Taipei Veterans General Hospital

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Sample Information

Patient Name: 趙瑞隆
Gender: Male
ID No.: R121781523
History No.: 44131171
Age: 62

Ordering Doctor: DOC1322F 趙毅
Ordering REQ.: D57NN71
Signing in Date: 2020/07/15

Path No.: S109-99691
MP No.: TM20002
Assay: Oncomine Tumor Mutation Load
Sample Type: FFPE
Block No.: S109-10958D
Percentage of tumor cells: 80%
Note:

Sample Cancer Type: Other Solid Tumor

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Relevant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
Tumor Mutational Burden 0.83 Mut/Mb measured	None	ipilimumab + nivolumab nivolumab	25

Public data sources included in relevant therapies: FDA1, 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
MUTYH	p.(=)	c.1449C>T	.	chr1:45796881	7.65%	NM_001128425.1	synonymous	2000
JAK1	p.(=)	c.1357T>C	.	chr1:65323440	7.95%	NM_002227.3	synonymous	2000
ABL2	p.(G1007E)	c.3020G>A	.	chr1:179077337	91.15%	NM_005158.4	missense	2000

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.03(007).

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
PIK3C2B	p.(=)	c.312C>T	.	chr1:204438619	8.05%	NM_002646.3	synonymous	1999
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.5	nonframeshift Insertion	403
FGFR3	p.(L164V)	c.490C>G	.	chr4:1803138	87.59%	NM_000142.4	missense	1975
PDGFRA	p.(S478fs)	c.1432delT	.	chr4:55139770	88.64%	NM_006206.5	frameshift Deletion	1989
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.75%	NM_006206.5	synonymous	1972
EPHB6	p.(S324A)	c.970T>G	.	chr7:142563253	49.35%	NM_004445.5	missense	1998
EPHB6	p.(=)	c.1770G>A	.	chr7:142565385	53.32%	NM_004445.5	synonymous	1309
EPHB6	p.(=)	c.1887G>A	.	chr7:142565776	52.53%	NM_004445.5	synonymous	1999
XRCC2	p.(=)	c.825T>C	.	chr7:152345745	50.50%	NM_005431.1	synonymous	1998
RECQL4	p.(R755Q)	c.2264G>A	.	chr8:145738801	87.44%	NM_004260.3	missense	1999
CDKN2B	p.(P40L)	c.119C>T	.	chr9:22008834	5.26%	NM_004936.3	missense	57
CDKN2B	p.(P40S)	c.118C>T	.	chr9:22008835	3.51%	NM_004936.3	missense	57
TAF1L	p.(C805Y)	c.2414G>A	.	chr9:32633164	4.40%	NM_153809.2	missense	159
TAF1L	p.(=)	c.1915C>T	.	chr9:32633663	4.15%	NM_153809.2	synonymous	241
RALGDS	p.(=)	c.2646G>A	.	chr9:135974070	5.41%	NM_001271775.1	synonymous	74
TET1	p.(E1170Q)	c.3508G>C	.	chr10:70405994	12.17%	NM_030625.2	missense	1997
MEN1	p.(=)	c.858G>C	.	chr11:64574552	91.33%	NM_000244.3	synonymous	1995
ATM	p.(D1853N)	c.5557G>A	.	chr11:108175462	90.20%	NM_000051.3	missense	2000
KMT2A	p.(=)	c.948G>C	.	chr11:118342822	91.39%	NM_001197104.1	synonymous	1602
KMT2D	p.(Q800*)	c.2398C>T	.	chr12:49445068	4.08%	NM_003482.3	nonsense	196
FLT3	p.(A642V)	c.1925C>T	.	chr13:28608041	3.28%	NM_004119.2	missense	61
HIF1A	p.(I345V)	c.1033A>G	.	chr14:62203611	18.84%	NM_001530.3	missense	1932
KNL1	p.(A406S)	c.1216G>T	.	chr15:40913678	87.57%	NM_144508.4	missense	1843
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	15.55%	NM_001795.4	missense	1576
BRIP1	p.(R814C)	c.2440C>T	.	chr17:59793364	7.75%	NM_032043.2	missense	1755
TCF3	p.(G431S)	c.1291_1293delGGCinsAGT	.	chr19:1619348	88.14%	NM_001136139.3	missense	1408
CIC	p.(=)	c.4826G>A	.	chr19:42799342	7.38%	NM_015125.4	synonymous	122
ERCC1	p.(?)	c.105+1G>A	.	chr19:45926527	3.96%	NM_001983.3	unknown	101

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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
ERCC1	p.(G4E)	c.11G>A	.	chr19:45926622	3.92%	NM_001983.3	missense	102
ERCC1	p.(G4R)	c.10G>A	.	chr19:45926623	4.90%	NM_001983.3	missense	102
MYH9	p.(=)	c.1458C>T	.	chr22:36710286	5.43%	NM_002473.5	synonymous	184
TAF1	p.(V802M)	c.2404G>A	.	chrX:70607228	7.14%	NM_004606.4	missense	56
TAF1	p.(V803I)	c.2407G>A	.	chrX:70607231	5.45%	NM_004606.4	missense	55

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].

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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

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ipilimumab + nivolumab	✖	○	✖	○	✖
nivolumab	✖	○	✖	✖	◑ (II)
atezolizumab	✖	✖	✖	✖	◑ (II/III)
durvalumab, tremelimumab	✖	✖	✖	✖	◑ (II)
ipilimumab, nivolumab	✖	✖	✖	✖	◑ (II)
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
chemotherapy, tremelimumab, durvalumab	✖	✖	✖	✖	● (I/II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BI 754091	✖	✖	✖	✖	● (I)
BI 754091, BI 754111	✖	✖	✖	✖	● (I)
zimberelimab	✖	✖	✖	✖	● (I)
atezolizumab, bevacizumab	✖	✖	✖	✖	○ (II)
nivolumab, ipilimumab	✖	✖	✖	✖	○ (II)
pembrolizumab	✖	✖	✖	✖	○ (II)
pembrolizumab, MK-1308, MK-4280, lenvatinib	✖	✖	✖	✖	○ (II)
KN046	✖	✖	✖	✖	○ (I)

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

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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 2019-11-01. 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 targeted agents

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

○ 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 targeted agents

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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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 2019-11-01. 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:

Laboratory Supervisor:

Pathologist:

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