Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 張傳雄
Gender: Male
ID No.: A123183978
History No.: 46167059
Age: 61

Ordering Doctor: DOC8095F 盧雅娣
Ordering REQ.: 0BRRASH
Signing in Date: 2022/02/11

Path No.: S111-98353
MP No.: TM22002
Assay: Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S109-22395A
Percentage of tumor cells: 70%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Colon Cancer

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Report Highlights

1 Relevant Biomarkers
1 Therapies Available
2 Clinical Trials

Relevant Colon Cancer Variants

Gene	Finding
BRAF	None detected
KRAS	None detected
NRAS	None detected
NTRK1	None detected
NTRK3	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*Tumor Mutational Burden* 18.82 Mut/Mb measured **Prognostic significance:** None **Diagnostic significance:** None	**pembrolizumab** [1]	pembrolizumab	2

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, 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
PAX7	p.(R56H)	c.167G>A	.	chr1:18960878	4.10%	NM_002584.3	missense	951
ARID1A	p.(L295F)	c.883C>T	.	chr1:27023777	4.00%	NM_006015.6	missense	75
CMPK1	p.(A53T)	c.157G>A	.	chr1:47799774	4.76%	NM_016308.3	missense	126
CMPK1	p.(A53V)	c.158C>T	.	chr1:47799775	11.90%	NM_016308.3	missense	126
CMPK1	p.([A53=;R54=])	c.159_162delCCGCinsTCGT	.	chr1:47799776	8.41%	NM_016308.3	synonymous, synonymous	107
NOTCH2NL	p.(C197Y)	c.590G>A	.	chr1:120539664	3.45%	NM_001364012.2	missense	116
NOTCH2	p.(C236Y)	c.707G>A	.	chr1:120539664	3.45%	NM_024408.4	missense	116
BCL9	p.(A411V)	c.1232C>T	.	chr1:147091193	6.15%	NM_004326.4	missense	65
ARNT	p.(?)	c.-73C>T	.	chr1:150849116	6.93%	NM_001668.4	unknown	202
PBX1	p.(G31E)	c.92G>A	.	chr1:164529151	5.53%	NM_002585.4	missense	217
PBX1	p.(G32E)	c.95G>A	.	chr1:164529154	5.45%	NM_002585.4	missense	220
ABL2	p.(G721=)	c.2163G>A	.	chr1:179078194	17.86%	NM_005158.5	synonymous	56
ABL2	p.(G718D)	c.2153G>A	.	chr1:179078204	6.00%	NM_005158.5	missense	50
ABL2	p.(Q709=)	c.2127G>A	.	chr1:179078230	3.64%	NM_005158.5	synonymous	55
ABL2	p.(Q522*)	c.1564C>T	.	chr1:179081486	3.86%	NM_005158.5	nonsense	207
ABL2	p.(T437I)	c.1310C>T	.	chr1:179086520	4.41%	NM_005158.5	missense	68
ABL2	p.(W436*)	c.1307G>A	.	chr1:179086523	4.41%	NM_005158.5	nonsense	68
RNASEL	p.(K326R)	c.977A>G	.	chr1:182554965	53.97%	NM_021133.4	missense	693
ALK	p.(G926E)	c.2777G>A	.	chr2:29451788	8.96%	NM_004304.5	missense	67
ALK	p.(W915*)	c.2745G>A	.	chr2:29451820	4.55%	NM_004304.5	nonsense	66
ALK	p.(A877T)	c.2629G>A	.	chr2:29455173	34.05%	NM_004304.5	missense	2000
EML4	p.(L259F)	c.775C>T	.	chr2:42508097	6.15%	NM_019063.5	missense	65
XPO1	p.(K112=)	c.336G>A	.	chr2:61729411	5.17%	NM_003400.4	synonymous	58
LRP1B	p.(C3534Y)	c.10601G>A	.	chr2:141135786	4.11%	NM_018557.3	missense	73

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
LRP1B	p.(E3024K)	c.9070G>A	.	chr2:141250227	4.35%	NM_018557.3	missense	69
LRP1B	p.(V132D)	c.395T>A	.	chr2:142012159	5.95%	NM_018557.3	missense	2000
ACVR2A	p.(C30Y)	c.89G>A	.	chr2:148653903	4.29%	NM_001616.5	missense	70
PMS1	p.(T144I)	c.431C>T	.	chr2:190682755	4.27%	NM_000534.5	missense	117
FN1	p.(G243R)	c.727G>A	.	chr2:216293020	3.70%	NM_212482.3	missense	297
MLH1	p.([I150=;T151M])	c.450_452delCACinsTAT	.	chr3:37048551	5.21%	NM_000249.4	synonymous, missense	96
CTNNB1	p.(C573Y)	c.1718G>A	.	chr3:41277249	3.85%	NM_001904.4	missense	52
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	100.00%	NM_002343.6	nonframeshift Insertion	1630
SETD2	p.(G508=)	c.1524C>T	.	chr3:47164602	4.69%	NM_014159.6	synonymous	64
BAP1	p.(?)	c.-59G>A	.	chr3:52443953	13.19%	NM_004656.4	unknown	91
PHF7	p.(?)	c.-2943C>T	.	chr3:52443953	13.19%	NM_016483.7	unknown	91
EPHB1	p.(P420A)	c.1258C>G	.	chr3:134851852	44.19%	NM_004441.5	missense	1747
ATR	p.(S2552N)	c.7655G>A	.	chr3:142176446	14.00%	NM_001184.4	missense	50
FGFR3	p.(R238W)	c.712C>T	.	chr4:1803443	4.00%	NM_000142.4	missense	50
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	100.00%	NM_006206.6	synonymous	1113
KDR	p.(D950=)	c.2850C>T	.	chr4:55961090	4.84%	NM_002253.3	synonymous	62
KDR	p.(R944*)	c.2830C>T	.	chr4:55961110	4.84%	NM_002253.3	nonsense	62
KDR	p.(G494R)	c.1480G>A	.	chr4:55972910	3.70%	NM_002253.3	missense	81
KDR	p.(S487N)	c.1460G>A	.	chr4:55972930	3.75%	NM_002253.3	missense	80
KDR	p.(T89I)	c.266C>T	.	chr4:55984863	5.36%	NM_002253.3	missense	56
AFF1	p.(S530=)	c.1590C>T	.	chr4:88035575	6.25%	NM_001166693.2	synonymous	80
IL7R	p.(H154Y)	c.460C>T	.	chr5:35871238	95.53%	NM_002185.5	missense	559
APC	p.(R216*)	c.646C>T	.	chr5:112128143	22.19%	NM_000038.6	nonsense	1541
APC	p.(G1312Dfs*4)	c.3932_3933insAGAT	.	chr5:112175219	21.99%	NM_000038.6	frameshift Insertion	1978
APC	p.(E2155K)	c.6463G>A	.	chr5:112177754	6.03%	NM_000038.6	missense	116
FLT4	p.(R1041Q)	c.3122G>A	.	chr5:180043464	8.11%	NM_182925.5	missense	1997
NOTCH4	p.([P271=;D272G])	c.813_815delAGAinsGGG	.	chr6:32188640	57.00%	NM_004557.4	synonymous, missense	1972
NOTCH4	p.(L13_L16del)	c.36_47delGCTGCTGCTGCT	.	chr6:32191658	66.24%	NM_004557.4	nonframeshift Deletion	
PKHD1	p.(N830K)	c.2490T>A	.	chr6:51910904	40.95%	NM_138694.4	missense	1995
TNFAIP3	p.(Q350*)	c.1048C>T	.	chr6:138199630	3.57%	NM_001270507.2	nonsense	112

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
SYNE1	p.(E1675K)	c.5023G>A	.	chr6:152748905	3.95%	NM_182961.4	missense	76
IGF2R	p.(S1760=)	c.5280G>A	.	chr6:160496992	49.70%	NM_000876.3	synonymous	2000
RPS6KA2	p.(T165=)	c.495G>A	.	chr6:166918089	27.00%	NM_001006932.3	synonymous	2000
TRRAP	p.(H64Y)	c.190C>T	.	chr7:98487997	3.92%	NM_001244580.1	missense	51
KMT2C	p.(V2414=)	c.7242G>A	.	chr7:151877119	5.41%	NM_170606.3	synonymous	74
ADGRA2	p.(L110=)	c.330G>A	.	chr8:37672477	6.98%	NM_032777.10	synonymous	172
HOOK3	p.(Q205=)	c.615G>A	.	chr8:42814457	33.60%	NM_032410.4	synonymous	2000
PRKDC	p.(R1062Q)	c.3185G>A	.	chr8:48815213	5.95%	NM_006904.7	missense	185
NCOA2	p.(G188D)	c.563G>A	.	chr8:71078968	5.36%	NM_006540.4	missense	56
RUNX1T1	p.(?)	c.-24CTGC>C	.	chr8:93107719	61.52%	NM_001198634.2	unknown	1957
CSMD3	p.(T2408M)	c.7223C>T	.	chr8:113332153	4.63%	NM_198123.2	missense	108
JAK2	p.(D758N)	c.2272G>A	.	chr9:5080369	11.11%	NM_004972.4	missense	54
CDKN2A	p.(L91=)	c.273G>A	.	chr9:21971085	4.47%	NM_001195132.1	synonymous	179
CDKN2A	p.(F90=)	c.270C>T	.	chr9:21971088	6.36%	NM_001195132.1	synonymous	173
CDKN2B-AS1			.	chr9:21994244	4.31%	NR_047543.1		116
TAF1L	p.(P1443L)	c.4328C>T	.	chr9:32631250	15.15%	NM_153809.2	missense	99
TAF1L	p.(I1439=)	c.4317C>T	.	chr9:32631261	7.69%	NM_153809.2	synonymous	52
TAF1L	p.(L753F)	c.2257C>T	.	chr9:32633321	4.31%	NM_153809.2	missense	116
TAF1L	p.(L639=)	c.1915C>T	.	chr9:32633663	7.34%	NM_153809.2	synonymous	109
TAF1L	p.(K556=)	c.1668G>A	.	chr9:32633910	4.38%	NM_153809.2	synonymous	160
GNAQ	p.(D130N)	c.388G>A	.	chr9:80430620	57.50%	NM_002072.5	missense	1901
TLR4	p.(T175=)	c.525C>T	.	chr9:120474931	5.80%	NM_138554.5	synonymous	69
TSC1	p.(E949K)	c.2845G>A	.	chr9:135772701	4.00%	NM_000368.5	missense	100
NOTCH1	p.(P2238=)	c.6714C>T	.	chr9:139391477	39.97%	NM_017617.5	synonymous	1999
NOTCH1	p.(C1253Y)	c.3758G>A	.	chr9:139401311	4.10%	NM_017617.5	missense	195
KAT6B	p.(E1308K)	c.3922G>A	.	chr10:76788504	5.66%	NM_012330.4	missense	106
SUFU	p.(?)	c.-5C>T	.	chr10:104263905	5.97%	NM_016169.4	unknown	67
BIRC3	p.(V60M)	c.178G>A	.	chr11:102195418	4.40%	NM_182962.3	missense	91
BIRC3	p.(V64I)	c.190G>A	.	chr11:102195430	4.30%	NM_182962.3	missense	93
BIRC2	p.(D30=)	c.90C>T	.	chr11:102220822	5.59%	NM_001256166.2	synonymous	304
ATM	p.(V382=)	c.1146C>T	.	chr11:108119740	59.74%	NM_000051.3	synonymous	991
ATM	p.(C2735Y)	c.8204G>A	.	chr11:108206624	4.48%	NM_000051.3	missense	201

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
KMT2A	p.(V1135I)	c.3403G>A	.	chr11:118348750	3.57%	NM_001197104.2	missense	56
KMT2A	p.(E3802=)	c.11406G>A	.	chr11:118390756	4.62%	NM_001197104.2	synonymous	65
ZNF384	p.(Q501Hfs*48)	c.1503delG	.	chr12:6777110	99.58%	NM_001135734.2	frameshift Deletion	960
KMT2D	p.(R3508Q)	c.10523G>A	.	chr12:49428067	58.85%	NM_003482.4	missense	2000
KMT2D	p.(Q800*)	c.2398C>T	.	chr12:49445068	7.37%	NM_003482.4	nonsense	95
KMT2D	p.(L797=)	c.2391G>A	.	chr12:49445075	4.12%	NM_003482.4	synonymous	97
KMT2D	p.(G794E)	c.2381G>A	.	chr12:49445085	7.07%	NM_003482.4	missense	99
KMT2D	p.(G794R)	c.2380G>A	.	chr12:49445086	4.04%	NM_003482.4	missense	99
KMT2D	p.(E793=)	c.2379G>A	.	chr12:49445087	11.11%	NM_003482.4	synonymous	99
KMT2D	p.(A792V)	c.2375C>T	.	chr12:49445091	6.06%	NM_003482.4	missense	99
KMT2D	p.(A792T)	c.2374G>A	.	chr12:49445092	4.08%	NM_003482.4	missense	98
KMT2D	p.(E784=)	c.2352G>A	.	chr12:49445114	5.05%	NM_003482.4	synonymous	99
KMT2D	p.(S771F)	c.2312C>T	.	chr12:49445154	7.14%	NM_003482.4	missense	98
CDK4	p.(T102=)	c.306A>G	.	chr12:58145038	87.09%	NM_000075.4	synonymous	1999
EP400	p.(L369=)	c.1107G>A	.	chr12:132446271	3.61%	NM_015409.5	synonymous	83
EP400	p.(D2036N)	c.6106G>A	.	chr12:132522540	4.40%	NM_015409.5	missense	182
BIVM-ERCC5	p.(V1434I)	c.4300G>A	.	chr13:103525667	4.17%	NM_001204425.2	missense	96
ERCC5	p.(V980I)	c.2938G>A	.	chr13:103525667	4.17%	NM_000123.4	missense	96
DICER1	p.(P651=)	c.1953T>C	.	chr14:95579516	55.91%	NM_030621.4	synonymous	1438
DICER1	p.(E252K)	c.754G>A	.	chr14:95593066	3.70%	NM_030621.4	missense	54
HSP90AA1	p.(E147K)	c.439G>A	.	chr14:102552643	9.47%	NM_001017963.3	missense	95
AKT1	p.(H238Y)	c.712C>T	.	chr14:105239908	3.94%	NM_001014431.2	missense	127
THBS1	p.(?)	c.1026+1G>A	.	chr15:39876624	5.45%	NM_003246.4	unknown	55
TGM7	p.(K559=)	c.1677G>A	.	chr15:43571824	4.69%	NM_052955.3	synonymous	64
TGM7	p.(H520Y)	c.1558C>T	.	chr15:43571943	6.25%	NM_052955.3	missense	64
TGM7	p.(T519I)	c.1556C>T	.	chr15:43571945	10.00%	NM_052955.3	missense	60
TGM7	p.(L45=)	c.133C>T	.	chr15:43585707	11.11%	NM_052955.3	synonymous	81
MYH11	p.(Q1554=)	c.4662G>A	.	chr16:15814846	5.12%	NM_001040114.1	synonymous	371
MMP2	p.(G418=)	c.1254G>A	.	chr16:55525786	50.44%	NM_004530.6	synonymous	571
CDH11	p.(D794=)	c.2382C>T	.	chr16:64981515	23.09%	NM_001797.4	synonymous	1286
CDH11	p.(V303I)	c.907G>A	.	chr16:65022152	5.42%	NM_001797.4	missense	203
CDH5	p.(R154Q)	c.461G>A	.	chr16:66420962	49.60%	NM_001795.5	missense	2000

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
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	48.83%	NM_001795.5	missense	1958
CDH1	p.(L630V)	c.1888C>G	.	chr16:68856080	54.97%	NM_004360.5	missense	1903
FANCA	p.(A889V)	c.2666C>T	.	chr16:89831410	3.41%	NM_000135.4	missense	88
TP53	p.(T125=)	c.375G>A	.	chr17:7579312	43.92%	NM_000546.5	synonymous	337
FLCN	p.(L460=)	c.1380C>G	.	chr17:17118551	71.64%	NM_144997.7	synonymous	1999
PGAP3	p.(?)	c.900-1G>A	.	chr17:37829120	9.09%	NM_033419.5	unknown	55
ERBB2	p.(P17L)	c.50C>T	.	chr17:37856541	4.60%	NM_004448.3	missense	87
ETV4	p.(T17I)	c.50C>T	.	chr17:41622936	4.40%	NM_001986.4	missense	91
HLF	p.(?)	c.-47T>TCTTTT	.	chr17:53342799	7.06%	NM_002126.5	unknown	85
BRIP1	p.(V82I)	c.244G>A	.	chr17:59934554	4.03%	NM_032043.3	missense	124
RNF213	p.(A531=)	c.1593G>A	.	chr17:78268640	47.02%	NM_001256071.3	synonymous	1999
RNF213	p.(T1382=)	c.4146T>G	.	chr17:78307907	51.69%	NM_001256071.3	synonymous	1979
CDH2	p.(N845S)	c.2534A>G	.	chr18:25532304	43.59%	NM_001792.5	missense	608
SMAD4	p.(P293L)	c.878C>T	.	chr18:48584800	5.88%	NM_005359.6	missense	51
SMAD4	p.(G299R)	c.895G>A	.	chr18:48584817	3.92%	NM_005359.6	missense	51
SMAD4	p.(R361C)	c.1081C>T	.	chr18:48591918	30.43%	NM_005359.6	missense	276
DCC	p.(?)	c.2689-1G>A	.	chr18:50923677	3.33%	NM_005215.4	unknown	60
STK11	p.(H168Y)	c.502C>T	.	chr19:1220409	4.41%	NM_000455.5	missense	136
TCF3	p.(R558=)	c.1674C>T	.	chr19:1612345	42.72%	NM_001136139.4	synonymous	1999
TCF3	p.(G431S)	c.1291_1293delGGCinsAGT	.	chr19:1619348	58.29%	NM_001136139.4	missense	398
TCF3	p.(Q169=)	c.507G>A	.	chr19:1623992	8.05%	NM_001136139.4	synonymous	87
MAP2K2	p.(A19=)	c.57C>T	.	chr19:4123816	7.27%	NM_030662.4	synonymous	165
SMARCA4	p.(P7=)	c.21C>A	.	chr19:11094848	46.42%	NM_001128849.3	synonymous	614
AKT2	p.(M180I)	c.540G>A	.	chr19:40747878	6.60%	NM_001626.6	missense	288
AKT2	p.(A179=)	c.537C>T	.	chr19:40747881	6.60%	NM_001626.6	synonymous	288
CIC	p.(G1607D)	c.4820G>A	.	chr19:42799336	16.52%	NM_015125.4	missense	115
CIC	p.(G1607=)	c.4821C>T	.	chr19:42799337	5.22%	NM_015125.4	synonymous	115
CIC	p.(*1609=)	c.4826G>A	.	chr19:42799342	5.22%	NM_015125.4	stoploss	115
BCL3	p.(E253D)	c.759G>C	.	chr19:45260618	39.48%	NM_005178.5	missense	1991
PLCG1	p.(T199=)	c.597G>A	.	chr20:39791176	49.27%	NM_002660.3	synonymous	1999
PTPRT	p.(E55K)	c.163G>A	.	chr20:41514498	3.92%	NM_133170.4	missense	51
PTPRT	p.(V45M)	c.133G>A	.	chr20:41514528	3.77%	NM_133170.4	missense	53

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
MN1	p.(G752D)	c.2255G>A	.	chr22:28194277	4.52%	NM_002430.3	missense	177
MYH9	p.(Q489*)	c.1465C>T	.	chr22:36710279	6.48%	NM_002473.6	nonsense	463
MYH9	p.(F485=)	c.1455C>T	.	chr22:36710289	6.67%	NM_002473.6	synonymous	120
MYH9	p.(T483=)	c.1449C>T	.	chr22:36710295	4.17%	NM_002473.6	synonymous	120
MYH9	p.(T483I)	c.1448C>T	.	chr22:36710296	8.33%	NM_002473.6	missense	120
MYH9	p.(L467=)	c.1399C>T	.	chr22:36710345	3.94%	NM_002473.6	synonymous	127
CYP2D6	p.(E196=)	c.588G>A	.	chr22:42524864	4.35%	NM_000106.6	synonymous	69
AMER1	p.(E1115K)	c.3343G>A	.	chrX:63409824	5.81%	NM_152424.4	missense	327
TAF1	p.(V783I)	c.2347G>A	.	chrX:70607231	15.38%	NM_004606.5	missense	52
TAF1	p.(R1182C)	c.3544C>T	.	chrX:70617240	6.90%	NM_004606.5	missense	87
ATRX	p.(V2190I)	c.6568G>A	.	chrX:76813053	4.15%	NM_000489.5	missense	313
G6PD	p.(T536I)	c.1607C>T	.	chrX:153760246	4.12%	NM_000402.4	missense	194
G6PD	p.(N195D)	c.583A>G	.	chrX:153762704	99.46%	NM_000402.4	missense	1107

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. Pembrolizumab was also approved (2014) 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 (dMMR) 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 promising

Biomarker Descriptions (continued)

previous trials 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 (pembrolizumab vs. chemotherapy), KEYNOTE 021 (pembrolizumab vs. pembrolizumab + 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]. Pembrolizumab is indicated for use in various cancer types with evidence of metastasis including Ewing sarcoma, salivary gland neoplasms, cervical cancer, uterine sarcoma, endometrial carcinoma, thyroid cancer, ovarian cancer, esophageal cancer, esophagogastric junction cancer, breast cancer, and germ cell tumors with high TMB[24,25,26,27,28,29,30,31,32]. TMB score estimation is affected by the utilized assays, therefore efforts are underway to develop a standardized approach for score calculation with the aim to support consistent reporting of TMB values across laboratories[33,34,35,36].

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)
atezolizumab	✖	✖	✖	✖	● (II)

* 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 2021-11-17. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2021-11-17 **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®.

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

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Tumor Mutational Burden (continued)

- 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]
- 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 treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.[1]
- as a single agent for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 (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 locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

Cervical Cancer

- in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

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 adult patients with advanced RCC.
- in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
- for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

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 in any setting and are not candidates for curative surgery or radiation.

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)and description of clinical benefit in the confirmatory trial

Tumor Mutational Burden (continued)

- for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.

Triple-Negative Breast Cancer (TNBC)

- for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test.

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/2021/125514s113lbl.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 2021-11-01. 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

○ pembrolizumab

Cancer type: Chondrosarcoma, Ewing Sarcoma, Osteosarcoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2022]

○ pembrolizumab

Cancer type: Breast Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IV; Invasive, Unresectable, Metastatic, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 8.2021]

○ pembrolizumab

Cancer type: Cervical Small Cell Neuroendocrine Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2022]

○ pembrolizumab

Cancer type: Cervical Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Squamous Cell, Adenocarcinoma, Adenosquamous; Recurrent, Metastatic, Progression (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2022]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Squamous Cell; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 4.2021]

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pembrolizumab

Cancer type: Gastric Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 5.2021]

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pembrolizumab

Cancer type: Head and Neck Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Nasopharyngeal; Recurrent, Unresectable, Metastatic (Subsequent therapy); Useful in certain circumstances
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

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pembrolizumab

Cancer type: Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2021]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Large Cell Neuroendocrine Carcinoma, Small Cell Neuroendocrine Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Poorly Differentiated (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 3.2021]

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pembrolizumab

Cancer type: Neuroendocrine Tumor

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Well Differentiated; G3; Locally Advanced, Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 3.2021]

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pembrolizumab

Cancer type: Ovarian Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 3.2021]

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pembrolizumab

Cancer type: Castration-Resistant Prostate Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma; Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2022]

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pembrolizumab

Cancer type: Testicular Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Germ Cell Tumor; Metastatic, Recurrent (Third-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Testicular Cancer [Version 1.2022]

Tumor Mutational Burden (continued)

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):
- Locally Recurrent, Advanced, Metastatic (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]

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pembrolizumab

Cancer type: Thyroid Gland Medullary Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Persistent, Local, Distant Metastases, Regional (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]

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pembrolizumab

Cancer type: Thyroid Gland Anaplastic Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVC; Metastatic (Second-line therapy); Useful in certain circumstances, Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]

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pembrolizumab

Cancer type: Endometrial Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 4.2021]

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pembrolizumab

Cancer type: Uterine Sarcoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Second-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 4.2021]

Tumor Mutational Burden (continued)

pembrolizumab

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Well Differentiated; G3; Locally Advanced, Metastatic, Progression, Unresectable (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 3.2021]

pembrolizumab

Cancer type: Castration-Resistant Prostate Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Adenocarcinoma; Visceral Metastases, Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2022]

Clinical Trials in Taiwan region:

Clinical Trials Summary

Tumor Mutational Burden

NCT ID	Title	Phase
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT02628067	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158).	II

Alerts Informed By Public Data Sources

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-11-01. 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

pembrolizumab

Cancer type: Giant Cell Tumor of Soft Tissue **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "NCCN does not recommend this systemic treatment for GCTB since it is not technically a malignant tumor."

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2022]

Signatures

Testing Personnel:

Shu-Ying Wang 2022.02.11 10:39:47 +08'00'

Laboratory Supervisor:

2022.02.11 10:40:02 +08'00'

Pathologist:

Yi-Chu Yeh 2022.02.11 10:40:20 +08'00'

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27. NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2022]
28. NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 4.2021]
29. NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]
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