Taipei Veterans General Hospital

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Sample Information

Patient Name: 王建發
Gender: Male
ID No.: A121170973
History No.: 42941662
Age: 53

Ordering Doctor: DOC6238J_李君陽
Ordering REQ.: 0BZRFET
Signing in Date: 2022/09/07

Path No.: S111-97877
MP No.: TM22010
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S109-44237A
Percentage of tumor cells: 40%

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

Note:

Sample Cancer Type: Rectal Cancer

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Relevant Rectal Cancer Variants

Gene	Finding
BRAF	None detected
KRAS	***KRAS p.(G12C) c.34G>T***
NRAS	None detected
NTRK1	None detected
NTRK3	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*Tumor Mutational Burden* 26.49 Mut/Mb measured	**pembrolizumab** [1]	pembrolizumab	2
IA	*KRAS p.(G12C) c.34G>T* KRAS proto-oncogene, GTPase Allele Frequency: 21.75%	None	**sotorasib** [1, 2]	4
IIC	*TP53 c.97-1G>T* tumor protein p53 Allele Frequency: 35.42%	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.(G12C) c.34G>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
FBXW7 p.(R505H) c.1514G>A

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
FBXW7	p.(R505H)	c.1514G>A	COSM133117	chr4:153247288	29.16%	NM_033632.3	missense	830
KRAS	p.(G12C)	c.34G>T	COSM516	chr12:25398285	21.75%	NM_033360.4	missense	1632
TP53	p.(?)	c.97-1G>T	.	chr17:7579591	35.42%	NM_000546.5	unknown	1993
PAX7	p.(R56H)	c.167G>A	.	chr1:18960878	3.62%	NM_002584.3	missense	968
CMPK1	p.(A53T)	c.157G>A	.	chr1:47799774	11.11%	NM_016308.3	missense	117
CMPK1	p.(A53V)	c.158C>T	.	chr1:47799775	6.84%	NM_016308.3	missense	117
CMPK1	p.(R54C)	c.160C>T	.	chr1:47799777	6.84%	NM_016308.3	missense	117
DPYD	p.(F438L)	c.1314T>G	.	chr1:98039341	53.25%	NM_000110.4	missense	385
NRAS	p.(D69N)	c.205G>A	.	chr1:115256506	5.80%	NM_002524.5	missense	500
ITGA10	p.(D792=)	c.2376C>T	.	chr1:145537205	3.45%	NM_003637.5	synonymous	87
ABL2	p.(G729=)	c.2187G>A	.	chr1:179078170	9.24%	NM_005158.5	synonymous	119
ABL2	p.(G729E)	c.2186G>A	.	chr1:179078171	5.88%	NM_005158.5	missense	119
ABL2	p.(G720S)	c.2158G>A	.	chr1:179078199	4.96%	NM_005158.5	missense	121
ABL2	p.(G719=)	c.2157G>A	.	chr1:179078200	6.72%	NM_005158.5	synonymous	119
NCOA1	p.(P518=)	c.1554C>T	.	chr2:24929893	6.56%	NM_003743.5	synonymous	122

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
DNMT3A	p.(C514F)	c.1541G>T	.	chr2:25468135	4.40%	NM_022552.4	missense	91
EML4	p.(K283E)	c.847A>G	.	chr2:42510018	99.68%	NM_019063.5	missense	1868
MSH6	p.(S668=)	c.2004C>T	.	chr2:48027126	7.14%	NM_000179.3	synonymous	56
REL	p.(P133L)	c.398C>T	.	chr2:61144015	5.08%	NM_002908.4	missense	59
XPO1	p.(L1019=)	c.3055C>T	.	chr2:61708334	4.29%	NM_003400.4	synonymous	70
LRP1B	p.(H42Y)	c.124C>T	.	chr2:142567929	4.28%	NM_018557.3	missense	444
FN1	p.(S247=)	c.741C>T	.	chr2:216293006	3.79%	NM_212482.3	synonymous	132
PAX3	p.(E501K)	c.1501G>A	.	chr2:223065910	3.95%	NM_181459.4	missense	76
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	99.95%	NM_002343.6	nonframeshift Insertion	1875
SETD2	p.(C2524Y)	c.7571G>A	.	chr3:47058707	4.94%	NM_014159.6	missense	81
MAGI1	p.(P931R)	c.2792C>G	.	chr3:65365139	57.16%	NM_001033057.2	missense	1996
FOXL2	p.(A14T)	c.40G>A	.	chr3:138665525	4.76%	NM_023067.4	missense	63
FOXL2	p.(A11V)	c.32C>T	.	chr3:138665533	4.76%	NM_023067.4	missense	63
PDGFRA	p.(S478Pfs*11)	c.1432delT	.	chr4:55139770	59.37%	NM_006206.6	frameshift Deletion	1841
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	99.66%	NM_006206.6	synonymous	1179
APC	p.(Q789*)	c.2365C>T	.	chr5:112173656	29.55%	NM_000038.6	nonsense	88
APC	p.(T1493Rfs*14)	c.4476delC	.	chr5:112175765	20.96%	NM_000038.6	frameshift Deletion	167
CSF1R	p.(W821*)	c.2462G>A	.	chr5:149435681	5.44%	NM_005211.3	nonsense	441
CSF1R	p.(K820=)	c.2460G>A	.	chr5:149435683	4.54%	NM_005211.3	synonymous	441
CSF1R	p.(P818S)	c.2452C>T	.	chr5:149435691	7.04%	NM_005211.3	missense	199
NSD1	p.(V1972M)	c.5914G>A	.	chr5:176709487	3.77%	NM_022455.4	missense	53
FLT4	p.(M894I)	c.2682G>A	.	chr5:180046332	3.45%	NM_182925.5	missense	58
PKHD1	p.(R994W)	c.2980C>T	.	chr6:51907774	49.85%	NM_138694.4	missense	2000
ADGRB3	p.(V157I)	c.469G>A	.	chr6:69349036	4.23%	NM_001704.3	missense	71
ADGRB3	p.(C178=)	c.534C>T	.	chr6:69349101	4.84%	NM_001704.3	synonymous	62
ADGRB3	p.(L1507=)	c.4521G>A	.	chr6:70098735	5.36%	NM_001704.3	synonymous	56
FOXO3	p.(P515Lfs*10)	c.1544_1547delCGATinsTGATA	.	chr6:108985580	3.64%	NM_001455.4	frameshift Block Substitution	55
SYNE1	p.(S3622=)	c.10866T>C	.	chr6:152675854	100.00%	NM_182961.4	synonymous	352
SYNE1	p.(L1884=)	c.5652C>T	.	chr6:152737920	3.92%	NM_182961.4	synonymous	102
SYNE1	p.(G1502E)	c.4505G>A	.	chr6:152751801	4.23%	NM_182961.4	missense	71

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
IGF2R	p.(A1074T)	c.3220G>A	.	chr6:160481707	33.96%	NM_000876.3	missense	53
CARD11	p.(V1102=)	c.3306G>A	.	chr7:2946431	4.35%	NM_032415.6	synonymous	69
SBDS	p.(R175W)	c.523C>T	.	chr7:66456225	47.67%	NM_016038.4	missense	772
SAMD9	p.(P1506L)	c.4517C>T	.	chr7:92730894	3.92%	NM_001193307.1	missense	51
TRRAP	p.(G1709E)	c.5126G>A	.	chr7:98547698	4.90%	NM_001244580.1	missense	102
TRRAP	p.(L2130=)	c.6388C>T	.	chr7:98557033	47.17%	NM_001244580.1	synonymous	547
EPHB6	p.(V196I)	c.586G>A	.	chr7:142562144	50.92%	NM_004445.6	missense	1687
EXT1	p.(P449S)	c.1345C>T	.	chr8:118834776	3.88%	NM_000127.3	missense	103
RECQL4	p.(P167L)	c.500C>T	.	chr8:145742003	5.00%	NM_004260.4	missense	60
RECQL4	p.(Q161*)	c.481C>T	.	chr8:145742022	5.00%	NM_004260.4	nonsense	60
JAK2	p.(Q175=)	c.525G>A	.	chr9:5050742	48.32%	NM_004972.4	synonymous	1997
JAK2	p.(I899T)	c.2696T>C	.	chr9:5089798	67.44%	NM_004972.4	missense	258
PTPRD	p.(N962=)	c.2886C>T	.	chr9:8485931	53.74%	NM_002839.4	synonymous	214
TAF1L	p.(M1444I)	c.4332G>A	.	chr9:32631246	6.96%	NM_153809.2	missense	158
TAF1L	p.(P1443S)	c.4327C>T	.	chr9:32631251	4.27%	NM_153809.2	missense	117
TAF1L	p.(R1442W)	c.4324C>T	.	chr9:32631254	10.26%	NM_153809.2	missense	117
TAF1L	p.(T1441I)	c.4322C>T	.	chr9:32631256	7.34%	NM_153809.2	missense	109
TAF1L	p.(I1440=)	c.4320C>T	.	chr9:32631258	9.26%	NM_153809.2	synonymous	108
TAF1L	p.(I1439=)	c.4317C>T	.	chr9:32631261	3.70%	NM_153809.2	synonymous	108
TAF1L	p.(H1422=)	c.4266C>T	.	chr9:32631312	4.55%	NM_153809.2	synonymous	110
TAF1L	p.(L639=)	c.1915C>T	.	chr9:32633663	7.92%	NM_153809.2	synonymous	101
TAF1L	p.(P638L)	c.1913C>T	.	chr9:32633665	8.91%	NM_153809.2	missense	101
TAF1L	p.(P638S)	c.1912C>T	.	chr9:32633666	6.93%	NM_153809.2	missense	101
PTCH1	p.(A572=)	c.1716G>A	.	chr9:98238328	27.24%	NM_000264.5	synonymous	1997
ABL1	p.(E453=)	c.1359G>A	.	chr9:133753890	4.35%	NM_005157.6	synonymous	69
ABL1	p.(S990=)	c.2970G>A	.	chr9:133760647	48.36%	NM_005157.6	synonymous	1923
NUP214	p.(A43S)	c.127G>T	.	chr9:134002992	45.80%	NM_005085.4	missense	1998
NOTCH1	p.(H1176=)	c.3528C>T	.	chr9:139401872	57.27%	NM_017617.5	synonymous	117
TET1	p.(N1273=)	c.3819C>T	.	chr10:70406305	22.65%	NM_030625.3	synonymous	1996
KAT6B	p.(L1896=)	c.5688G>A	.	chr10:76790270	6.33%	NM_012330.4	synonymous	79
BIRC2	p.(D445N)	c.1333G>A	.	chr11:102248340	6.10%	NM_001256166.2	missense	82
ATM	p.(A2635=)	c.7905C>T	.	chr11:108203605	5.26%	NM_000051.3	synonymous	57

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
ZNF384	p.(Q501Hfs*48)	c.1503delG	.	chr12:6777110	100.00%	NM_001135734.2	frameshift Deletion	616
ARID2	p.(H675Y)	c.2023C>T	.	chr12:46243929	5.63%	NM_152641.4	missense	71
KMT2D	p.(A3855V)	c.11564C>T	.	chr12:49426924	5.41%	NM_003482.4	missense	74
KMT2D	p.(Q800*)	c.2398C>T	.	chr12:49445068	3.91%	NM_003482.4	nonsense	128
KMT2D	p.(L797=)	c.2391G>A	.	chr12:49445075	8.03%	NM_003482.4	synonymous	137
KMT2D	p.(P795S)	c.2383C>T	.	chr12:49445083	5.07%	NM_003482.4	missense	138
KMT2D	p.(G794E)	c.2381G>A	.	chr12:49445085	3.62%	NM_003482.4	missense	138
KMT2D	p.(G794R)	c.2380G>A	.	chr12:49445086	6.52%	NM_003482.4	missense	138
KMT2D	p.(E793=)	c.2379G>A	.	chr12:49445087	5.07%	NM_003482.4	synonymous	138
KMT2D	p.(A792V)	c.2375C>T	.	chr12:49445091	7.91%	NM_003482.4	missense	139
KMT2D	p.(Q791=)	c.2373G>A	.	chr12:49445093	5.76%	NM_003482.4	synonymous	139
MDM2	p.(E333=)	c.999G>A	.	chr12:69233134	4.35%	NM_002392.5	synonymous	92
EP400	p.(P32L)	c.95C>T	.	chr12:132445259	5.60%	NM_015409.5	missense	125
EP400	p.(S37F)	c.110C>T	.	chr12:132445274	5.51%	NM_015409.5	missense	127
IRS2	p.(A1123=)	c.3369C>T	.	chr13:110435032	5.48%	NM_003749.3	synonymous	73
IRS2	p.(A696=)	c.2088C>T	.	chr13:110436313	40.68%	NM_003749.3	synonymous	59
KNL1	p.(P1453S)	c.4357C>T	.	chr15:40916819	4.32%	NM_144508.5	missense	139
ERCC4	p.(?)	c.-46G>A	.	chr16:14013977	5.17%	NM_005236.3	unknown	58
MYH11	p.(N1906S)	c.5717A>G	.	chr16:15808856	44.00%	NM_001040114.1	missense	1759
MYH11	p.(N1240=)	c.3720C>T	.	chr16:15820864	50.98%	NM_001040114.1	synonymous	508
PALB2	p.(R825T)	c.2474G>C	.	chr16:23641001	50.00%	NM_024675.4	missense	68
MMP2	p.(R500H)	c.1499G>A	.	chr16:55530864	47.55%	NM_004530.6	missense	673
CDH11	p.(Y207*)	c.621T>A	.	chr16:65026840	15.85%	NM_001797.4	nonsense	2000
CDK12	p.(Y968=)	c.2904C>T	.	chr17:37673750	5.00%	NM_016507.4	synonymous	80
MIR4728			.	chr17:37882110	48.15%	NR_039881.2		2000
ZNF521	p.(E39=)	c.117G>A	.	chr18:22902075	3.80%	NM_015461.3	synonymous	79
DCC	p.(A1240T)	c.3718G>A	.	chr18:50994362	5.45%	NM_005215.4	missense	55
BCL2	p.(A42Pfs*54)	c.124delG	.	chr18:60985775	48.36%	NM_000633.2	frameshift Deletion	397
BCL2	p.(P40Rfs*112)	c.119_127delCGGGGGCCGinsGGGGCCA	.	chr18:60985773	51.64%	NM_000633.2	frameshift Block Substitution	397
JAK3	p.(C16=)	c.48C>T	.	chr19:17955179	10.34%	NM_000215.4	synonymous	116
CCNE1	p.(R374*)	c.1120C>T	.	chr19:30314571	3.77%	NM_001238.4	nonsense	53

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency) (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
CEBPA	p.(P188L)	c.563C>T	.	chr19:33792758	4.82%	NM_004364.4	missense	83
AKT2	p.(K181=)	c.543G>A	.	chr19:40747875	7.50%	NM_001626.6	synonymous	160
AKT2	p.(M180I)	c.540G>A	.	chr19:40747878	9.26%	NM_001626.6	missense	162
AKT2	p.(A179=)	c.537C>T	.	chr19:40747881	6.13%	NM_001626.6	synonymous	163
AKT2	p.(A179V)	c.536C>T	.	chr19:40747882	6.13%	NM_001626.6	missense	163
AKT2	p.(Y177=)	c.531C>T	.	chr19:40747887	6.45%	NM_001626.6	synonymous	124
AKT2	p.(R176H)	c.527G>A	.	chr19:40747891	3.60%	NM_001626.6	missense	111
AKT2	p.(?)	c.-17C>T	.	chr19:40771191	5.22%	NM_001626.6	unknown	575
CIC	p.(A1605V)	c.4814C>T	.	chr19:42799330	8.82%	NM_015125.4	missense	102
CIC	p.(G1607D)	c.4820G>A	.	chr19:42799336	5.88%	NM_015125.4	missense	102
CIC	p.(*1609=)	c.4826G>A	.	chr19:42799342	3.92%	NM_015125.4	stoploss	102
ERCC2	p.(G413D)	c.1238G>A	.	chr19:45860957	5.97%	NM_000400.4	missense	67
BCR	p.(?)	c.2116-1G>A	.	chr22:23626163	4.13%	NM_004327.4	unknown	121
MN1	p.(P766S)	c.2296C>T	.	chr22:28194236	3.88%	NM_002430.3	missense	129
MYH9	p.(E488=)	c.1464G>A	.	chr22:36710280	4.70%	NM_002473.6	synonymous	298
MYH9	p.(I486=)	c.1458C>T	.	chr22:36710286	7.38%	NM_002473.6	synonymous	122
MYH9	p.(T483I)	c.1448C>T	.	chr22:36710296	4.92%	NM_002473.6	missense	122
CYP2D6	p.(G42E)	c.125G>A	.	chr22:42526669	72.78%	NM_000106.6	missense	687
GATA1	p.(N260=)	c.780C>T	.	chrX:48651614	3.77%	NM_002049.4	synonymous	106
TFE3	p.(A223T)	c.667G>A	.	chrX:48895835	99.52%	NM_006521.6	missense	1262
TAF1	p.(R1199Q)	c.3596G>A	.	chrX:70617292	7.46%	NM_004606.5	missense	67

Biomarker Descriptions

FBXW7 (F-box and WD repeat domain containing 7)

Background: The FBXW7 gene encodes a member of the F-box protein family that functions as the substrate recognition component of the SCF complex, which is responsible for protein ubiquitination and subsequent degradation by the proteasome[1]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes. Aberrations such as mutations or deletions that alter the tumor suppression function can lead to the deregulation of downstream genes, including MYC, MTOR, and NOTCH1, thereby promoting cell proliferation and survival[1,2,3,4,5,6,7].

Alterations and prevalence: Mutations in FBXW7 occur at high frequencies in various malignancies, including 40% of uterine carcinoma and 10-15% of stomach, bladder, cervical, and colorectal cancers[8,9,10,11,12].

Potential relevance: Currently, no therapies are approved for FBXW7 aberrations. Missense mutations in FBXW7 are associated with poor prognosis and worse overall survival (OS) in comparison to FBXW7 wild-type metastatic colorectal cancer[8]. In a clinical case report, a patient with FBXW7 R465H-mutated, EGFR/ALK-wildtype lung adenocarcinoma demonstrated tumor shrinkage after treatment

Biomarker Descriptions (continued)

with the mTOR inhibitor temsirolimus. In a phase I clinical trial of sirolimus, one hepatocellular fibrolamellar carcinoma patient with the FBXW7 E192A mutation demonstrated stable disease for over 6 months[7].

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[13,14,15].

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[11]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[11,16,17]. Mutations at A59, K117, and A146 have also been observed but are less frequent[12,18].

Potential relevance: The KRAS inhibitor, sotorasib[19], 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[20].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[21]. Additionally, onvansertib[22] was granted fast track designation (2020) for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab[23] and panitumumab[24], 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)[18]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[25].

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[26]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[27,28].

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%)[11,12,29,30,31,32]. 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[11,12]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[33,34,35,36].

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[37]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[38] and breakthrough designation[39] (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[40,41]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL)[42,43,44,45]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[46]. 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[47].

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

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[58]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation

Biomarker Descriptions (continued)

burden and median TMB values <1 mut/Mb[55,58]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[55,58]. 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)[55,58,59]. 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[58,60,61]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[62,63,64,65].

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[66] 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[63,67,68]. 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[69]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[70]. 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[71,72,73,74,75,76,77,78,79]. 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[80,81,82,83].

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)

KRAS p.(G12C) c.34G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
sotorasib	○	○	○	✖	✖
adagrasib, cetuximab	✖	✖	✖	✖	● (III)
D-1553	✖	✖	✖	✖	● (I/II)
JDQ-443, TNO-155, tislelizumab	✖	✖	✖	✖	● (I/II)
IMP7068	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

TP53 c.97-1G>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.

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 2022-07-13. For the most up-to-date information, search www.fda.gov.

Tumor Mutational Burden

● pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2022-06-21 **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

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 not MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
- 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

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/2022/125514s131lbl.pdf

KRAS p.(G12C) c.34G>T

○ sotorasib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2021-05-28 **Variant class:** KRAS G12C mutation

Indications and usage:
LUMAKRAS™ is an inhibitor of the RAS GTPase family indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214665s000lbl.pdf

Current NCCN Information

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

NCCN information is current as of 2022-07-01. 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]

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 2.2022]

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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 1.2022]

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 1.2022]

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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]

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]

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]

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]

KRAS p.(G12C) c.34G>T

sotorasib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** KRAS G12C mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

Current EMA Information

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

EMA information is current as of 2022-07-13. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12C) c.34G>T

○ sotorasib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-03-31 **Variant class:** KRAS G12C mutation

Reference:

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

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 2022-07-01. 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. (Pre-proof)]

Clinical Trials in Taiwan region:

Clinical Trials Summary

KRAS p.(G12C) c.34G>T + TP53 c.97-1G>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

KRAS p.(G12C) c.34G>T

NCT ID	Title	Phase
NCT04793958	A Randomized Phase III Study of MRTX849 in Combination With Cetuximab Versus Chemotherapy in Patients With Advanced Colorectal Cancer With KRAS G12C Mutation With Disease Progression On or After Standard First-Line Therapy	III
NCT04585035	A Phase I/II, Open Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of D-1553 in Subjects With Advanced or Metastatic Solid Tumors With KRasG12C Mutation	I/II
NCT04699188	A Phase Ib/II Open-label, Multi-center Dose Escalation Study of JDQ443 in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation	I/II

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2022-07-13. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12C) c.34G>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

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

KRAS p.(G12C) c.34G>T (continued)

adagrasib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** KRAS G12C mutation

Supporting Statement:
The FDA has granted Breakthrough Designation to the small molecule inhibitor, adagrasib, for KRAS G12C positive in non-small cell lung cancer following prior systemic therapy.

Reference:

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

defactinib + RO-5126766

Cancer type: Endometrial Carcinoma **Variant class:** KRAS 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 2022-07-01. 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]

KRAS p.(G12C) c.34G>T

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]

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]

KRAS p.(G12C) c.34G>T (continued)

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]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2022-07-13. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12C) c.34G>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 2022-07-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12C) c.34G>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)]

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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

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- "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)]

KRAS p.(G12C) c.34G>T (continued)

⊘ 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)]

Signatures

Testing Personnel:

2022.09.13
08:50:10 +08'00'

Laboratory Supervisor:

2022.09.13
08:50:22 +08'00'

Pathologist:

2022.09.13
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