Taipei Veterans General Hospital

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Sample Information

Patient Name: 許珍惠
Gender: Female
ID No.: X220401077
History No.: 43689425
Age: 38

Ordering Doctor: DOC5380C 于洪元
Ordering REQ.: 0BGKGZK
Signing in Date: 2021/05/27

Path No.: S110-98892
MP No.: TM21008
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S106-07429B
Percentage of tumor cells: 80%
Note:

Sample Cancer Type: Liver Cancer

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Report Highlights

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Relevant Liver Cancer Variants

Gene	Finding
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
IIC	*PTEN p.(T319fs) c.956delC* phosphatase and tensin homolog Allele Frequency: 43.19%	None	None	24

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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
	Tumor Mutational Burden 26.27 Mut/Mb measured	**pembrolizumab** [1]	pembrolizumab	17

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.

Prevalent cancer biomarkers without relevant evidence based on included data sources

ASXL1 p.(Q225) c.673C>T, CREBBP p.(Q2140*) c.6418C>T*

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
PTEN	p.(T319fs)	c.956delC	.	chr10:89720804	43.19%	NM_000314.6	frameshift Deletion	1454
CREBBP	p.(Q2140*)	c.6418C>T	.	chr16:3778630	6.94%	NM_004380.2	nonsense	72
ASXL1	p.(Q225*)	c.673C>T	.	chr20:31017811	4.26%	NM_015338.5	nonsense	141
PAX7	p.(=)	c.162C>T	.	chr1:18960873	3.76%	NM_002584.2	synonymous	532
PAX7	p.(R56H)	c.167G>A	.	chr1:18960878	3.79%	NM_002584.2	missense	528
PAX7	p.(=)	c.171C>T	.	chr1:18960882	3.64%	NM_002584.2	synonymous	467
ARID1A	p.(=)	c.120G>A	.	chr1:27023014	4.88%	NM_006015.5	synonymous	82
LCK	p.(=)	c.36C>T	.	chr1:32739966	3.37%	NM_001042771.2	synonymous	89
TAL1	p.(G266R)	c.796G>A	.	chr1:47685592	4.46%	NM_003189.5	missense	112
TAL1	p.(P101S)	c.301C>T	.	chr1:47691260	4.02%	NM_003189.5	missense	199
CMPK1	p.(=)	c.117C>T	.	chr1:47799734	5.13%	NM_016308.2	synonymous	156
CMPK1	p.(A53T)	c.157G>A	.	chr1:47799774	9.09%	NM_016308.2	missense	132
CMPK1	p.(A53V)	c.158C>T	.	chr1:47799775	4.55%	NM_016308.2	missense	132
CMPK1	p.(=)	c.159C>T	.	chr1:47799776	4.65%	NM_016308.2	synonymous	129
PDE4DIP	p.(G1882E)	c.5645G>A	.	chr1:144866597	5.63%	NM_001198834.3	missense	71
BCL9	p.(G664S)	c.1990G>A	.	chr1:147091951	8.98%	NM_004326.3	missense	256
ARNT	p.(?)	c.-72C>T	.	chr1:150849115	4.98%	NM_001668.3	unknown	201
ARNT	p.(?)	c.-73C>T	.	chr1:150849116	6.97%	NM_001668.3	unknown	201
NTRK1	p.(=)	c.1149C>T	.	chr1:156843723	53.20%	NM_002529.3	synonymous	344
PBX1	p.(G31E)	c.92G>A	.	chr1:164529151	4.90%	NM_002585.3	missense	429
PBX1	p.(=)	c.108G>A	.	chr1:164529167	4.17%	NM_002585.3	synonymous	432
ABL2	p.(=)	c.2187G>A	.	chr1:179078170	7.08%	NM_005158.4	synonymous	113
ABL2	p.(G721E)	c.2162G>A	.	chr1:179078195	5.13%	NM_005158.4	missense	117

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
ABL2	p.(G719E)	c.2156G>A	.	chr1:179078201	5.22%	NM_005158.4	missense	115
RNASEL	p.(=)	c.2169C>T	.	chr1:182544584	50.70%	NM_021133.3	synonymous	1998
PARP1	p.(=)	c.1638G>A	.	chr1:226566950	5.56%	NM_001618.3	synonymous	378
ALK	p.(G925E)	c.2774G>A	.	chr2:29451791	5.00%	NM_004304.4	missense	140
ALK	p.(G924S)	c.2770G>A	.	chr2:29451795	5.11%	NM_004304.4	missense	137
PMS1	p.(=)	c.2358T>C	.	chr2:190732540	40.27%	NM_000534.4	synonymous	899
PMS1	p.(T806S)	c.2417C>G	.	chr2:190732599	51.10%	NM_000534.4	missense	1552
FN1	p.(W246*)	c.737G>A	.	chr2:216293010	7.66%	NM_212482.2	nonsense	248
FN1	p.(=)	c.378C>T	.	chr2:216298084	46.13%	NM_212482.2	synonymous	1910
MLH1	p.(=)	c.351G>A	.	chr3:37045936	5.33%	NM_000249.3	synonymous	75
MLH1	p.(Q701K)	c.2101C>A	.	chr3:37090506	48.69%	NM_000249.3	missense	1109
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	99.95%	NM_002343.5	nonframeshift Insertion	1928
PBRM1	p.(D358N)	c.1072G>A	.	chr3:52675985	4.03%	NM_018313.4	missense	124
EPHB1	p.(D772Y)	c.2314G>T	.	chr3:134920499	8.84%	NM_004441.4	missense	1754
TNK2	p.(P908L)	c.2723C>T	.	chr3:195594635	8.64%	NM_001010938.1	missense	81
FGFR3	p.(=)	c.717G>A	.	chr4:1803448	6.33%	NM_000142.4	synonymous	79
NSD2	p.(D1009N)	c.3025G>A	.	chr4:1961237	4.80%	NM_001042424.2	missense	125
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.69%	NM_006206.5	synonymous	1296
CTNNA1	p.(L39F)	c.115C>T	.	chr5:138118875	3.92%	NM_001903.4	missense	102
POU5F1	p.(D291N)	c.871G>A	.	chr6:31132590	5.19%	NM_002701.5	missense	77
POU5F1	p.(V276M)	c.826G>A	.	chr6:31132635	3.75%	NM_002701.5	missense	80
NOTCH4	p.(?)	c.-26C>T	.	chr6:32191731	3.17%	NM_004557.3	unknown	63
FOXO3	p.(=)	c.1932C>T	.	chr6:108985968	3.77%	NM_001455.3	synonymous	53
IGF2R	p.(=)	c.3939C>T	.	chr6:160485485	3.76%	NM_000876.3	synonymous	133
IKZF1	p.(C126Y)	c.377G>A	.	chr7:50444447	8.65%	NM_006060.5	missense	2000
AKAP9	p.(D2172N)	c.6514G>A	.	chr7:91700225	3.23%	NM_005751.4	missense	62
TRRAP	p.(=)	c.10470G>A	.	chr7:98602015	51.05%	NM_001244580.1	synonymous	2000
EPHB4	p.(=)	c.2949G>A	.	chr7:100401098	43.64%	NM_004444.4	synonymous	220
MET	p.(=)	c.1320A>G	.	chr7:116371841	45.36%	NM_001127500.2	synonymous	1012
POT1	p.(D291Y)	c.871G>T	.	chr7:124492004	48.67%	NM_015450.2	missense	1467
SMO	p.(T179M)	c.536C>T	.	chr7:128843429	51.70%	NM_005631.4	missense	2000
KAT6A	p.(E1109del)	c.3326_3328delAAG	.	chr8:41794797	40.29%	NM_006766.4	nonframeshift Deletion	1452

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
LOC10192			.	chr8:42128961	5.88%	NR_125823.1		204
IKBKB	p.(?)	c.-658C>T	.	chr8:42128961	5.88%	NM_001556.2	unknown	204
LOC10192			.	chr8:42128963	4.90%	NR_125823.1		204
IKBKB	p.(?)	c.-656C>T	.	chr8:42128963	4.90%	NM_001556.2	unknown	204
MYC	p.(V126M)	c.376G>A	.	chr8:128750839	5.88%	NM_002467.4	missense	68
JAK2	p.(V567G)	c.1700T>G	.	chr9:5072550	24.77%	NM_004972.3	missense	1332
CDKN2A	p.(=)	c.273G>A	.	chr9:21971085	14.12%	NM_001195132.1	synonymous	85
CDKN2A	p.(=)	c.270C>T	.	chr9:21971088	6.10%	NM_001195132.1	synonymous	82
CDKN2B	p.(=)	c.120C>T	.	chr9:22008833	5.88%	NM_004936.3	synonymous	102
CDKN2B	p.(P40L)	c.119C>T	.	chr9:22008834	3.92%	NM_004936.3	missense	102
CDKN2B	p.(P40S)	c.118C>T	.	chr9:22008835	4.90%	NM_004936.3	missense	102
CDKN2B	p.(=)	c.114G>A	.	chr9:22008839	6.86%	NM_004936.3	synonymous	102
CDKN2B	p.(A38T)	c.112G>A	.	chr9:22008841	3.96%	NM_004936.3	missense	101
CDKN2B	p.(G37D)	c.110G>A	.	chr9:22008843	3.96%	NM_004936.3	missense	101
TAF1L	p.(A1513V)	c.4538C>T	.	chr9:32631040	7.75%	NM_153809.2	missense	129
TAF1L	p.(M1444I)	c.4332G>A	.	chr9:32631246	6.38%	NM_153809.2	missense	235
TAF1L	p.(P1443S)	c.4327C>T	.	chr9:32631251	6.19%	NM_153809.2	missense	210
TAF1L	p.(=)	c.2151C>T	.	chr9:32633427	4.21%	NM_153809.2	synonymous	95
TAF1L	p.(A716T)	c.2146G>A	.	chr9:32633432	4.12%	NM_153809.2	missense	97
TAF1L	p.(V713I)	c.2137G>A	.	chr9:32633441	5.15%	NM_153809.2	missense	97
TAF1L	p.(=)	c.1915C>T	.	chr9:32633663	10.74%	NM_153809.2	synonymous	121
TAF1L	p.(P638S)	c.1912C>T	.	chr9:32633666	6.35%	NM_153809.2	missense	126
FANCC	p.(=)	c.1215G>A	.	chr9:97873859	4.79%	NM_000136.2	synonymous	167
RALGDS	p.(=)	c.2649C>T	.	chr9:135974067	10.71%	NM_001271775.1	synonymous	56
RALGDS	p.(T883I)	c.2648C>T	.	chr9:135974068	16.07%	NM_001271775.1	missense	56
NOTCH1	p.(=)	c.2454G>A	.	chr9:139407486	4.68%	NM_017617.4	synonymous	235
KAT6B	p.(=)	c.369C>T	.	chr10:76602984	12.50%	NM_012330.3	synonymous	56
KAT6B	p.(=)	c.372C>T	.	chr10:76602987	10.71%	NM_012330.3	synonymous	56
KAT6B	p.(S1717N)	c.5150G>A	.	chr10:76789732	10.53%	NM_012330.3	missense	57
KAT6B	p.(S1726F)	c.5177C>T	.	chr10:76789759	5.56%	NM_012330.3	missense	54
CYP2C19	p.(=)	c.426G>A	.	chr10:96535241	3.80%	NM_000769.2	synonymous	79
NFKB2	p.(=)	c.1269A>G	.	chr10:104159196	100.00%	NM_001077494.3	synonymous	256
SUFU	p.(=)	c.27C>T	.	chr10:104263936	3.91%	NM_016169.3	synonymous	128

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
SUFU	p.(P18L)	c.53C>T	.	chr10:104263962	5.56%	NM_016169.3	missense	90
SUFU	p.(=)	c.57C>T	.	chr10:104263966	4.55%	NM_016169.3	synonymous	88
SUFU	p.(P23L)	c.68C>T	.	chr10:104263977	4.29%	NM_016169.3	missense	70
NUP98	p.(T1755I)	c.5264C>T	.	chr11:3697528	4.99%	NM_016320.4	missense	361
NUP98	p.(S1754L)	c.5261C>T	.	chr11:3697531	3.88%	NM_016320.4	missense	361
WT1	p.(S138F)	c.413C>T	.	chr11:32456479	3.67%	NM_024426.4	missense	109
MEN1	p.(?)	c.-11C>T	.	chr11:64577592	5.93%	NM_000244.3	unknown	118
KMT2D	p.(=)	c.2391G>A	.	chr12:49445075	5.26%	NM_003482.3	synonymous	114
KMT2D	p.(=)	c.2379G>A	.	chr12:49445087	5.13%	NM_003482.3	synonymous	117
KMT2D	p.(E793K)	c.2377G>A	.	chr12:49445089	6.78%	NM_003482.3	missense	118
KMT2D	p.(A792V)	c.2375C>T	.	chr12:49445091	5.08%	NM_003482.3	missense	118
KMT2D	p.(A792T)	c.2374G>A	.	chr12:49445092	4.24%	NM_003482.3	missense	118
CDK4	p.(=)	c.306A>G	.	chr12:58145038	46.78%	NM_000075.3	synonymous	1150
EP400	p.(P34L)	c.101C>T	.	chr12:132445265	4.95%	NM_015409.4	missense	101
CDK8	p.(A329V)	c.986C>T	.	chr13:26974642	3.97%	NM_001260.2	missense	126
FLT3	p.(E648K)	c.1942G>A	.	chr13:28608024	4.00%	NM_004119.2	missense	75
FLT3	p.(G619S)	c.1855G>A	.	chr13:28608111	4.11%	NM_004119.2	missense	73
FLT1	p.(=)	c.2901G>A	.	chr13:28896979	46.62%	NM_002019.4	synonymous	1999
IRS2	p.(=)	c.633G>A	.	chr13:110437768	4.65%	NM_003749.2	synonymous	86
IRS2	p.(G206S)	c.616G>A	.	chr13:110437785	4.76%	NM_003749.2	missense	84
IRS2	p.(=)	c.570C>T	.	chr13:110437831	7.41%	NM_003749.2	synonymous	81
IRS2	p.(=)	c.312C>T	.	chr13:110438089	55.28%	NM_003749.2	synonymous	1999
TRIP11	p.(T1829I)	c.5486C>T	.	chr14:92441059	9.79%	NM_004239.4	missense	143
TCL1A	p.(D16N)	c.46G>A	.	chr14:96180358	5.70%	NM_021966.2	missense	158
HSP90AA1	p.(A146T)	c.436G>A	.	chr14:102552646	4.30%	NM_001017963.2	missense	279
TCF12	p.(H85Y)	c.253C>T	.	chr15:57384017	3.70%	NM_207037.1	missense	108
BLM	p.(R808C)	c.2422C>T	.	chr15:91312683	4.69%	NM_000057.3	missense	64
CREBBP	p.(=)	c.6420G>A	.	chr16:3778628	4.17%	NM_004380.2	synonymous	72
CREBBP	p.(=)	c.6415C>T	.	chr16:3778633	8.22%	NM_004380.2	synonymous	73
CREBBP	p.(P2137L)	c.6410C>T	.	chr16:3778638	5.48%	NM_004380.2	missense	73
CREBBP	p.(P1947L)	c.5840C>T	.	chr16:3779208	4.81%	NM_004380.2	missense	187
MYH11	p.(=)	c.4662G>A	.	chr16:15814846	4.70%	NM_001040114.1	synonymous	298
MYH11	p.(=)	c.4656G>A	.	chr16:15814852	6.44%	NM_001040114.1	synonymous	295

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
MYH11	p.(M1548I)	c.4644G>A	.	chr16:15814864	4.18%	NM_001040114.1	missense	287
MMP2	p.(=)	c.1254G>A	.	chr16:55525786	50.00%	NM_004530.5	synonymous	1784
CDH11	p.(=)	c.135G>A	.	chr16:65038638	3.65%	NM_001797.3	synonymous	301
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	99.93%	NM_001795.4	missense	1412
CDK12	p.(P536S)	c.1606C>T	.	chr17:37627691	4.88%	NM_016507.3	missense	164
STK11	p.(=)	c.501G>A	.	chr19:1220408	8.57%	NM_000455.4	synonymous	70
STK11	p.(=)	c.519G>A	.	chr19:1220426	8.57%	NM_000455.4	synonymous	70
STK11	p.(H174Y)	c.520C>T	.	chr19:1220427	4.29%	NM_000455.4	missense	70
MAP2K2	p.(R397C)	c.1189C>T	.	chr19:4090610	4.20%	NM_030662.3	missense	143
MAP2K2	p.(G393S)	c.1177G>A	.	chr19:4090622	6.25%	NM_030662.3	missense	144
MAP2K2	p.(P392S)	c.1174C>T	.	chr19:4090625	5.56%	NM_030662.3	missense	144
JAK3	p.(H583Y)	c.1747C>T	.	chr19:17947977	4.60%	NM_000215.3	missense	87
AKT2	p.(M180I)	c.540G>A	.	chr19:40747878	6.73%	NM_001626.5	missense	223
AKT2	p.(=)	c.537C>T	.	chr19:40747881	4.05%	NM_001626.5	synonymous	222
AKT2	p.(A179V)	c.536C>T	.	chr19:40747882	8.64%	NM_001626.5	missense	220
AKT2	p.(=)	c.502C>T	.	chr19:40747916	4.35%	NM_001626.5	synonymous	138
CIC	p.(=)	c.3528C>T	.	chr19:42797166	3.92%	NM_015125.4	synonymous	51
CIC	p.(G1607D)	c.4820G>A	.	chr19:42799336	9.45%	NM_015125.4	missense	201
MARK4	p.(G584S)	c.1750G>A	.	chr19:45801085	5.13%	NM_001199867.1	missense	195
ERCC1	p.(G4R)	c.10G>A	.	chr19:45926623	8.21%	NM_001983.3	missense	207
ASXL1	p.(=)	c.672C>T	.	chr20:31017810	4.26%	NM_015338.5	synonymous	141
ITGB2	p.(=)	c.906A>G	.	chr21:46319069	55.70%	NM_000211.4	synonymous	1264
MYH9	p.(?)	c.2838+1G>A	.	chr22:36696896	5.48%	NM_002473.5	unknown	146
MYH9	p.(=)	c.1449C>T	.	chr22:36710295	13.64%	NM_002473.5	synonymous	88
KDM5C	p.(P362S)	c.1084C>T	.	chrX:53243909	3.89%	NM_004187.3	missense	386
AMER1	p.(E1115K)	c.3343G>A	.	chrX:63409824	8.24%	NM_152424.3	missense	182
TAF1	p.(V802M)	c.2404G>A	.	chrX:70607228	10.61%	NM_004606.4	missense	66
TAF1	p.(=)	c.3612G>A	.	chrX:70617248	5.75%	NM_004606.4	synonymous	87
TAF1	p.(=)	c.3642C>T	.	chrX:70617278	4.55%	NM_004606.4	synonymous	88
TAF1	p.(=)	c.3657G>A	.	chrX:70617293	3.41%	NM_004606.4	synonymous	88

Biomarker Descriptions

ASXL1 (ASXL transcriptional regulator 1)

Background: The ASXL1 gene encodes the ASXL transcriptional regulator 1 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation[1,2]. ASXL1 belongs to the ASXL gene family, which also includes ASXL2 and ASXL3[2]. ASXL proteins contain a conserved c-terminal plant homeodomain (PHD) which facilitates interaction with DNA and histones[2,3]. ASXL1 influences chromatin remodeling and transcription through interaction with BAP1 and polycomb repressive complex (PRC) proteins, as well as other transcriptional activators and repressors[2,4]. In cancer, ASXL1 is the target of somatic mutations which often result in a truncated ASXL1 protein and loss of its PHD[5,6,7]. Such mutations can lead to impaired protein function and consequent upregulation of HOXA gene expression, supporting a tumor suppressor role for ASXL1[8].

Alterations and prevalence: Missense, nonsense, and frameshift mutations in ASXL1 are reported in 3-6% of de novo acute myeloid leukemia (AML), up to 36% of secondary AML, approximately 15% of myelodysplastic syndromes (MDS), up to 23% of myeloproliferative neoplasms (MPN), up to 30% of systemic mastocytosis (SM), and approximately 45% of chronic myelomonocytic leukemia (CMML)[4,9,10,11,12,13,14,15,16]. The ASXL1 G646Wfs*12 mutation accounts for over 50% of ASXL1 mutated cases in myeloid malignancies[6,11,17]. This mutation results from a single nucleotide expansion that occurs within an eight base pair guanine repeat that extends from c.1927 to c.1934. It is proposed that the high prevalence of the G646Wfs*12 variant is due to replication slippage which can occur in areas of repetitive sequence[18]. As a consequence, detection of G646Wfs*12 may result as an artifact of PCR and/or sequencing[19]. However, multiple studies observe an increase in the frequency of G646Wfs*12 in myeloid cancer relative to normal suggesting that G646Wfs*12 is a bona fide somatic mutation[9,18,20].

Potential relevance: The majority of frameshift and nonsense mutations in ASXL1 that result in protein truncation and removal of the PHD domain are considered pathogenic[21]. Mutations in ASXL1 confer poor/adverse risk in AML and are associated with poor outcomes[16]. Additionally, ASXL1 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and CMML[22]. Moreover, ASXL1 mutations are independently associated with inferior overall survival (OS) in patients with MPN or SM[23,24].

CREBBP (CREB binding protein)

Background: The CREBBP gene encodes the CREB binding protein (also known as CBP), a highly conserved and ubiquitously expressed tumor suppressor. CREBBP is a member of the KAT3 family of lysine acetyl transferases, which, along with EP300, interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[25,26]. CREBBP functions as a global transcriptional coactivator through the modification of lysines on nuclear proteins[25]. CREBBP binds to cAMP-response element binding protein (CREB) and is known to play a role in embryonic development, growth, and chromatin remodeling[25]. Upon disruption of normal CREBBP functions through genomic alterations, cells become susceptible to defects in differentiation and malignant transformation[27]. Inherited CREBBP mutations and deletions result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[28].

Alterations and prevalence: Mutations in CREBBP are observed in up to 12% of bladder urothelial carcinoma, uterine corpus endometrial carcinoma, and skin cutaneous melanoma, and in 5-10% of stomach adenocarcinoma, lung squamous cell carcinoma, and cervical squamous cell carcinoma[12,29]. CREBBP is frequently mutated in 15-17% of small cell lung cancer (SCLC)[30]. Inactivating mutations and deletions of CREBBP account for over 70% of all B-cell non-Hodgkin lymphoma diagnoses including 60% of follicular lymphoma and 30% of diffuse large-B-cell lymphoma (DLBCL)[25]. The rare t(11;16)(q23;p13) translocation fuses CREBBP with the partner gene KMT2A/MLL, in 0.2% secondary AML and 0.1% myelodysplastic syndrome (MDS)[31,32,33]. Elevated expression of CBP was detected in lung cancer cells and tumor tissue as compared to normal lung cells in one study[34].

Potential relevance: The t(11;16)(q23;p13.3) translocation is recognized by the World Health Organization (WHO) as one of the balanced abnormalities that define AML with myelodysplasia-related changes[35]. The t(11;16)(q23;p13.3) translocation and resulting CREBBP-KMT2A fusion is considered a diagnostic marker of myelodysplastic syndrome[36]. SCLC patients with CREBBP-positive SCLC demonstrate lower overall survival (OS) and disease free survival (DFS) compared to those with CREBBP-negative tumors[37].

PTEN (phosphatase and tensin homolog)

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[38]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[39,40]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[41]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[42].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer[12,29]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173,

Biomarker Descriptions (continued)

and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[40,43,44,45,46]. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer[12,29].

Potential relevance: Currently, no therapies are approved for PTEN aberrations. However, due to the role of PTEN in genome stability, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[47,48].

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[49]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[50,51,52,53,54]. 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[55,56,57,58].

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[59]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[56,59]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[56,59]. 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)[56,59,60]. 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[59,61,62]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[63,64,65,66].

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[67] 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[64,68,69]. In contrast, several promising 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[70]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[71]. 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[72,73,74,75,76,77,78,79,80]. 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[81,82,83,84].

Relevant Therapy Summary

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

PTEN p.(T319fs) c.956delC

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
atezolizumab	✖	✖	✖	✖	● (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

PTEN p.(T319fs) c.956delC (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
copanlisib	✖	✖	✖	✖	● (II)
ipatasertib	✖	✖	✖	✖	● (II)
niraparib	✖	✖	✖	✖	● (II)
olaparib	✖	✖	✖	✖	● (II)
paxalisib	✖	✖	✖	✖	● (II)
samotolisib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
temsirolimus	✖	✖	✖	✖	● (II)
copanlisib, nivolumab, ipilimumab	✖	✖	✖	✖	● (I/II)
ipatasertib, atezolizumab	✖	✖	✖	✖	● (I/II)
TAS-117, futibatinib	✖	✖	✖	✖	● (I/II)
xevinapant, nivolumab	✖	✖	✖	✖	● (I/II)
AZD-8186, chemotherapy	✖	✖	✖	✖	● (I)
BAY-1895344, niraparib	✖	✖	✖	✖	● (I)
copanlisib, olaparib, durvalumab	✖	✖	✖	✖	● (I)
HWH-340	✖	✖	✖	✖	● (I)
paxalisib, radiation therapy	✖	✖	✖	✖	● (I)
talazoparib, palbociclib, axitinib, crizotinib	✖	✖	✖	✖	● (I)
TAS-0612	✖	✖	✖	✖	● (I)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	◑	✖	✖	● (II)
atezolizumab	✖	✖	✖	✖	● (II)
atezolizumab + chemotherapy	✖	✖	✖	✖	● (II)
atezolizumab, nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (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*
nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
chemotherapy, tremelimumab, durvalumab	✖	✖	✖	✖	● (I/II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BAY1905254	✖	✖	✖	✖	● (I)
nivolumab, ipilimumab	✖	✖	✖	✖	● (I)
pembrolizumab, targinine	✖	✖	✖	✖	● (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 2021-04-14. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2021-03-22 **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 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

- 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)

Tumor Mutational Burden (continued)

- 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)

- 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/2021/125514s096lbl.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 2021-04-01. 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: Cholangiocarcinoma, Liver Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Gallbladder Cancer, Intrahepatic, Extrahepatic; Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 1.2021]

○ pembrolizumab

Cancer type: Chondrosarcoma, 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 1.2021]

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

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

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2021]

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 1.2021]

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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 2.2021]

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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 2.2021]

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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 1.2021]

Tumor Mutational Burden (continued)

pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Testicular Cancer [Version 1.2021]

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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)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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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 (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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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 (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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pembrolizumab

Cancer type: Endometrial Cancer, Uterine Sarcoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Metastatic (Line of therapy not specified); Useful in certain circumstances

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

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Ewing Sarcoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 1.2021]

Clinical Trials Summary

PTEN p.(T319fs) c.956delC

NCT ID	Title	Phase
NCT04122625	A Dose-optimization, Exploratory Phase Ib/II Study to Assess Safety and Efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) Mimetic Debio 1143, When Given in Combination With the Anti-PD-1 Antibody Nivolumab in Patients With Specific Solid Tumors Who Have Progressed During or Immediately After Anti-PD-1/PD-L1 Treatment	I/II
NCT02465060	Molecular Analysis for Therapy Choice (MATCH).	II
NCT03207347	A Phase II Trial of the PARP Inhibitor, Niraparib, in BAP1 and Other DNA Damage Response (DDR) Pathway Deficient Neoplasms (UF-STO-ETI-001).	II
NCT04042831	A Phase II Study of Olaparib in Patients With Advanced Biliary Tract Cancer With Aberrant DNA Repair Gene Mutations	II
NCT02286687	Phase II Study of the PARP Inhibitor Talazoparib in Advanced Cancer Patients With Somatic Alterations in BRCA1/2, Mutations/Deletions in Other BRCA Pathway Genes and Germline Mutation in BRCA1/2 (Not Breast or Ovarian Cancer)	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
NCT04317105	A Phase I/II Biomarker Driven Combination Trial of Copanlisib and Immune Checkpoint Inhibitors in Patients With Advanced Solid Tumors	I/II
NCT03218826	A Phase I Study of AZD8186 in Combination With Docetaxel in Patients With PTEN Mutated or PIK3CB Mutated Advanced Solid Tumors, Potentially Amenable to Docetaxel	I
NCT03842228	A Phase Ib Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and Durvalumab (MEDI4736) in Patients With Advanced Solid Tumors	I
NCT04192981	A Phase I Study With Expansion Cohort of Concurrent GDC-0084 With Radiation Therapy for Patients With Solid Tumor Brain Metastases or Leptomeningeal Metastases Harboring PI3K Pathway Mutations	I
NCT04586270	A Phase I Study of TAS0612 in Patients With Locally Advanced or Metastatic Solid Tumors	I
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	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

Clinical Trials Summary (continued)

PTEN p.(T319fs) c.956delC (continued)

NCT ID	Title	Phase
No NCT ID	Phase I/II Study of TAS-117 In Combination With TAS-120 In Patients With Advanced Solid Tumors	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
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
NCT03994796	Genomically-Guided Treatment Trial in Brain Metastases	II
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT03213678	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase II Subprotocol of LY3023414 in Patients With Solid Tumors	II
NCT03233204	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase 2 Subprotocol of Olaparib in Patients With Tumors Harboring Defects in DNA Damage Repair Genes	II
NCT03673787	Ice-CAP: A Phase I Trial of Ipatasertib in Combination With Atezolizumab in Patients With Advanced Solid Tumours With PI3K Pathway Hyperactivation	I/II
NCT04267939	An Open-label Phase Ib Study to Determine the Maximum Tolerated and/or Recommended Phase II Dose of the ATR Inhibitor BAY 1895344 in Combination With PARP Inhibitor Niraparib, in Patients With Recurrent Advanced Solid Tumors and Ovarian Cancer	I
NCT04693468	Modular Phase IB Hypothesis-Testing, Biomarker-Driven, Talazoparib Combination Trial (TalaCom)	I

Tumor Mutational Burden

NCT ID	Title	Phase
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
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT04632992	MyTACTIC: An Open-Label Phase II Study Evaluating Targeted Therapies in Patients Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response	II
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	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
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
No NCT ID	A Multicenter Phase II Study Of Nivolumab Monotherapy In Recurrent And/Or Metastatic Gastrointestinal Cancer Patients With High Tumor Mutation Burden (TMB-H)	II

Clinical Trials Summary (continued)

Tumor Mutational Burden (continued)

NCT ID	Title	Phase
No NCT ID	TR Accompanied with the Study Titled A Multicenter Phase II Study of Nivolumab Monotherapy in Recurrent and/or Metastatic Gastrointestinal Cancer Patients with High Tumor Mutation 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
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
NCT03838042	INFORM2 Exploratory Multinational Phase I/II Combination Study of Nivolumab and Entinostat in Children and Adolescents with Refractory High-risk Malignancies	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
NCT04500548	3CI Study: Childhood Cancer Combination Immunotherapy. Phase Ib and Expansion Study of Nivolumab Combination Immunotherapy in Children, Adolescent, and Young Adult (CAYA) Patients With Relapsed/Refractory Hypermutant Cancers	I
NCT03236935	Phase Ib Trial of L-NMMA in Combination With Pembrolizumab in Patients With Melanoma, Non-Small Cell Lung Cancer, Head and Neck Squamous Cell Carcinoma, Classical Hodgkin Lymphoma, Urothelial Carcinoma, Cervical Cancer, Esophageal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Primary Mediastinal Large B-cell Lymphoma, Renal Cell Carcinoma, Small Cell Lung Cancer, Microsatellite Instability-High/Mismatch Repair Deficient Cancer, or for the Treatment of Adult Patients With Unresectable or Metastatic Tumor Mutational Burden-High Solid Tumors	I

Signatures

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