.2907A>G	.	chr4:106158006	52.01%	NM_001127208.2	synonymous	1567
RAD50	p.(Q404R)	c.1211A>G	.	chr5:131924538	46.39%	NM_005732.3	missense	1494
NOTCH4	p.(L13_L16del)	c.36_47delGCTGCTGCTGCT	.	chr6:32191658	43.32%	NM_004557.3	nonframeshift Deletion	
SYNE1	p.(=)	c.9897G>T	.	chr6:152688428	47.81%	NM_182961.3	synonymous	1257
KMT2C	p.(=)	c.6729C>T	.	chr7:151878216	50.75%	NM_170606.2	synonymous	2000
TAF1L	p.(D314V)	c.941A>T	.	chr9:32634637	49.60%	NM_153809.2	missense	1998
FANCG	p.(D606H)	c.1816G>C	.	chr9:35074158	49.35%	NM_004629.1	missense	1996
KAT6B	p.(S124F)	c.371C>T	.	chr10:76602986	4.48%	NM_012330.3	missense	67
KAT6B	p.(=)	c.372C>T	.	chr10:76602987	4.41%	NM_012330.3	synonymous	68
KAT6B	p.(S1229G)	c.3685A>G	.	chr10:76788267	29.00%	NM_012330.3	missense	2000
KMT2A	p.(=)	c.10746A>T	.	chr11:118377353	52.95%	NM_001197104.1	synonymous	1998
TSHR	p.(A275T)	c.823G>A	.	chr14:81606153	64.76%	NM_000369.2	missense	1887
DICER1	p.(?)	c.4206+21GTGTGTGTGTGTG>T	.	chr14:95566096	45.13%	NM_030621.4	unknown	698
DICER1	p.(?)	c.4206+19ATGGTAAGTTTGTGTGTGTGTG>TGTAAGTT	.	chr14:95566098	29.94%	NM_030621.4	unknown	698
CDH11	p.(=)	c.409C>A	.	chr16:65032579	48.29%	NM_001797.3	synonymous	1139
TP53	p.(V274A)	c.821T>C	.	chr17:7577117	97.74%	NM_000546.5	missense	1548
ITGB3	p.(S411F)	c.1232C>T	.	chr17:45368426	48.82%	NM_000212.2	missense	1999
KEAP1	p.(G9R)	c.25G>A	.	chr19:10610685	48.45%	NM_203500.1	missense	2000
AKT2	p.(=)	c.543G>A	.	chr19:40747875	3.70%	NM_001626.5	synonymous	54

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
CHEK2	p.(=)	c.1428G>A	.	chr22:29090053	3.85%	NM_007194.3	synonymous	52
EP300	p.(=)	c.1104C>T	.	chr22:41523688	50.58%	NM_001429.3	synonymous	1999
EP300	p.(=)	c.2925A>G	.	chr22:41547944	52.37%	NM_001429.3	synonymous	972

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

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

NFE2L2 p.(D29Y) c.85G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
telaglenastat	✖	✖	✖	✖	● (II)
IPN-60090, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (I)

Tumor Mutational Burden

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

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⛔ Not recommended ⛊ Resistance

NCCN information is current as of 2020-05-01. 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 4.2020]

○ 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 4.2020]

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⊖ Not recommended ⛊ Resistance

ESMO information is current as of 2020-05-01. For the most up-to-date information, search www.esmo.org.

Tumor Mutational Burden

○ ipilimumab + nivolumab

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

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Stage IV Squamous and Non-squamous (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

Signatures

Testing Personnel:

2020.09.25
08:33:35 +08'00'

Laboratory Supervisor:

Pathologist:

2020.09.25
08:33:51 +08'00'

2020.09.25
08:34:04 +08'00'

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