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: 林麗姬
Gender: Female
ID No.: Q200696897
History No.: 45889074
Age: 67

Ordering Doctor: DOC1322F 趙毅
Ordering REQ.: H44F8HH
Signing in Date: 2022/10/05

Path No.: S111-97922
MP No.: TM22011
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S108-64091E
Percentage of tumor cells: 30%

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

Note:

Sample Cancer Type: Colon Cancer

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Relevant Colon Cancer Variants

Gene	Finding
BRAF	None detected
KRAS	***KRAS p.(G12V) c.35G>T***
NRAS	None detected
NTRK1	None detected
NTRK3	None detected

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Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*Tumor Mutational Burden* 35.46 Mut/Mb measured	**pembrolizumab** [1]	pembrolizumab	2
IIC	*PALB2 c.2514+1G>A* partner and localizer of BRCA2 Allele Frequency: 7.55%	None	**olaparib** [1] rucaparib	0
IA	*KRAS p.(G12V) c.35G>T* KRAS proto-oncogene, GTPase Allele Frequency: 31.07%	None	None	1
IIC	*TP53 p.(R248W) c.742C>T* tumor protein p53 Allele Frequency: 38.71%	None	None	1

Public data sources included in relevant therapies: FDA[1], NCCN, **EMA**[2], ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Alerts informed by public data sources: ⊘ Contraindicated, Resistance

KRAS p.(G12V) c.35G>T	⊘ **cetuximab** [1, 2], **cetuximab + chemotherapy** [2], **panitumumab** [1], **panitumumab + chemotherapy** [2]

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

Prevalent cancer biomarkers without relevant evidence based on included data sources
MSH6 p.(Q177) c.529C>T, SETD2 p.(Q1288*) c.3862C>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
MSH6	p.(Q177*)	c.529C>T	.	chr2:48023104	3.92%	NM_000179.3	nonsense	102
SETD2	p.(Q1288*)	c.3862C>T	.	chr3:47162264	41.31%	NM_014159.6	nonsense	1951
KRAS	p.(G12V)	c.35G>T	COSM520	chr12:25398284	31.07%	NM_033360.4	missense	1445
PALB2	p.(?)	c.2514+1G>A	.	chr16:23640960	7.55%	NM_024675.4	unknown	53
TP53	p.(R248W)	c.742C>T	COSM10656	chr17:7577539	38.71%	NM_000546.5	missense	1997
PIK3CD	p.(R512W)	c.1534C>T	.	chr1:9780812	48.39%	NM_005026.5	missense	1866
ARID1A	p.(F1343=)	c.4029C>T	.	chr1:27100317	4.41%	NM_006015.6	synonymous	68
CMPK1	p.(R54C)	c.160C>T	.	chr1:47799777	14.78%	NM_016308.3	missense	115
TRIM33	p.(V1062I)	c.3184G>A	.	chr1:114940470	3.37%	NM_015906.4	missense	89
NRAS	p.(D69=)	c.207C>T	.	chr1:115256504	6.25%	NM_002524.5	synonymous	352
NRAS	p.(M67I)	c.201G>A	.	chr1:115256510	6.88%	NM_002524.5	missense	349
NOTCH2	p.(T858I)	c.2573C>T	.	chr1:120491656	3.33%	NM_024408.4	missense	60
BCL9	p.(G664D)	c.1991G>A	.	chr1:147091952	4.20%	NM_004326.4	missense	262

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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
ARNT	p.(?)	c.-73C>T	.	chr1:150849116	4.62%	NM_001668.4	unknown	260
DDR2	p.(G61R)	c.181G>A	.	chr1:162722983	4.35%	NM_006182.4	missense	138
PBX1	p.(G35=)	c.105G>A	.	chr1:164529164	4.76%	NM_002585.4	synonymous	168
PBX1	p.(G38E)	c.113G>A	.	chr1:164529172	6.04%	NM_002585.4	missense	149
ABL2	p.(G729E)	c.2186G>A	.	chr1:179078171	5.45%	NM_005158.5	missense	110
ABL2	p.(G727R)	c.2179G>A	.	chr1:179078178	7.07%	NM_005158.5	missense	99
ABL2	p.(G720S)	c.2158G>A	.	chr1:179078199	5.05%	NM_005158.5	missense	99
ABL2	p.(G719=)	c.2157G>A	.	chr1:179078200	7.14%	NM_005158.5	synonymous	98
ABL2	p.(T671M)	c.2012C>T	.	chr1:179078345	30.78%	NM_005158.5	missense	718
ABL2	p.(M468I)	c.1404G>A	.	chr1:179084125	4.55%	NM_005158.5	missense	66
ABL2	p.(T465I)	c.1394C>T	.	chr1:179084135	4.55%	NM_005158.5	missense	66
MDM4	p.(D423N)	c.1267G>A	.	chr1:204518604	4.84%	NM_002393.5	missense	62
MARK1	p.(S429F)	c.1286C>T	.	chr1:220809184	3.17%	NM_018650.5	missense	63
DNMT3A	p.(P41=)	c.123C>G	.	chr2:25523062	48.75%	NM_022552.4	synonymous	1998
ALK	p.(G925R)	c.2773G>A	.	chr2:29451792	5.61%	NM_004304.5	missense	107
MSH6	p.(S998F)	c.2993C>T	.	chr2:48028115	4.05%	NM_000179.3	missense	74
BCL11A	p.(P269L)	c.806C>T	.	chr2:60689241	6.00%	NM_022893.4	missense	50
TCF7L1	p.(D166=)	c.498C>T	.	chr2:85510674	4.35%	NM_031283.3	synonymous	69
LRP1B	p.(W3103*)	c.9308G>A	.	chr2:141243029	6.17%	NM_018557.3	nonsense	81
LRP1B	p.(R1464=)	c.4392A>G	.	chr2:141625346	51.20%	NM_018557.3	synonymous	2000
LRP1B	p.(H42=)	c.126C>T	.	chr2:142567927	4.83%	NM_018557.3	synonymous	352
PMS1	p.(V508M)	c.1522G>A	.	chr2:190719520	3.70%	NM_000534.5	missense	162
FN1	p.(S247=)	c.741C>T	.	chr2:216293006	3.92%	NM_212482.3	synonymous	255
VHL	p.(E47K)	c.139G>A	.	chr3:10183670	3.70%	NM_000551.4	missense	108
TGFBR2	p.(P583S)	c.1747C>T	.	chr3:30733059	5.00%	NM_001024847.2	missense	60
BAP1	p.(?)	c.-45G>A	.	chr3:52443939	5.56%	NM_004656.4	unknown	72
PHF7	p.(?)	c.-2957C>T	.	chr3:52443939	5.56%	NM_016483.7	unknown	72
BAP1	p.(?)	c.-57G>A	.	chr3:52443951	4.17%	NM_004656.4	unknown	72
PHF7	p.(?)	c.-2945C>T	.	chr3:52443951	4.17%	NM_016483.7	unknown	72
BAP1	p.(?)	c.-60G>A	.	chr3:52443954	4.29%	NM_004656.4	unknown	70
PHF7	p.(?)	c.-2942C>T	.	chr3:52443954	4.29%	NM_016483.7	unknown	70
PBRM1	p.(T444I)	c.1331C>T	.	chr3:52663022	4.76%	NM_018313.5	missense	63
EPHA3	p.(I682=)	c.2046C>T	.	chr3:89468512	4.35%	NM_005233.6	synonymous	138

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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
ATR	p.(L2246R)	c.6737T>G	.	chr3:142185326	35.06%	NM_001184.4	missense	445
ATR	p.(L1208=)	c.3624G>A	.	chr3:142257425	4.41%	NM_001184.4	synonymous	68
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	99.49%	NM_006206.6	synonymous	1185
KDR	p.(P1107L)	c.3320C>T	.	chr4:55955625	3.76%	NM_002253.3	missense	133
APC	p.(D807N)	c.2419G>A	.	chr5:112173710	5.17%	NM_000038.6	missense	58
APC	p.(Y1135*)	c.3405T>A	.	chr5:112174696	33.67%	NM_000038.6	nonsense	1996
CSF1R	p.(W821*)	c.2463G>A	.	chr5:149435680	3.59%	NM_005211.3	nonsense	362
NPM1	p.(D246N)	c.736G>A	.	chr5:170832372	4.00%	NM_002520.6	missense	100
FGFR4	p.(E156K)	c.466G>A	.	chr5:176517968	4.26%	NM_213647.3	missense	94
NSD1	p.(D1824N)	c.5470G>A	.	chr5:176696769	3.95%	NM_022455.4	missense	76
NOTCH4	p.(R1680Q)	c.5039G>A	.	chr6:32165089	4.00%	NM_004557.4	missense	50
NOTCH4	p.(P1660L)	c.4979C>T	.	chr6:32165149	5.88%	NM_004557.4	missense	51
NOTCH4	p.(N1659=)	c.4977C>T	.	chr6:32165151	3.92%	NM_004557.4	synonymous	51
NOTCH4	p.(P1194L)	c.3581C>T	.	chr6:32170027	52.49%	NM_004557.4	missense	543
NOTCH4	p.(?)	c.-28G>A	.	chr6:32191733	6.67%	NM_004557.4	unknown	60
NOTCH4	p.(?)	c.-30G>A	.	chr6:32191735	3.33%	NM_004557.4	unknown	60
CILK1	p.(D423N)	c.1267G>A	.	chr6:52876911	3.85%	NM_014920.5	missense	130
DST	p.(N4032S)	c.12095A>G	.	chr6:56380372	5.19%	NM_001144769.5	missense	77
ADGRB3	p.(P1353S)	c.4057C>T	.	chr6:70071222	4.08%	NM_001704.3	missense	98
TNFAIP3	p.(R691=)	c.2073G>A	.	chr6:138201374	5.97%	NM_001270507.2	synonymous	67
ESR1	p.(M342I)	c.1026G>A	.	chr6:152265573	4.21%	NM_001122740.1	missense	95
SYNE1	p.(E8397K)	c.25189G>A	.	chr6:152462395	3.53%	NM_182961.4	missense	85
SYNE1	p.(E7752K)	c.23254G>A	.	chr6:152510434	4.82%	NM_182961.4	missense	83
SYNE1	p.(T4621=)	c.13863G>A	.	chr6:152651957	5.43%	NM_182961.4	synonymous	92
SYNE1	p.(K4121S)	c.12362_12363delAG insGT	.	chr6:152658141	49.33%	NM_182961.4	missense	371
SYNE1	p.(K4121R)	c.12362A>G	.	chr6:152658142	49.60%	NM_182961.4	missense	371
SYNE1	p.(S471F)	c.1412C>T	.	chr6:152793487	4.00%	NM_182961.4	missense	50
SYNE1	p.(A458=)	c.1374C>T	.	chr6:152793525	4.00%	NM_182961.4	synonymous	50
IGF2R	p.(P298S)	c.892C>T	.	chr6:160453592	3.45%	NM_000876.3	missense	58
TRRAP	p.(E1112=)	c.3336G>A	.	chr7:98527772	3.23%	NM_001244580.1	synonymous	62
TRRAP	p.(D2110N)	c.6328G>A	.	chr7:98556973	4.37%	NM_001244580.1	missense	252
EPHB4	p.(V683I)	c.2047G>A	.	chr7:100410440	6.06%	NM_004444.5	missense	66

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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
EPHB4	p.(P674L)	c.2021C>T	.	chr7:100410466	4.55%	NM_004444.5	missense	66
PIK3CG	p.(D964N)	c.2890G>A	.	chr7:106526597	5.08%	NM_002649.3	missense	59
GRM8	p.(S821=)	c.2463C>T	.	chr7:126086394	3.64%	NM_000845.3	synonymous	55
GRM8	p.(S821F)	c.2462C>T	.	chr7:126086395	3.64%	NM_000845.3	missense	55
BRAF	p.(G652R)	c.1954G>A	.	chr7:140449125	3.45%	NM_004333.6	missense	87
EPHB6	p.(C975Y)	c.2924G>A	.	chr7:142568405	4.84%	NM_004445.6	missense	62
KMT2C	p.(N4807=)	c.14421C>T	.	chr7:151836799	50.30%	NM_170606.3	synonymous	2000
ADGRA2	p.(S40F)	c.119C>T	.	chr8:37654905	7.35%	NM_032777.10	missense	68
FGFR1	p.(G512D)	c.1535G>A	.	chr8:38275498	31.53%	NM_001174067.1	missense	1719
KAT6A	p.(R865K)	c.2594G>A	.	chr8:41798805	5.48%	NM_006766.5	missense	73
CSMD3	p.(I578=)	c.1734C>T	.	chr8:113871395	4.35%	NM_198123.2	synonymous	115
CDKN2A	p.(T93M)	c.278C>T	.	chr9:21971080	3.85%	NM_001195132.1	missense	156
CDKN2B-AS1			.	chr9:21994187	4.00%	NR_047543.1		50
CDKN2B	p.(A50T)	c.148G>A	.	chr9:22008805	4.94%	NM_004936.4	missense	81
CDKN2B	p.(R49C)	c.145C>T	.	chr9:22008808	7.41%	NM_004936.4	missense	81
CDKN2B	p.(N41=)	c.123C>T	.	chr9:22008830	5.56%	NM_004936.4	synonymous	54
CDKN2B	p.(P40=)	c.120C>T	.	chr9:22008833	7.41%	NM_004936.4	synonymous	54
CDKN2B	p.(G37=)	c.111C>T	.	chr9:22008842	3.70%	NM_004936.4	synonymous	54
TAF1L	p.(R1509H)	c.4526G>A	.	chr9:32631052	4.35%	NM_153809.2	missense	69
TAF1L	p.(E1502=)	c.4506G>A	.	chr9:32631072	4.29%	NM_153809.2	synonymous	70
TAF1L	p.(P1443L)	c.4328C>T	.	chr9:32631250	6.72%	NM_153809.2	missense	119
TAF1L	p.(R1442W)	c.4324C>T	.	chr9:32631254	10.92%	NM_153809.2	missense	119
TAF1L	p.(P637L)	c.1910C>T	.	chr9:32633668	4.32%	NM_153809.2	missense	185
TAF1L	p.(R636=)	c.1908C>T	.	chr9:32633670	4.26%	NM_153809.2	synonymous	188
TAF1L	p.(R636C)	c.1906C>T	.	chr9:32633672	5.32%	NM_153809.2	missense	188
TAF1L	p.(K555=)	c.1665G>A	.	chr9:32633913	6.32%	NM_153809.2	synonymous	285
PTCH1	p.(S825N)	c.2474G>A	.	chr9:98229484	3.85%	NM_000264.5	missense	78
PTCH1	p.(M803I)	c.2409G>A	.	chr9:98229549	4.76%	NM_000264.5	missense	84
NUP214	p.(R783G)	c.2347A>G	.	chr9:134027192	49.21%	NM_005085.4	missense	756
TSC1	p.(P684L)	c.2051C>T	.	chr9:135779195	3.95%	NM_000368.5	missense	177
NOTCH1	p.(A1349T)	c.4045G>A	.	chr9:139400303	3.70%	NM_017617.5	missense	54
MLLT10	p.(T835I)	c.2504C>T	.	chr10:22022704	44.65%	NM_001195626.3	missense	159

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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
RET	p.(A416T)	c.1246G>A	.	chr10:43604661	7.87%	NM_020975.6	missense	89
KAT6B	p.(Q1716=)	c.5148G>A	.	chr10:76789730	7.63%	NM_012330.4	synonymous	118
KAT6B	p.(C1746Y)	c.5237G>A	.	chr10:76789819	4.20%	NM_012330.4	missense	119
SUFU	p.(?)	c.-14C>T	.	chr10:104263896	5.36%	NM_016169.4	unknown	56
TCF7L2	p.(G8E)	c.23G>A	.	chr10:114710538	5.36%	NM_001146274.2	missense	56
TCF7L2	p.(M107I)	c.321G>A	.	chr10:114711306	4.05%	NM_001146274.2	missense	74
FGFR2	p.(P303F)	c.907_908delCCinsTT	.	chr10:123279524	3.95%	NM_000141.5	missense	76
BIRC2	p.(V32I)	c.94G>A	.	chr11:102220826	4.68%	NM_001256166.2	missense	406
BIRC2	p.(L427F)	c.1279C>T	.	chr11:102248286	3.77%	NM_001256166.2	missense	53
GUCY1A2	p.(V452=)	c.1356C>A	.	chr11:106681055	29.29%	NM_000855.3	synonymous	1997
ATM	p.(I2316=)	c.6948C>T	.	chr11:108196925	3.28%	NM_000051.3	synonymous	61
KMT2A	p.(Y3945Tfs*26)	c.11832_11835delTTAC	.	chr11:118392797	34.86%	NM_001197104.2	frameshift Deletion	1968
ZNF384	p.(Q386*)	c.1156C>T	.	chr12:6779943	3.85%	NM_001135734.2	nonsense	104
ARID2	p.(T360I)	c.1079C>T	.	chr12:46231159	4.23%	NM_152641.4	missense	71
KMT2D	p.(A5363=)	c.16089A>G	.	chr12:49416622	51.35%	NM_003482.4	synonymous	1998
KMT2D	p.(A4362=)	c.13086T>G	.	chr12:49425402	54.67%	NM_003482.4	synonymous	75
KMT2D	p.(A3855V)	c.11564C>T	.	chr12:49426924	4.92%	NM_003482.4	missense	61
KMT2D	p.(Q800*)	c.2398C>T	.	chr12:49445068	4.27%	NM_003482.4	nonsense	164
KMT2D	p.(A792V)	c.2375C>T	.	chr12:49445091	5.36%	NM_003482.4	missense	168
ERBB3	p.(R488Q)	c.1463G>A	.	chr12:56487317	48.07%	NM_001982.4	missense	1999
ERBB3	p.(S1207N)	c.3620G>A	.	chr12:56495430	5.26%	NM_001982.4	missense	57
EP400	p.(P34L)	c.101C>T	.	chr12:132445265	8.45%	NM_015409.5	missense	71
EP400	p.(P581=)	c.1743G>A	.	chr12:132466837	46.45%	NM_015409.5	synonymous	887
EP400	p.(T2856I)	c.8567C>T	.	chr12:132551332	3.37%	NM_015409.5	missense	89
FOXO1	p.(T103=)	c.309C>T	.	chr13:41240041	5.26%	NM_002015.4	synonymous	95
BIVM-ERCC5	p.(A1440V)	c.4319C>T	.	chr13:103525686	5.17%	NM_001204425.2	missense	116
ERCC5	p.(A986V)	c.2957C>T	.	chr13:103525686	5.17%	NM_000123.4	missense	116
NIN	p.(L1906=)	c.5718G>A	.	chr14:51204915	4.17%	NM_020921.3	synonymous	168
NIN	p.(E1298=)	c.3894G>A	.	chr14:51223854	3.82%	NM_020921.3	synonymous	157
NIN	p.(S76F)	c.227C>T	.	chr14:51273493	3.33%	NM_020921.3	missense	60
DICER1	p.(P1231S)	c.3691C>T	.	chr14:95570042	3.23%	NM_030621.4	missense	62

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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
HSP90AA1	p.(A146T)	c.436G>A	.	chr14:102552646	4.96%	NM_001017963.3	missense	141
HSP90AA1	p.(Q145=)	c.435G>A	.	chr14:102552647	3.57%	NM_001017963.3	synonymous	140
KNL1	p.(D873N)	c.2617G>A	.	chr15:40915079	5.26%	NM_144508.5	missense	57
LTK	p.(L815=)	c.2443C>T	.	chr15:41796346	4.32%	NM_002344.6	synonymous	162
LTK	p.(G207S)	c.619G>A	.	chr15:41804053	3.17%	NM_002344.6	missense	63
TGM7	p.(T519=)	c.1557C>T	.	chr15:43571944	8.77%	NM_052955.3	synonymous	57
TGM7	p.(S518=)	c.1554C>T	.	chr15:43571947	7.02%	NM_052955.3	synonymous	57
IGF1R	p.(F420=)	c.1260C>T	.	chr15:99451926	3.64%	NM_000875.5	synonymous	55
CREBBP	p.(P1946S)	c.5836C>T	.	chr16:3779212	5.03%	NM_004380.3	missense	179
MYH11	p.(K1552=)	c.4656G>A	.	chr16:15814852	5.45%	NM_001040114.1	synonymous	110
MYH11	p.(M1551I)	c.4653G>A	.	chr16:15814855	6.84%	NM_001040114.1	missense	117
MYH11	p.(E1550=)	c.4650G>A	.	chr16:15814858	9.73%	NM_001040114.1	synonymous	113
MYH11	p.(D258N)	c.772G>A	.	chr16:15872676	28.08%	NM_001040114.1	missense	1282
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	45.83%	NM_001795.5	missense	1270
MAF	p.(A387T)	c.1159G>A	.	chr16:79628410	3.70%	NM_005360.5	missense	81
FANCA	p.(G106E)	c.317G>A	.	chr16:89877446	4.17%	NM_000135.4	missense	120
CDK12	p.(S1191=)	c.3573A>G	.	chr17:37682382	47.25%	NM_016507.4	synonymous	2000
PGAP3	p.(H284=)	c.852T>C	.	chr17:37829351	53.07%	NM_033419.5	synonymous	1924
ERBB2	p.(V1180I)	c.3538G>A	.	chr17:37884067	4.00%	NM_004448.3	missense	75
ITGB3	p.(S411F)	c.1232C>T	.	chr17:45368426	43.25%	NM_000212.3	missense	2000
DCC	p.(R668=)	c.2004G>A	.	chr18:50832040	5.06%	NM_005215.4	synonymous	158
DCC	p.(E670=)	c.2010G>A	.	chr18:50832046	4.43%	NM_005215.4	synonymous	158
BCL2	p.(A42Pfs*54)	c.124delG	.	chr18:60985775	72.79%	NM_000633.2	frameshift Deletion	441
BCL2	p.(P40Rfs*112)	c.119_127delCGGGGGCCGinsGGGGCCA	.	chr18:60985773	27.21%	NM_000633.2	frameshift Block Substitution	441
STK11	p.(Y166=)	c.498C>T	.	chr19:1220405	9.38%	NM_000455.5	synonymous	64
STK11	p.(L167=)	c.501G>A	.	chr19:1220408	4.62%	NM_000455.5	synonymous	65
TCF3	p.(H513=)	c.1539C>T	.	chr19:1615732	3.64%	NM_001136139.4	synonymous	55
GNA11	p.(L273=)	c.819C>T	.	chr19:3119287	3.87%	NM_002067.5	synonymous	181
MAP2K2	p.(P395=)	c.1185C>T	.	chr19:4090614	7.62%	NM_030662.4	synonymous	210
MAP2K2	p.(T394I)	c.1181C>T	.	chr19:4090618	5.71%	NM_030662.4	missense	210
MAP2K2	p.(G393S)	c.1177G>A	.	chr19:4090622	6.19%	NM_030662.4	missense	210

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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
JAK3	p.(L587=)	c.1761C>T	.	chr19:17947963	3.45%	NM_000215.4	synonymous	58
JAK3	p.(C16=)	c.48C>T	.	chr19:17955179	30.00%	NM_000215.4	synonymous	50
PIK3R2	p.(S158F)	c.473C>T	.	chr19:18271870	3.39%	NM_005027.4	missense	59
CCNE1	p.(G400S)	c.1198G>A	.	chr19:30314649	26.35%	NM_001238.4	missense	2000
CEBPA	p.(P198L)	c.593C>T	.	chr19:33792728	4.08%	NM_004364.4	missense	98
CEBPA	p.(P184S)	c.550C>T	.	chr19:33792771	3.77%	NM_004364.4	missense	106
AKT2	p.(G287D)	c.860G>A	.	chr19:40742264	5.59%	NM_001626.6	missense	143
AKT2	p.(M180I)	c.540G>A	.	chr19:40747878	12.87%	NM_001626.6	missense	101
AKT2	p.(Y178=)	c.534C>T	.	chr19:40747884	7.29%	NM_001626.6	synonymous	96
CIC	p.(E513K)	c.1537G>A	.	chr19:42794457	5.71%	NM_015125.4	missense	70
CIC	p.(L1283=)	c.3847C>T	.	chr19:42797795	51.55%	NM_015125.4	synonymous	772
CIC	p.(G1607D)	c.4820G>A	.	chr19:42799336	5.32%	NM_015125.4	missense	263
CIC	p.(G1607=)	c.4821C>T	.	chr19:42799337	5.34%	NM_015125.4	synonymous	262
CIC	p.(*1609=)	c.4826G>A	.	chr19:42799342	4.14%	NM_015125.4	stoploss	266
MIR8085			.	chr19:45261477	44.05%	NR_107052.1		479
ERCC2	p.(F654=)	c.1962C>T	.	chr19:45855848	48.50%	NM_000400.4	synonymous	2000
PPP2R1A	p.([L388=;D389N])	c.1164_1165delGGinsAA	.	chr19:52722979	4.71%	NM_014225.6	synonymous, missense	85
MAFB	p.(P97=)	c.291C>T	.	chr20:39317200	3.45%	NM_005461.5	synonymous	87
MAFB	p.(S6=)	c.18C>T	.	chr20:39317473	4.95%	NM_005461.5	synonymous	101
PTPRT	p.(G1127R)	c.3379G>A	.	chr20:40735494	5.41%	NM_133170.4	missense	74
PTPRT	p.(N344=)	c.1032C>T	.	chr20:41306627	4.81%	NM_133170.4	synonymous	104
AURKA	p.(P12L)	c.35C>T	.	chr20:54963219	4.00%	NM_003600.4	missense	100
ITGB2	p.(D272=)	c.816C>T	.	chr21:46320316	3.91%	NM_000211.5	synonymous	128
MYH9	p.(I486=)	c.1458C>T	.	chr22:36710286	7.46%	NM_002473.6	synonymous	67
MYH9	p.(F485=)	c.1455C>T	.	chr22:36710289	16.42%	NM_002473.6	synonymous	67
MYH9	p.(T483I)	c.1448C>T	.	chr22:36710296	7.46%	NM_002473.6	missense	67
USP9X	p.(L276F)	c.826C>T	.	chrX:41000274	4.92%	NM_001039590.3	missense	61
AMER1	p.(P746L)	c.2237C>T	.	chrX:63410930	4.20%	NM_152424.4	missense	143
AMER1	p.(K166*)	c.496A>T	.	chrX:63412671	30.75%	NM_152424.4	nonsense	2000
TAF1	p.(V782M)	c.2344G>A	.	chrX:70607228	4.35%	NM_004606.5	missense	69
TAF1	p.(V783I)	c.2347G>A	.	chrX:70607231	5.80%	NM_004606.5	missense	69
TAF1	p.(?)	c.3228-1G>A	.	chrX:70613916	4.11%	NM_004606.5	unknown	73

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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
TAF1	p.(D1097N)	c.3289G>A	.	chrX:70613978	4.11%	NM_004606.5	missense	73
TAF1	p.(R1182C)	c.3544C>T	.	chrX:70617240	5.88%	NM_004606.5	missense	204
TAF1	p.(E1184K)	c.3550G>A	.	chrX:70617246	7.04%	NM_004606.5	missense	199
TAF1	p.(E1184=)	c.3552G>A	.	chrX:70617248	4.52%	NM_004606.5	synonymous	199
TBX22	p.(P66L)	c.197C>T	.	chrX:79278580	46.39%	NM_016954.2	missense	429
BTK	p.(I94=)	c.282C>T	.	chrX:100626648	4.13%	NM_000061.3	synonymous	121
PAK3	p.(P560S)	c.1678C>T	.	chrX:110463610	4.00%	NM_001128168.3	missense	50
PAK3	p.(L567=)	c.1701G>A	.	chrX:110463633	5.88%	NM_001128168.3	synonymous	51

Biomarker Descriptions

KRAS (KRAS proto-oncogene, GTPase)

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[1,2,3].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[4]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[4,5,6]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,8].

Potential relevance: The KRAS inhibitor, sotorasib[9], is approved (2021) for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The FDA has granted breakthrough therapy designation (2021) to the small molecule inhibitor, adagrasib, for KRAS G12C positive in non-small cell lung cancer following prior systemic therapy[10].The small molecular inhibitor, RO-5126766, was also granted breakthrough designation (2021) alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer[11]. Additionally, onvansertib[12] was granted fast track designation (2020) for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab[13] and panitumumab[14], are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[8]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[15].

MSH6 (mutS homolog 6)

Background: The MSH6 gene encodes the mutS homolog 6 protein[16]. MSH6 is a tumor suppressor gene that heterodimerizes with MSH2 to form the MutSα complex[17]. The MutSα complex functions in the DNA damage recognition of base-base mismatches or insertion/deletion (indels) of 1-2 nucleotides[17]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication. Mutations in MSH2 result in the degradation of MSH6[18]. MSH6, along with MLH1, MSH2, and PMS2 form the core components of the MMR pathway[17]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[19,20,21]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[19,22]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[20,22,23,24]. Specifically, MSH6 mutations are associated with increased risk of ovarian and pancreatic cancer[25].

Alterations and prevalence: Somatic mutations in MSH6 are observed in 11% of uterine corpus endometrial carcinoma, 4% colorectal adenocarcinoma, and 3% skin cutaneous melanoma[4,7].

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Biomarker Descriptions (continued)

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[26]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[27,28].

PALB2 (partner and localizer of BRCA2)

Background: The PALB2 gene encodes the partner and localizer of BRCA2 protein that binds to and promotes intranuclear localization of the breast cancer 2 early onset (BRCA2) protein[29]. Also known as FANCN, PALB2 belongs to the Fanconi Anemia (FA) complementation group of proteins that also include FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, and FANCM. FA genes are tumor suppressors that play a role in interstrand cross-link (ICL) DNA repair through homologous recombination repair (HRR) of double-strand breaks (DSB) and nucleotide excision repair (NER)[30]. Loss of function mutations of genes in the FA family and HRR pathway, including PALB2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[31,32]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities including bone marrow failure and cancer predisposition[33,34]. Specifically, biallelic germline mutations resulting in PALB2 loss of function confer a predisposition to pediatric malignancies[35,36]. Additionally, monoallelic germline mutations in PALB2 have been associated with an increased risk of developing breast cancer[35,37].

Alterations and prevalence: Somatic alterations in PALB2 include missense or truncating mutations and are observed in 2-6% of melanoma, uterine, bladder, breast, lung, stomach and colorectal cancers[4].

Potential relevance: The PARP inhibitor, olaparib[38] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes PALB2. In a phase II trial of patients with metastatic, castration-resistant prostate cancer, one patient exhibiting a somatic PALB2 frameshift mutation exhibited durable response to olaparib for 39 weeks[39,40]. However, olaparib resistance was observed following 9-months of treatment due to the emergence of a secondary deletion which restored the PALB2 reading frame, a resistance mechanism similar to that observed in PARPi treated BRCA mutated patients[40,41]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[42], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

SETD2 (SET domain containing 2, histone lysine methyltransferase)

Background: The SETD2 gene encodes the SET domain containing 2 histone lysine methyltransferase, a protein responsible for the trimethylation of lysine-36 on histone H3 (H3K36)[43,44]. Methylation of H3K36 is a hallmark of active transcription and can be either mono-, di-, or tri-methylated where di- and tri-methylation are thought to be responsible for transcriptional regulation[45]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[46,47]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[44]. Specifically, H3K36 tri-methylation by SETD2 has been shown to regulate mismatch repair (MMR) in vivo, wherein the loss of SETD2 results in MMR deficiency (dMMR) and consequent microsatellite instability (MSI)[48]. Both copy number deletion and mutations resulting in SETD2 loss of function have been observed in a variety of cancers, suggesting a tumor suppressor role for SETD2[44,49].

Alterations and prevalence: Inactivating somatic mutations in SETD2 were first described in clear cell renal cell carcinoma (ccRCC) and are observed to be predominantly missense or truncating[4,49,50]. Mutations at codon R1625 are observed to be the most recurrent with R1625C having been identified to result in loss of SETD2 H3K36 trimethylase activity[4,43]. SETD2 mutation is observed in about 14% of uterine cancer, 12% of ccRCC, 9% of mesothelioma, and 6-7% of melanoma, lung adenocarcinoma, papillary renal cell carcinoma (pRCC), colorectal and bladder cancers[43]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[43].

Potential relevance: Currently, no therapies are approved for SETD2 aberrations. Mutations in SETD2 can be used to support diagnosis of hepatosplenic T-cell lymphoma (HSTCL)[51].

TP53 (tumor protein p53)

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[52]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[53,54].

Biomarker Descriptions (continued)

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[4,7,55,56,57,58]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[4,7]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[59,60,61,62].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation[63]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[64] and breakthrough designation[65] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[66,67]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL)[68,69,70,71]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[72]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[73].

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[74]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[75,76,77,78,79]. 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[80,81,82,83].

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[84]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[81,84]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[81,84]. 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)[81,84,85]. 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[84,86,87]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[88,89,90,91].

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[26] 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[89,92,93]. 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[94]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[95]. 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[96,97,98,99,100,101,102,103,104]. 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[105,106,107,108].

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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)

PALB2 c.2514+1G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	○	○	✖	✖	✖
rucaparib	✖	○	✖	✖	✖

KRAS p.(G12V) c.35G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IMP7068	✖	✖	✖	✖	● (I)

TP53 p.(R248W) c.742C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IMP7068	✖	✖	✖	✖	● (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 FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

FDA information is current as of 2022-08-17. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2022-08-05 **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 adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

Tumor Mutational Burden (continued)

- 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
- 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, 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 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) as determined by an FDA-approved test.

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]

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 mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
- as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, 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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

Tumor Mutational Burden (continued)

- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1]
- Limitations of Use: The safety and effectiveness of KEYTRUDA® in pediatric patients with TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma (cSCC)

- for the treatment of patients with recurrent or metastatic 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/2022/125514s133lbl.pdf

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

PALB2 c.2514+1G>A

olaparib

Cancer type: Castration-Resistant Prostate Cancer **Label as of:** 2022-03-11 **Variant class:** PALB2 mutation

Indications and usage:

LYNPARZA® is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

Ovarian cancer

- for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.
- in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:
  - a deleterious or suspected deleterious BRCA mutation, and/or
  - genomic instability.

Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
- for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

Breast cancer

- for the adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.
- for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

Pancreatic cancer

- for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

Prostate cancer

- for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208558s023lbl.pdf

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

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 2022-08-01. 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 4.2022]

○ 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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

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 3.2022]

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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 2.2022]

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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 2.2022]

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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 2.2022]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Large Cell Neuroendocrine Carcinoma, Mixed Neuroendocrine Non-Neuroendocrine Neoplasm, Small Cell Neuroendocrine Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 1.2022]

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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, Progression, Unresectable (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 1.2022]

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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 3.2022]

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pembrolizumab

Cancer type: Pancreatic Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma; Metastatic (First-line therapy); Useful in certain circumstances
- Adenocarcinoma; Locally Advanced, Metastatic, Recurrent (Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 1.2022]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

Tumor Mutational Burden (continued)

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 4.2022]

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pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 2.2022]

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pembrolizumab

Cancer type: Myxofibrosarcoma, Undifferentiated Pleomorphic Sarcoma, Undifferentiated Sarcoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 2.2022]

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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 2.2022]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

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); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2022]

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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 2.2022]

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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 2.2022]

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pembrolizumab

Cancer type: Endometrial Carcinoma, Endometrial Clear Cell Adenocarcinoma, Endometrial Serous Adenocarcinoma, Undifferentiated and Dedifferentiated Carcinomas of the Uterine Corpus, Uterine Corpus Carcinosarcoma

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 1.2022]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

Tumor Mutational Burden (continued)

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 1.2022]

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 4.2022]

PALB2 c.2514+1G>A

olaparib

Cancer type: Castration-Resistant Prostate Cancer **Variant class:** PALB2 mutation

NCCN Recommendation category: 1

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

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2022]

rucaparib

Cancer type: Pancreatic Cancer **Variant class:** PALB2 mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 1.2022]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

PALB2 c.2514+1G>A (continued)

olaparib

Cancer type: Castration-Resistant Prostate Cancer **Variant class:** PALB2 mutation

NCCN Recommendation category: 2B

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

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2022]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2022-08-01. For the most up-to-date information, search www.esmo.org.

Tumor Mutational Burden

○ pembrolizumab

Cancer type: Endometrial Carcinoma **Variant class:** Tumor Mutational Burden

ESMO Level of Evidence/Grade of Recommendation: III / B

Population segment (Line of therapy):
- Progression (Line of therapy not specified); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Endometrial Cancer [Annals of Oncology (2022), doi: https://doi.org/10.1016/j.annonc.2022.05.009.]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

Clinical Trials in Taiwan region:

Clinical Trials Summary

KRAS p.(G12V) c.35G>T + TP53 p.(R248W) c.742C>T

NCT ID	Title	Phase
NCT04768868	A Phase I, Open-Label, Multi-Center, Dose Escalation and Expansion Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of the WEE1 Inhibitor IMP7068 Monotherapy in Patients With Advanced Solid Tumors	I

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 FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2022-08-17. For the most up-to-date information, search www.fda.gov.

PALB2 c.2514+1G>A

pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer

Variant class: PALB2 mutation

Supporting Statement:
The FDA has granted Fast Track Designation to the small molecule inhibitor, pidnarulex for BRCA1/2, PALB2, or other HRD mutations in breast and ovarian cancers.

Reference:

https://www.senhwabio.com//en/news/20220125

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

KRAS p.(G12V) c.35G>T

⊘ cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2021-09-24 **Variant class:** KRAS G12 mutation

Indications and usage:

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved test

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: Erbitux® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

- in combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf

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⊘ panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2021-08-25 **Variant class:** KRAS G12 mutation

Indications and usage:

VECTIBIX® is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC):

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.
- Limitation of Use: VECTIBIX® is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125147s210lbl.pdf

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Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

KRAS p.(G12V) c.35G>T (continued)

RO-5126766, defactinib + RO-5126766

Cancer type: Endometrial Carcinoma, Non-Small Cell Lung Cancer

Variant class: KRAS G12V mutation

Supporting Statement:
The FDA has granted Breakthrough Designation to the small molecule inhibitor, RO-5126766 alone for KRAS G12V mutant non-small cell lung cancer or in combination with defactinib, for KRAS mutant endometrial carcinoma and KRAS G12V mutant non-small cell lung cancer.

Reference:

https://investor.verastem.com//news-releases/news-release-details/verastem-oncology-receives-breakthrough-therapy-designation-vs

bevacizumab + onvansertib + FOLFIRI

Cancer type: Colorectal Cancer

Variant class: KRAS mutation

Supporting Statement:
The FDA has granted Fast Track Designation to the Polo-like Kinase 1 (PLK1) inhibitor, onvansertib, in combination with FOLFIRI and bevacizumab, for KRAS mutations in metastatic colorectal cancer in the second line.

Reference:

https://cardiffoncology.investorroom.com/2020-05-28-Cardiff-Oncology-Announces-Fast-Track-Designation-Granted-by-the-FDA-to-Onvansertib-for-Second-Line-Treatment-of-KRAS-Mutated-Colorectal-Cancer

Current NCCN Information

Contraindicated | Not recommended | Resistance | Breakthrough | Fast Track

NCCN information is current as of 2022-08-01. 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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

KRAS p.(G12V) c.35G>T

cetuximab

Cancer type: Colon Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

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

panitumumab

Cancer type: Colon Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

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

cetuximab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

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

panitumumab

Cancer type: Rectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab."

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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2022-08-17. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12V) c.35G>T

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2022-05-25 **Variant class:** KRAS exon 2 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf

panitumumab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2022-07-06 **Variant class:** KRAS exon 2 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2022-08-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12V) c.35G>T

cetuximab

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

KRAS p.(G12V) c.35G>T (continued)

cetuximab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."
- "Thus, the activity of the anti-EGFR antibodies is confined to RAS WT tumours (and not only KRAS WT tumours). This is true for the combinations of cetuximab or panitumumab alone or with irinotecan- and oxaliplatin-based regimens. Treatment with anti-EGFR antibodies may even harm patients with a RAS mutation, especially when combined with oxaliplatin [I/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

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panitumumab

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

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panitumumab + chemotherapy

Cancer type: Colorectal Cancer **Variant class:** KRAS exon 2 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "It has been demonstrated that the (potential) benefit of anti-EGFR antibodies in all treatment lines and either as a single agent or in combination with any chemotherapy regimen is limited to patients in whom a RAS mutation is excluded. It was shown that the 'expanded RAS' analysis (also including the detection of mutations in exons 3 and 4 of the KRAS gene as well as mutations in the NRAS [exons 2-4] gene) is superior to the KRAS (exon 2) analysis in predicting both more efficacy in the expanded RAS wild-type (WT) patients and a potential detrimental effect in patients harbouring any RAS mutation in their tumour genome [II/A]."
- "Thus, the activity of the anti-EGFR antibodies is confined to RAS WT tumours (and not only KRAS WT tumours). This is true for the combinations of cetuximab or panitumumab alone or with irinotecan- and oxaliplatin-based regimens. Treatment with anti-EGFR antibodies may even harm patients with a RAS mutation, especially when combined with oxaliplatin [I/A]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2014) 25 (suppl 3): iii1-iii9. (eUpdate: 20 September 2016; Corrigendum: 21 July 2015)]

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Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:

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References

1. Pylayeva-Gupta et al. RAS oncogenes: weaving a tumorigenic web. Nat. Rev. Cancer. 2011 Oct 13;11(11):761-74. PMID: 21993244
2. Karnoub et al. Ras oncogenes: split personalities. Nat. Rev. Mol. Cell Biol. 2008 Jul;9(7):517-31. PMID: 18568040
3. Scott et al. Therapeutic Approaches to RAS Mutation. Cancer J. 2016 May-Jun;22(3):165-74. doi: 10.1097/PPO.0000000000000187. PMID: 27341593
4. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
5. Román et al. KRAS oncogene in non-small cell lung cancer: clinical perspectives on the treatment of an old target. Mol Cancer. 2018 Feb 19;17(1):33. doi: 10.1186/s12943-018-0789-x. PMID: 29455666
6. Dinu et al. Prognostic significance of KRAS gene mutations in colorectal cancer--preliminary study. J Med Life. 2014 Oct-Dec;7(4):581-7. PMID: 25713627
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
8. Allegra et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J. Clin. Oncol. 2016 Jan 10;34(2):179-85. PMID: 26438111
9. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214665s000lbl.pdf
10. https://ir.mirati.com/press-releases/press-release-details/2021/Mirati-Therapeutics-Adagrasib-Receives-Breakthrough-Therapy-Designation-from-U.S.-Food-and-Drug-Administration-for-Patients-with-Advanced-Non-Small-Cell-Lung-Cancer-Harboring-the-KRAS-G12C-Mutation/default.aspx
11. https://investor.verastem.com//news-releases/news-release-details/verastem-oncology-receives-breakthrough-therapy-designation-vs
12. https://cardiffoncology.investorroom.com/2020-05-28-Cardiff-Oncology-Announces-Fast-Track-Designation-Granted-by-the-FDA-to-Onvansertib-for-Second-Line-Treatment-of-KRAS-Mutated-Colorectal-Cancer
13. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
14. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125147s210lbl.pdf
15. Slebos et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N. Engl. J. Med. 1990 Aug 30;323(9):561-5. PMID: 2199829
16. O'Leary et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016 Jan 4;44(D1):D733-45. PMID: 26553804
17. Li. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008 Jan;18(1):85-98. PMID: 18157157
18. Zhao et al. Mismatch Repair Deficiency/Microsatellite Instability-High as a Predictor for anti-PD-1/PD-L1 Immunotherapy Efficacy. J Hematol Oncol. 12(1),54. PMID: 31151482
19. Lynch et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin. Genet. 2009 Jul;76(1):1-18. PMID: 19659756
20. Baudrin et al. Molecular and Computational Methods for the Detection of Microsatellite Instability in Cancer. Front Oncol. 2018 Dec 12;8:621. doi: 10.3389/fonc.2018.00621. eCollection 2018. PMID: 30631754
21. Saeed et al. Microsatellites in Pursuit of Microbial Genome Evolution. Front Microbiol. 2016 Jan 5;6:1462. doi: 10.3389/fmicb.2015.01462. eCollection 2015. PMID: 26779133
22. Nojadeh et al. Microsatellite instability in colorectal cancer. EXCLI J. 2018;17:159-168. PMID: 29743854
23. Imai et al. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis. 2008 Apr;29(4):673-80. PMID: 17942460
24. Latham et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. J. Clin. Oncol. 2019 Feb 1;37(4):286-295. PMID: 30376427
25. NCCN-Genetic/Familial High-Risk Assessment:Breast, Ovarian, and Pancreatic. NCCN-Genetic/Familial High-Risk Assessment:Breast, Ovarian, and Pancreatic
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s133lbl.pdf
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125554s114lbl.pdf
28. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125377s122lbl.pdf
29. Xia et al. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol. Cell. 2006 Jun 23;22(6):719-29. PMID: 16793542
30. Niraj et al. The Fanconi Anemia Pathway in Cancer. Annu Rev Cancer Biol. 2019 Mar;3:457-478. PMID: 30882047

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

References (continued)

31. Lord et al. BRCAness revisited. Nat. Rev. Cancer. 2016 Feb;16(2):110-20. PMID: 26775620
32. Byrum et al. Defining and Modulating 'BRCAness'. Trends Cell Biol. 2019 Sep;29(9):740-751. PMID: 31362850
33. Michl et al. Interplay between Fanconi anemia and homologous recombination pathways in genome integrity. EMBO J. 2016 May 2;35(9):909-23. PMID: 27037238
34. Abbasi et al. A rare FANCA gene variation as a breast cancer susceptibility allele in an Iranian population. Mol Med Rep. 2017 Jun;15(6):3983-3988. PMID: 28440412
35. Tischkowitz et al. PALB2/FANCN: recombining cancer and Fanconi anemia. Cancer Res. 2010 Oct 1;70(19):7353-9. PMID: 20858716
36. Reid et al. Biallelic mutations in PALB2 cause Fanconi anemia subtype FA-N and predispose to childhood cancer. Nat. Genet. 2007 Feb;39(2):162-4. PMID: 17200671
37. Rahman et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat. Genet. 2007 Feb;39(2):165-7. PMID: 17200668
38. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208558s023lbl.pdf
39. Mateo et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N. Engl. J. Med. 2015 Oct 29;373(18):1697-708. PMID: 26510020
40. Goodall et al. Circulating Cell-Free DNA to Guide Prostate Cancer Treatment with PARP Inhibition. Cancer Discov. 2017 Sep;7(9):1006-1017. PMID: 28450425
41. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437
42. https://www.senhwabio.com//en/news/20220125
43. Hacker et al. Structure/Function Analysis of Recurrent Mutations in SETD2 Protein Reveals a Critical and Conserved Role for a SET Domain Residue in Maintaining Protein Stability and Histone H3 Lys-36 Trimethylation. J. Biol. Chem. 2016 Sep 30;291(40):21283-21295. PMID: 27528607
44. Fahey et al. SETting the Stage for Cancer Development: SETD2 and the Consequences of Lost Methylation. Cold Spring Harb Perspect Med. 2017 May 1;7(5). PMID: 28159833
45. Zaghi et al. H3K36 Methylation in Neural Development and Associated Diseases. Front Genet. 2020 Jan 9;10:1291. doi: 10.3389/fgene.2019.01291. eCollection 2019. PMID: 31998360
46. Suzuki et al. H3K36 methylation state and associated silencing mechanisms. Transcription. 2017 Jan;8(1):26-31. PMID: 27723431
47. Sun et al. H3K36me3, Message From Chromatin to DNA Damage Repair. Cell Biosci . 2020 Jan 31;10:9. doi: 10.1186/s13578-020-0374-z. eCollection 2020. PMID: 32021684
48. Li et al. The Histone Mark H3K36me3 Regulates Human DNA Mismatch Repair Through Its Interaction With MutSα. Cell. 2013 Apr 25;153(3):590-600. PMID: 23622243
49. Duns et al. Histone methyltransferase gene SETD2 is a novel tumor suppressor gene in clear cell renal cell carcinoma. Cancer Res. 2010 Jun 1;70(11):4287-91. PMID: 20501857
50. Dalgliesh et al. Systematic sequencing of renal carcinoma reveals inactivation of histone modifying genes. Nature. 2010 Jan 21;463(7279):360-3. PMID: 20054297
51. NCCN Guidelines® - NCCN-T-Cell Lymphomas [Version 2.2022]
52. Muller et al. Mutant p53 in cancer: new functions and therapeutic opportunities. Cancer Cell. 2014 Mar 17;25(3):304-17. PMID: 24651012
53. Olivier et al. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010 Jan;2(1):a001008. PMID: 20182602
54. Guha et al. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. Cold Spring Harb Perspect Med. 2017 Apr 3;7(4). PMID: 28270529
55. Peter et al. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25. PMID: 22960745
56. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
57. Campbell et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. Nat. Genet. 2016 Jun;48(6):607-16. PMID: 27158780
58. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017 Jan 12;541(7636):169-175. doi: 10.1038/nature20805. Epub 2017 Jan 4. PMID: 28052061

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

References (continued)

59. Olivier et al. The IARC TP53 database: new online mutation analysis and recommendations to users. Hum. Mutat. 2002 Jun;19(6):607-14. PMID: 12007217
60. Rivlin et al. Mutations in the p53 Tumor Suppressor Gene: Important Milestones at the Various Steps of Tumorigenesis. Genes Cancer. 2011 Apr;2(4):466-74. PMID: 21779514
61. Petitjean et al. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. Oncogene. 2007 Apr 2;26(15):2157-65. PMID: 17401424
62. Soussi et al. Recommendations for analyzing and reporting TP53 gene variants in the high-throughput sequencing era. Hum. Mutat. 2014 Jun;35(6):766-78. PMID: 24729566
63. https://www.globenewswire.com/news-release/2020/10/13/2107498/0/en/PMV-Pharma-Granted-FDA-Fast-Track-Designation-of-PC14586-for-the-Treatment-of-Advanced-Cancer-Patients-that-have-Tumors-with-a-p53-Y220C-Mutation.html
64. https://ir.aprea.com//news-releases/news-release-details/aprea-therapeutics-receives-fda-fast-track-designation
65. http://vp280.alertir.com/en/pressreleases/karolinska-development%27s-portfolio-company-aprea-therapeutics-receives-fda-breakthrough-therapy-designation-1769167
66. Parrales et al. Targeting Oncogenic Mutant p53 for Cancer Therapy. Front Oncol. 2015 Dec 21;5:288. doi: 10.3389/fonc.2015.00288. eCollection 2015. PMID: 26732534
67. Zhao et al. Molecularly targeted therapies for p53-mutant cancers. Cell. Mol. Life Sci. 2017 Nov;74(22):4171-4187. PMID: 28643165
68. NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]
69. NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 3.2022]
70. NCCN Guidelines® - NCCN-Myeloproliferative Neoplasms [Version 2.2022]
71. NCCN Guidelines® - NCCN-Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma [Version 3.2022]
72. NCCN Guidelines® - NCCN-B-Cell Lymphomas [Version 5.2022]
73. Bernard et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat. Med. 2020 Aug 3. PMID: 32747829
74. Yuan et al. Novel technologies and emerging biomarkers for personalized cancer immunotherapy. 4:3. PMID: 26788324
75. Temko et al. Somatic POLE exonuclease domain mutations are early events in sporadic endometrial and colorectal carcinogenesis, determining driver mutational landscape, clonal neoantigen burden and immune response. J. Pathol. 2018 Jul;245(3):283-296. PMID: 29604063
76. Mehnert et al. Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer. 126(6):2334-40. PMID: 27159395
77. Bouffet et al. Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency. J. Clin. Oncol. 2016 Jul 1;34(19):2206-11. PMID: 27001570
78. Humphris et al. Hypermutation In Pancreatic Cancer. Gastroenterology. 2017 Jan;152(1):68-74.e2. PMID: 27856273
79. Bonneville et al. Landscape of Microsatellite Instability Across 39 Cancer Types. JCO Precis Oncol. 2017;2017. PMID: 29850653
80. Snyder et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N. Engl. J. Med. 2014 Dec 4;371(23):2189-2199. PMID: 25409260
81. Alexandrov et al. Signatures of mutational processes in human cancer. Nature. 2013 Aug 22;500(7463):415-21. PMID: 23945592
82. Rizvi et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015 Apr 3;348(6230):124-8. PMID: 25765070
83. Van et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science. 2015 Oct 9;350(6257):207-211. PMID: 26359337
84. Chalmers et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. 9:34. PMID: 28420421
85. Govindan et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell. 2012 Sep 14;150(6):1121-34. PMID:22980976
86. Endris et al. Measurement of tumor mutational burden (TMB) in routine molecular diagnostics: in silico and real-life analysis of three larger gene panels. Int. J. Cancer. 2019 May 1;144(9):2303-2312. PMID: 30446996
87. Meléndez et al. Methods of measurement for tumor mutational burden in tumor tissue. Transl Lung Cancer Res. 2018 Dec;7(6):661-667. PMID: 30505710

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2022.09(005).

References (continued)

88. Hellmann et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N. Engl. J. Med. 2018 May 31;378(22):2093-2104. PMID: 29658845
89. Ready et al. First-Line Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers. J. Clin. Oncol. 2019 Apr 20;37(12):992-1000. PMID: 30785829
90. Alborelli et al. Tumor mutational burden assessed by targeted NGS predicts clinical benefit from immune checkpoint inhibitors in non-small cell lung cancer. J. Pathol. 2020 Jan;250(1):19-29. PMID: 31471895
91. Heeke et al. In-house Implementation of Tumor Mutational Burden Testing to Predict Durable Clinical Benefit in Non-small Cell Lung Cancer and Melanoma Patients. Cancers (Basel). 2019 Aug 29;11(9). PMID: 31470674
92. F. et al. CheckMate 817: First-Line Nivolumab + Ipilimumab in Patients with ECOG PS 2 and Other Special Populations with Advanced NSCLC. Volume 14, Issue 10, Supplement, Pages S214–S215. Abstract OA04.02
93. Zhu et al. Association Between Tumor Mutation Burden (TMB) and Outcomes of Cancer Patients Treated With PD-1/PD-L1 Inhibitions: A Meta-Analysis. Front Oncol, 9:1161, 04 Nov 2019. PMID: 31258479
94. Castellanos et al. Tumor mutational burden (TMB) and PD-L1 expression as predictors of response to immunotherapy (IO) in NSCLC. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 2630-2630. Abstract 2630
95. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]
96. NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2022]
97. NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2022]
98. NCCN Guidelines® - NCCN-Testicular Cancer [Version 2.2022]
99. NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2022]
100. NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2022]
101. NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2022]
102. NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]
103. NCCN Guidelines® - NCCN-Ovarian Cancer [Version 3.2022]
104. NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]
105. https://www.focr.org/tmb
106. http://www.iqnpath.org/category/tmb
107. Stenzinger et al. Tumor mutational burden standardization initiatives: Recommendations for consistent tumor mutational burden assessment in clinical samples to guide immunotherapy treatment decisions. Genes Chromosomes Cancer. 2019 Aug;58(8):578-588. PMID: 30664300
108. Merino et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. J Immunother Cancer. 2020 Mar;8(1). PMID: 32217756

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