Sample Information

Patient Name: 林張阿美
Gender: Female
ID No.: C200126059
History No.: 34799003
Age: 72

Ordering Doctor: DOC5390F 高冠鈞
Ordering REQ.: 0AZFHAU
Signing in Date: 2020/12/03

Path No.: S109-96812
MP No.: TM20008
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S109-75328J
Percentage of tumor cells: 50%
Note:

Sample Cancer Type: Colorectal Cancer

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Relevant Colorectal Cancer Findings

Gene	Finding
BRAF	Not detected
KRAS	***KRAS p.(G12D) c.35G>A***
NRAS	Not detected
NTRK1	Not detected
NTRK3	Not detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*PIK3CA p.(E545K) c.1633G>A* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Fraction: 0.102	None	**alpelisib + hormone therapy** [1, 2]	13
IA	*KRAS p.(G12D) c.35G>A* KRAS proto-oncogene, GTPase Allele Fraction: 0.326	None	cabozantinib	47
IIC	*CREBBP p.(R1446C) c.4336C>T* CREB binding protein Allele Fraction: 0.196	None	None	1
	Tumor Mutational Burden 19.27 Mut/Mb measured	**pembrolizumab** [1]	ipilimumab + nivolumab nivolumab pembrolizumab	13

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.
Although no fusion transcript can be detected, there is high imbalance of the number of 3' reads and 5' reads in the RET gene (3'/5' imbalance value: 25.86). A high 3'/5' imbalance value is suggestive of the presence of gene fusion. The possibility of RET fusion involving partners other than those targeted by the panel cannot be excluded. Further confirmation with other methodologies is suggested.

Alerts informed by public data sources: ⊘ Contraindicated, Resistance

KRAS p.(G12D) c.35G>A	⊘ **cetuximab** [1, 2], **cetuximab + chemotherapy** [2], **panitumumab** [1], **panitumumab + chemotherapy** [2]

Public data sources included in alerts: FDA1, NCCN, **EMA**2, ESMO

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

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
PIK3CA	p.(E545K)	c.1633G>A	COSM763	chr3:178936091	0.102	NM_006218.3	missense	2000
KRAS	p.(G12D)	c.35G>A	COSM521	chr12:25398284	0.326	NM_033360.3	missense	1997
CREBBP	p.(R1446C)	c.4336C>T	COSM88749	chr16:3788618	0.196	NM_004380.2	missense	2000
ARNT	p.(?)	c.-73C>T	.	chr1:150849116	0.053	NM_001668.3	unknown	114
PBX1	p.(G35R)	c.103G>A	.	chr1:164529162	0.043	NM_002585.3	missense	324
PBX1	p.(=)	c.108G>A	.	chr1:164529167	0.061	NM_002585.3	synonymous	327
ABL2	p.(=)	c.2163G>A	.	chr1:179078194	0.071	NM_005158.4	synonymous	127
ABL2	p.(=)	c.2157G>A	.	chr1:179078200	0.056	NM_005158.4	synonymous	125
PACERR			.	chr1:186649353	0.615	NR_125801.1		1436
PARP1	p.(=)	c.1203G>T	.	chr1:226568866	0.430	NM_001618.3	synonymous	2000

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

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
AFF3	p.(Q144K)	c.430C>A	.	chr2:100623742	0.096	NM_001025108.1	missense	1995
LRP1B	p.(L4021F)	c.12061C>T	.	chr2:141093239	0.124	NM_018557.2	missense	1999
NFE2L2	p.(E358Q)	c.1072G>C	.	chr2:178096259	0.474	NM_006164.4	missense	1997
XPC	p.(P246L)	c.737C>T	.	chr3:14206970	0.431	NM_004628.4	missense	1998
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	1.000	NM_002343.5	nonframeshift Insertion	1897
BAP1	p.(?)	c.-45GG>AA	.	chr3:52443939	0.034	NM_004656.3	unknown	149
PHF7	p.(?)	c.-2957CC>TT	.	chr3:52443939	0.034	NM_016483.6	unknown	149
PBRM1	p.(=)	c.4335A>G	.	chr3:52584787	1.000	NM_018313.4	synonymous	1991
NSD2	p.(E1023K)	c.3067G>A	.	chr4:1961279	0.052	NM_001042424.2	missense	77
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	1.000	NM_006206.5	synonymous	1965
IL6ST	p.(=)	c.567G>T	.	chr5:55260065	0.313	NM_002184.3	synonymous	115
APC	p.(Q412*)	c.1234C>T	.	chr5:112154963	0.256	NM_000038.5	nonsense	1998
FLT4	p.(=)	c.897C>T	.	chr5:180056347	0.212	NM_182925.4	synonymous	1398
NOTCH4	p.(L15fs)	c.43_45delCTGinsA	.	chr6:32191661	1.000	NM_004557.3	frameshift Block Substitution	327
PKHD1	p.(=)	c.2853C>T	.	chr6:51907901	0.507	NM_138694.3	synonymous	373
DST	p.(P4497S)	c.13489C>T	.	chr6:56365928	0.503	NM_001144769.2	missense	2000
MAP3K7	p.(?)	c.-44C>T	.	chr6:91296646	0.056	NM_145331.2	unknown	179
EPHA7	p.(L195fs)	c.585_586delGGinsTGGT	.	chr6:94120465	0.067	NM_004440.3	frameshift Block Substitution	1969
SYNE1	p.(L5015M)	c.15043T>A	.	chr6:152647681	1.000	NM_182961.3	missense	1887
SYNE1	p.(=)	c.10866T>C	.	chr6:152675854	0.996	NM_182961.3	synonymous	1992
IGF2R	p.(I2416T)	c.7247T>C	.	chr6:160525887	0.549	NM_000876.3	missense	1998
CARD11	p.(A581T)	c.1741G>A	.	chr7:2968245	0.479	NM_032415.5	missense	2000
TRRAP	p.(V2615I)	c.7843G>A	.	chr7:98573796	0.499	NM_001244580.1	missense	1994
MET	p.(L211W)	c.632T>G	.	chr7:116339770	0.502	NM_001127500.2	missense	1995
EPHB6	p.(=)	c.2562G>A	.	chr7:142567674	0.056	NM_004445.5	synonymous	2000
FGFR1	p.(P842S)	c.2524C>T	.	chr8:38271184	0.057	NM_001174067.1	missense	70
CDKN2B	p.(=)	c.123C>T	.	chr9:22008830	0.069	NM_004936.3	synonymous	58

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

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
CDKN2B	p.(P40S)	c.118C>T	.	chr9:22008835	0.086	NM_004936.3	missense	58
CDKN2B	p.(=)	c.114G>A	.	chr9:22008839	0.069	NM_004936.3	synonymous	58
TAF1L	p.(A1513V)	c.4538C>T	.	chr9:32631040	0.062	NM_153809.2	missense	129
TAF1L	p.(T1441I)	c.4322C>T	.	chr9:32631256	0.043	NM_153809.2	missense	188
TAF1L	p.(P806L)	c.2417C>T	.	chr9:32633161	0.040	NM_153809.2	missense	99
TAF1L	p.(P638S)	c.1912C>T	.	chr9:32633666	0.044	NM_153809.2	missense	205
TAF1L	p.(=)	c.498G>A	.	chr9:32635080	0.069	NM_153809.2	synonymous	87
TAF1L	p.(P156L)	c.467C>T	.	chr9:32635111	0.188	NM_153809.2	missense	80
TAF1L	p.(P156S)	c.466C>T	.	chr9:32635112	0.112	NM_153809.2	missense	80
TAF1L	p.(=)	c.462G>A	.	chr9:32635116	0.087	NM_153809.2	synonymous	80
TAF1L	p.(C152Y)	c.455G>A	.	chr9:32635123	0.075	NM_153809.2	missense	80
RALGDS	p.(=)	c.2649C>T	.	chr9:135974067	0.078	NM_001271775.1	synonymous	77
BRD3	p.(=)	c.789G>A	.	chr9:136913502	0.538	NM_007371.3	synonymous	1080
TET1	p.(K22R)	c.65_66delAGinsGA	.	chr10:70332160	0.050	NM_030625.2	missense	1000
KAT6B	p.(S1717N)	c.5150G>A	.	chr10:76789732	0.051	NM_012330.3	missense	118
SUFU	p.(P12L)	c.35C>T	.	chr10:104263944	0.051	NM_016169.3	missense	78
SUFU	p.(P15L)	c.44C>T	.	chr10:104263953	0.065	NM_016169.3	missense	62
IGF2	p.(H224D)	c.670C>G	.	chr11:2154258	0.126	NM_001127598.2	missense	1995
EP400	p.(=)	c.3066G>A	.	chr12:132490787	0.506	NM_015409.4	synonymous	2000
LTK	p.(P227L)	c.680C>T	.	chr15:41803754	0.517	NM_002344.5	missense	661
TGM7	p.(L610V)	c.1828T>G	.	chr15:43571326	0.085	NM_052955.2	missense	1999
CREBBP	p.(=)	c.6417G>A	.	chr16:3778631	0.047	NM_004380.2	synonymous	64
CREBBP	p.(S2138N)	c.6413G>A	.	chr16:3778635	0.063	NM_004380.2	missense	64
CREBBP	p.(=)	c.6411C>T	.	chr16:3778637	0.078	NM_004380.2	synonymous	64
CREBBP	p.(=)	c.681T>C	.	chr16:3900415	0.502	NM_004380.2	synonymous	1991
SOCS1	p.(R65Q)	c.194G>A	.	chr16:11349142	0.038	NM_003745.1	missense	160
MYH11	p.(M1551I)	c.4653G>A	.	chr16:15814855	0.057	NM_001040114.1	missense	368
CDH11	p.(G42S)	c.124G>A	.	chr16:65038649	0.059	NM_001797.3	missense	337
CDH11	p.(=)	c.91C>T	.	chr16:65038682	0.092	NM_001797.3	synonymous	65
CDH11	p.(R27W)	c.79C>T	.	chr16:65038694	0.045	NM_001797.3	missense	66

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

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect	Coverage
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	1.000	NM_001795.4	missense	1952
HLF	p.(?)	c.-47T>TCTTTT	.	chr17:53342799	0.038	NM_002126.4	unknown	986
RNF213	p.(C1156F)	c.3467G>T	.	chr17:78302227	0.406	NM_001256071.2	missense	1017
CDH20	p.(V388M)	c.1162G>A	.	chr18:59195344	0.107	NM_031891.3	missense	1996
STK11	p.(=)	c.499C>T	.	chr19:1220406	0.151	NM_000455.4	synonymous	53
TCF3	p.(G431S)	c.1291_1293delGGCinsAGT	.	chr19:1619348	0.502	NM_001136139.3	missense	590
MAP2K2	p.(P392L)	c.1175C>T	.	chr19:4090624	0.040	NM_030662.3	missense	176
AKT2	p.(M180I)	c.540G>A	.	chr19:40747878	0.051	NM_001626.5	missense	177
AKT2	p.(=)	c.531C>T	.	chr19:40747887	0.178	NM_001626.5	synonymous	107
CIC	p.(=)	c.4826G>A	.	chr19:42799342	0.050	NM_015125.4	synonymous	219
ERCC1	p.(G4R)	c.10G>A	.	chr19:45926623	0.052	NM_001983.3	missense	116
MN1	p.(Q530*)	c.1588C>T	.	chr22:28194944	0.038	NM_002430.2	nonsense	52
MYH9	p.(=)	c.1458C>T	.	chr22:36710286	0.110	NM_002473.5	synonymous	145
MYH9	p.(=)	c.1455C>T	.	chr22:36710289	0.055	NM_002473.5	synonymous	146
MYH9	p.(=)	c.1449C>T	.	chr22:36710295	0.048	NM_002473.5	synonymous	147
MYH9	p.(C468Y)	c.1403G>A	.	chr22:36710341	0.040	NM_002473.5	missense	151
MYH9	p.(?)	c.490+1G>A	.	chr22:36737414	0.041	NM_002473.5	unknown	664
EP300	p.(=)	c.3183T>A	.	chr22:41551039	1.000	NM_001429.3	synonymous	1983
TAF1	p.(V802M)	c.2404G>A	.	chrX:70607228	0.086	NM_004606.4	missense	81
TAF1	p.(=)	c.2604G>A	.	chrX:70608203	0.088	NM_004606.4	synonymous	148
TAF1	p.(L869F)	c.2605C>T	.	chrX:70608204	0.055	NM_004606.4	missense	146
TAF1	p.(R1202C)	c.3604C>T	.	chrX:70617240	0.041	NM_004606.4	missense	269
TAF1	p.(H1427Y)	c.4279C>T	.	chrX:70627836	0.040	NM_004606.4	missense	124
TAF1	p.(R1444Q)	c.4331G>A	.	chrX:70627888	0.041	NM_004606.4	missense	122
TAF1	p.(P1445L)	c.4334C>T	.	chrX:70627891	0.041	NM_004606.4	missense	122
TAF1	p.(M1446I)	c.4338G>A	.	chrX:70627895	0.067	NM_004606.4	missense	120

Biomarker Descriptions

CREBBP (CREB binding protein)

Background: The CREBBP gene encodes the CREB binding protein (also known as CBP), a highly conserved and ubiquitously expressed tumor suppressor. CREBBP is a member of the KAT3 family of histone acetyltransferases, which, along with EP300, interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[1,2]. CREBBP functions as a global transcriptional coactivator through the modification of lysines on nuclear proteins[1]. CREBBP binds to cAMP-response element binding protein (CREB) and is known to play a role in embryonic development, growth, and chromatin remodeling[1]. Upon disruption of normal CREBBP functions through genomic alterations, cells become susceptible to defects in differentiation and malignant transformation[3]. Inherited CREBBP mutations and deletions result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[4].

Alterations and prevalence: Mutations in CREBBP are observed in up to 12% of bladder urothelial carcinoma, uterine corpus endometrial carcinoma, and skin cutaneous melanoma, and in 5-10% of stomach adenocarcinoma, lung squamous cell carcinoma, and cervical squamous cell carcinoma[5,6]. CREBBP is frequently mutated in 15-17% of small cell lung cancer (SCLC)[7]. Inactivating mutations and deletions of CREBBP account for over 70% of all B-cell non-Hodgkin lymphoma diagnoses including 60% of follicular lymphoma and 30% of diffuse large-B-cell lymphoma (DLBCL)[1]. The rare t(11;16)(q23;p13) translocation fuses CREBBP with the partner gene KMT2A/MLL, in 0.2% secondary AML and 0.1% myelodysplastic syndrome (MDS)[8,9,10]. Elevated expression of CBP was detected in lung cancer cells and tumor tissue as compared to normal lung cells in one study[11].

Potential relevance: The t(11;16)(q23;p13.3) translocation is recognized by the World Health Organization (WHO) as one of the balanced abnormalities that define AML with myelodysplasia-related changes[12]. The t(11;16)(q23;p13.3) translocation and resulting CREBBP-KMT2A fusion is considered a diagnostic marker of myelodysplastic syndrome[13]. SCLC patients with CREBBP-positive SCLC demonstrate lower overall survival (OS) and disease free survival (DFS) compared to those with CREBBP-negative tumors[14].

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[15,16,17].

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[5]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[5,18,19]. Mutations at A59, K117, and A146 have also been observed but are less frequent[6,20].

Potential relevance: Currently, no therapies are approved for KRAS aberrations. However, the KRAS G12C inhibitor, sotorasib (AMG 510)[21], was granted fast track designation (2019) for previously treated non-small cell lung cancer (NSCLC) patients with KRAS G12C mutations. 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)[20]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[25].

PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[26]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[27,28]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[27]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[29,30]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[29,30,31,32]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[33,34,35].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[5,6]. Activating mutations in PIK3CA commonly cluster in two regions corresponding to the exon 9 helical (codons E542/E545) and exon 20 kinase

Biomarker Descriptions (continued)

(codon H1047) domains, each having distinct mechanisms of activation[36,37,38]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[5,6].

Potential relevance: The PI3K inhibitor, alpelisib[39], is FDA approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer, the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[40]. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations[40]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[41]. Case studies with MTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[42,43].

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[44]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[45,46,47,48,49]. 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[50,51,52,53].

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[54]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[51,54]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[51,54]. 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)[51,54,55]. 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[54,56,57]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[58,59,60,61].

Potential relevance: ICIs stimulate a patient's own T-cells to kill tumors and have exhibited benefits in some patients. The first ICI to be approved by the FDA was ipilimumab (2011), an anti-CTLA4 antibody indicated for the treatment of metastatic melanoma. In 2014, anti-PD-1 antibodies nivolumab (2014) and pembrolizumab (2014) were subsequently approved, for the treatment of metastatic melanoma, and pembrolizumab also for advanced esophageal squamous cell carcinoma. In 2020, the indication for pembrolizumab[62] 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 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[59,63,64]. In contrast, several previously promising trials have failed to show an improvement in survival outcomes between high and low TMB including CheckMate 227 (ipilimumab + nivolumab vs. chemotherapy), CheckMate 026 (nivolumab vs. chemotherapy), KEYNOTE 189 (pembroluzimab vs. chemotherapy), KEYNOTE 021 (pembroluzimab vs. pembroluzimab + chemotherapy), and Lung-MAP (nivolumab + ipilimumab vs. nivolumab). In response, suggestions to combine TMB score with PD-L1 expression as a way to increase the predictive power for patient stratification have been reported[65]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[66]. TMB score estimation is affected by the utilized assays, therefore efforts are underway to develop a standardized approach to calculate with the aim to support consistent reporting of TMB values across laboratories[67,68,69,70].

Relevant Therapy Summary

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

PIK3CA p.(E545K) c.1633G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	○	○	✖
everolimus	✖	✖	✖	✖	● (II)
paxalisib	✖	✖	✖	✖	● (II)
samotolisib	✖	✖	✖	✖	● (II)
sirolimus	✖	✖	✖	✖	● (II)
temsirolimus	✖	✖	✖	✖	● (II)
copanlisib, nivolumab, ipilimumab	✖	✖	✖	✖	● (I/II)
TAS-117, futibatinib	✖	✖	✖	✖	● (I/II)
telaglenastat, chemotherapy	✖	✖	✖	✖	● (I/II)
copanlisib, olaparib, durvalumab	✖	✖	✖	✖	● (I)
GDC-0077	✖	✖	✖	✖	● (I)
gedatolisib + palbociclib	✖	✖	✖	✖	● (I)
paxalisib, radiation therapy	✖	✖	✖	✖	● (I)

KRAS p.(G12D) c.35G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	✖	✖	○	✖
apatinib + chemotherapy	✖	✖	✖	✖	● (IV)
bevacizumab, chemotherapy	✖	✖	✖	✖	● (III)
avelumab	✖	✖	✖	✖	● (II)
binimetinib, palbociclib	✖	✖	✖	✖	● (II)
cetuximab, chemotherapy	✖	✖	✖	✖	● (II)
nivolumab, chemotherapy, bevacizumab	✖	✖	✖	✖	● (II)
panitumumab, trametinib	✖	✖	✖	✖	● (II)
pembrolizumab, chemotherapy	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

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

KRAS p.(G12D) c.35G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
selumetinib, ulixertinib	✖	✖	✖	✖	● (II)
anti-KRAS G12D mTCR	✖	✖	✖	✖	● (I/II)
ASTX029	✖	✖	✖	✖	● (I/II)
avelumab, binimetinib, talazoparib	✖	✖	✖	✖	● (I/II)
BMS-986179, nivolumab	✖	✖	✖	✖	● (I/II)
cobimetinib, atezolizumab, antimalarial	✖	✖	✖	✖	● (I/II)
durvalumab, tremelimumab, chemotherapy	✖	✖	✖	✖	● (I/II)
HH-2710	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	✖	✖	● (I/II)
neratinib, valproic acid	✖	✖	✖	✖	● (I/II)
onvansertib, chemotherapy, bevacizumab	✖	✖	✖	✖	● (I/II)
RMC-4630, cobimetinib	✖	✖	✖	✖	● (I/II)
zotatifin	✖	✖	✖	✖	● (I/II)
BCA101	✖	✖	✖	✖	● (I)
BGB-3245	✖	✖	✖	✖	● (I)
BI-1701963, trametinib	✖	✖	✖	✖	● (I)
chemotherapy, binimetinib	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
COM701, nivolumab	✖	✖	✖	✖	● (I)
eftozanermin alfa, chemotherapy, bevacizumab	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
JSI-1187	✖	✖	✖	✖	● (I)
LXH254	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (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

KRAS p.(G12D) c.35G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
MLN-2480	✖	✖	✖	✖	● (I)
neratinib, trametinib	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RMC-4630, pembrolizumab	✖	✖	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	✖	✖	● (I)
selinexor, pembrolizumab	✖	✖	✖	✖	● (I)
siremadlin, trametinib	✖	✖	✖	✖	● (I)
TAK 659, chemotherapy	✖	✖	✖	✖	● (I)
TNO-155, ribociclib	✖	✖	✖	✖	● (I)
trametinib, ruxolitinib	✖	✖	✖	✖	● (I)
ulixertinib, antimalarial	✖	✖	✖	✖	● (I)
utomilumab, cetuximab, chemotherapy	✖	✖	✖	✖	● (I)

CREBBP p.(R1446C) c.4336C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
CCS-1477	✖	✖	✖	✖	● (I/II)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	○	✖	✖	● (II)
ipilimumab + nivolumab	✖	○	✖	✖	● (II)
nivolumab	✖	○	✖	✖	● (II)
atezolizumab	✖	✖	✖	✖	● (II)
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, chemotherapy	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

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

Tumor Mutational Burden (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BAY1905254	✖	✖	✖	✖	● (I)
zimberelimab	✖	✖	✖	✖	● (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 2020-10-14. For the most up-to-date information, search www.fda.gov.

PIK3CA p.(E545K) c.1633G>A

○ alpelisib + fulvestrant

Cancer type: Breast Cancer **Label as of:** 2020-09-01 **Variant class:** PIK3CA E545K mutation

Other criteria: ERBB2 negative, Hormone receptor positive

Indications and usage:
PIQRAY® is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212526s001lbl.pdf

Tumor Mutational Burden

pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2020-10-14 **Variant class:** Tumor Mutational Burden

Indications and usage:

KEYTRUDA® is a programmed death receptor-1 (PD-1)-blocking antibody indicated:

Melanoma

- for the treatment of patients with unresectable or metastatic melanoma.
- for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

Non-Small Cell Lung Cancer (NSCLC)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥ 1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic.
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA®.

Small Cell Lung Cancer (SCLC)

- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[1]

Head and Neck Squamous Cell Cancer (HNSCC)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult patients with relapsed or refractory cHL.
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.
- Limitations of Use: KEYTRUDA® is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[1]

Tumor Mutational Burden (continued)

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Microsatellite Instability-High Cancer or Mismatch Repair Deficient Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options,[1] or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1]
- Limitations of Use: The safety and effectiveness of KEYTRUDA® in pediatric patients with MSI-H central nervous system cancers have not been established.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

- for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

Gastric Cancer

- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1]

Esophageal Cancer

- for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

Cervical Cancer

- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test.[1]

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC who have been previously treated with sorafenib.[1]

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1]

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of patients with advanced RCC.

Endometrial Carcinoma

- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.[1]

Tumor Mutational Burden-High (TMB-H) Cancer

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

Cutaneous Squamous Cell Carcinoma (cSCC)

Tumor Mutational Burden (continued)

- for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

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/2020/125514s085lbl.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 2020-10-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

PIK3CA p.(E545K) c.1633G>A

○ alpelisib + fulvestrant

Cancer type: Breast Cancer **Variant class:** PIK3CA mutation

Other criteria: ERBB2 negative, ER positive, PR positive

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Recurrent or Stage IV Invasive Breast Cancer; Postmenopausal or Premenopausal receiving ovarian ablation or suppression (Second-line or subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 6.2020]

Tumor Mutational Burden

○ ipilimumab + nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging biomarker in metastatic disease (Not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2020]

○ nivolumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-Small Cell Lung Cancer; Emerging biomarker in metastatic disease (Not specified)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2020]

Tumor Mutational Burden (continued)

pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent or Metastatic Cervical Cancer; Progressed on prior treatment and does not have satisfactory alternative treatment options; Tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] as determined by an FDA-approved test (Second-line therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 2.2020]

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pembrolizumab

Cancer type: Thyroid Gland Anaplastic Carcinoma, Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Medullary Carcinoma, Thyroid Gland Papillary Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; Unresectable locoregional recurrent/persistent disease not amenable to RAI therapy (Not specified)
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; CNS or soft tissue or bone metastases not amenable to RAI therapy (Not specified)
- Thyroid Gland Medullary Carcinoma; Locoregional recurrent/persistent disease (Not specified) (Useful in Certain Circumstances)
- Thyroid Gland Medullary Carcinoma; Recurrent or persistent disease; Distant metastases; Asymptomatic, symptomatic or progression of disease (Not specified) (Useful in Certain Circumstances)
- Thyroid Gland Anaplastic Carcinoma; Metastatic (Not specified) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2020]

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pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable or Metastatic Endometrial Carcinoma or Uterine Sarcoma; Progressed on prior treatment and does not have satisfactory alternative treatment options; Tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] as determined by an FDA-approved test (Not specified) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 2.2020]

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 2020-10-14. For the most up-to-date information, search www.ema.europa.eu/ema.

PIK3CA p.(E545K) c.1633G>A

○ alpelisib + fulvestrant

Cancer type: Breast Cancer **Label as of:** 2020-07-30 **Variant class:** PIK3CA mutation

Other criteria: ERBB2 mutation negative, Hormone receptor positive

Reference:

https://www.ema.europa.eu/en/documents/product-information/piqray-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 2020-10-01. For the most up-to-date information, search www.esmo.org.

PIK3CA p.(E545K) c.1633G>A

○ alpelisib + fulvestrant

Cancer type: Breast Cancer **Variant class:** PIK3CA exon 9 mutation

Other criteria: ERBB2 negative, ER positive

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

Population segment (Line of therapy):
- Luminal Advanced Breast Cancer; ESMO-MCBS v1.1 score: 3 (Not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-ESO-ESMO Advanced Breast Cancer [Annals of Oncology (2020), doi: https://doi.org/10.1016/j.annonc.2020.09.010 (ABC 5)]

KRAS p.(G12D) c.35G>A

○ cabozantinib

Cancer type: Thyroid Gland Medullary Carcinoma **Variant class:** RAS mutation

ESMO Level of Evidence/Grade of Recommendation: II / C

Population segment (Line of therapy):
- Metastatic Thyroid Gland Medullary Carcinoma (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Annals of Oncology 30: 1856–1883, 2019 doi:10.1093/annonc/mdz400]

Clinical Trials Summary

KRAS p.(G12D) c.35G>A + Tumor Mutational Burden

NCT ID	Title	Phase
NCT03519412	Pembrolizumab in MMR-Proficient Metastatic Colorectal Cancer Pharmacologically Primed to Trigger Dynamic Hypermutation Status	II

PIK3CA p.(E545K) c.1633G>A

NCT ID	Title	Phase
NCT02861300	Phase I/II Study of CB-839 and Capecitabine in Patients With Advanced Solid Tumors and Fluoropyrimidine Resistant PIK3CA Mutant Colorectal Cancer	I/II

Clinical Trials Summary (continued)

PIK3CA p.(E545K) c.1633G>A (continued)

NCT ID	Title	Phase
NCT02688881	Study to Evaluate the Safety and Efficacy of Sirolimus, in Subject With Refractory Solid Tumors	II
NCT03239015	Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event	II
NCT03994796	Genomically-Guided Treatment Trial in Brain Metastases	II
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT03213678	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase II Subprotocol of LY3023414 in Patients With Solid Tumors	II
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT04317105	A Phase I/II Biomarker Driven Combination Trial of Copanlisib and Immune Checkpoint Inhibitors in Patients With Advanced Solid Tumors	I/II
No NCT ID	Phase I/II Study of TAS-117 In Combination With TAS-120 In Patients With Advanced Solid Tumors	I/II
NCT03842228	A Phase Ib Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors	I
NCT03006172	A Phase I, Open-Label, Dose-Escalation Study Evaluating the Safety, Tolerability, and Pharmacokinetics of GDC-0077 as a Single Agent in Patients With Locally Advanced or Metastatic PIK3CA-Mutant Solid Tumors and in Combination With Endocrine and Targeted Therapies in Patients With Locally Advanced or Metastatic PIK3CA-Mutant Hormone-Receptor Positive Breast Cancer	I
NCT03065062	Phase I Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors	I
NCT04192981	A Phase I Study With Expansion Cohort of Concurrent GDC-0084 With Radiation Therapy for Patients With Solid Tumor Brain Metastases or Leptomeningeal Metastases Harboring PI3K Pathway Mutations	I

KRAS p.(G12D) c.35G>A

NCT ID	Title	Phase
No NCT ID	Exploratory Study Of Apatinib For Advanced Colorectal Cancer	IV
NCT02885753	Systemic Oxaliplatin or Intra-arterial Chemotherapy Combined With LV5FU2 and an Target Therapy in First Line Treatment of Metastatic Colorectal Cancer Restricted to the Liver	III
NCT02162563	Treatment Strategies in Colorectal Cancer Patients With Initially Unresectable Liver-only Metastases CAIRO5 a Randomized Phase III Study of the Dutch Colorectal Cancer Group (DCCG)	III
NCT03981614	Combination of MEK Inhibitor Binimetinib and CDK4/6 Inhibitor Palbociclib in KRAS and NRAS Mutant Metastatic Colorectal Cancers	II
NCT03087071	A Phase II Enrichment Study of Panitumumab as a Single Agent or in Combination With Trametinib in Anti-EGFR-Refractory Stage IV Colorectal Cancer Patients	II
NCT04189055	Cetuximab as Salvage herapy in Patients with Neo Wild-type RAS/RAF Metastatic Colorectal Cancer. A Proof-of-concept Study	II

Clinical Trials Summary (continued)

KRAS p.(G12D) c.35G>A (continued)

NCT ID	Title	Phase
NCT04072198	Phase II Study on NIVolumab in Combination With FOLFOXIRI/Bevacizumab in First Line Chemotherapy of Advanced COloRectal Cancer RASm/BRAFm Patients	II
NCT02619435	Regorafenib Monotherapy as Second-line Treatment of Patients With RAS-mutant Advanced Colorectal Cancer: a Multicentre, Single-arm, Two-stage, Phase II Study	II
NCT03186326	Multicenter Randomized Phase II Study Comparing the Effectiveness and Tolerance of Avelumab Versus Standard 2nd Line Treatment Chemotherapy in Patients With Colorectal Metastatic Cancer With Microsatellite Instability (MSI)	II
NCT03745326	A Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced with a Murine T-Cell Receptor Recognizing the G12D Variant of Mutated RAS in HLA-A*11:01 Patients	I/II
NCT04214418	Phase I/II Open-label Study of Combination Therapy With The MEK Inhibitor, Cobimetinib, Immune Checkpoint Blockade, Atezolizumab, And The AUTOphagy Inhibitor, Hydroxychloroquine In KRAS-mutated Advanced Malignancies	I/II
NCT03829410	A Phase Ib/II Study of Onvansertib (PCM-075) in Combination With FOLFIRI and Bevacizumab for Second Line Treatment of Metastatic Colorectal Cancer in Patients With a KRAS Mutation	I/II
NCT03202758	Phase Ib/II Trial Evaluating the Safety, Tolerability and Immunological Activity of Durvalumab (MEDI4736) (Anti-PD-L1) Plus Tremelimumab (Anti-CTLA-4) Combined With FOLFOX in Patients With Metastatic Colorectal Cancer	I/II
NCT03919292	Phase 1/2 Study of Neratinib and Divalproex Sodium (Valproate) in Advanced Solid Tumors, With an Expansion Cohort in Ras-Mutated Cancers	I/II
NCT02754141	A Phase I/IIa Study of BMS-986179 Administered Alone and in Combination With Nivolumab (BMS-936558) in Subjects With Advanced Solid Tumors	I/II
NCT03905148	A Phase Ib, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of a RAF Dimer Inhibitor BGB-283 in Combination With MEK Inhibitor PD-0325901 in Patients With Advanced or Refractory Solid Tumors	I/II
NCT04045496	A Phase I, Multi-Center, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Evidence of Antitumor Activity of JAB-3312 in Adult Patients With Advanced Solid Tumors	I
NCT04000529	A Phase Ib, Open-label, Multi-center Study to Characterize the Safety, Tolerability, and Preliminary Efficacy of TNO155 in Combination With Spartalizumab or Ribociclib in Selected Malignancies	I
NCT04249843	A First-in-Human, Phase Ia/Ib, Open Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor BGB-3245 in Patients With Advanced or Refractory Tumors	I
NCT03667716	A Phase Ia/Ib Study of COM701 as Monotherapy and In Combination With an Anti-PD-1 Antibody in Subjects With Advanced Solid Tumors	I
NCT03082209	An Open-Label, Phase I, First-In-Human Study of TRAIL Receptor Agonist ABBV-621 in Subjects With Previously Treated Solid Tumors and Hematologic Malignancies	I
NCT04256707	Open-Label, Phase I Study Evaluating the Bioequivalence of Different Formulations of Selinexor, and the Tolerability and Antitumor Activity of Selinexor Combination Treatment (SPRINT)	I

Clinical Trials Summary (continued)

KRAS p.(G12D) c.35G>A (continued)

NCT ID	Title	Phase
NCT03714958	A Single-center, Phase I Dose Escalation Study of Trametinib Combined With HDM201 in Patients With RAS/RAF Mutant and TP53 Wild-type Advanced/Metastatic Colorectal Cancer.	I
NCT04145297	A Phase I Trial of Ulixertinib (BVD-523) and Hydroxychloroquine in Patients With Advanced MAPK-Mutated Gastrointestinal Adenocarcinomas	I
NCT03284502	A Phase Ib, Open-label, Multicenter, Dose Escalation Study of the Safety, Tolerability, and Pharmacokinetics of Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors	I
NCT02857270	A Phase I Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	I
NCT03290937	Phase I Clinical Trial Evaluating the Safety and Response With PF-05082566, Cetuximab and Irinotecan in Patients With Advanced Colorectal Cancer	I
NCT02613650	A Phase Ib Trial of a Combination of mFOLFIRI With MEK162 in Patients With Advanced RAS (HRAS, NRAS, or KRAS) Positive Metastatic Colorectal Cancers	I
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT02079740	An Open Label, Two-Part, Phase Ib/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor Trametinib and the BCL2-Family Inhibitor Navitoclax (ABT-263) in Combination in Subjects With KRAS or NRAS Mutation-Positive Advanced Solid Tumors	I/II
NCT04092673	A Phase I-II Dose-Escalation and Cohort-Expansion Study of Intravenous eFT226 in Subjects With Selected Advanced Solid Tumor Malignancies	I/II
NCT03637491	A Phase Ib/II Study To Evaluate Safety And Clinical Activity Of Combinations Of Avelumab, Binimetinib And Talazoparib In Patients With Locally Advanced Or Metastatic Ras-Mutant Solid Tumors	I/II
NCT03989115	A Phase Ib/II, Open-Label, Multicenter Dose-Escalation and Dose-Expansion Study of the Combination of RMC-4630 and Cobimetinib in Adult Participants With Relapsed/Refractory Solid Tumors With Specific Genomic Aberrations	I/II
NCT04198818	A First-in-Human, Open Label, Phase I/II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HH2710 in Patients With Advanced Tumors	I/II
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT04429542	First-in-Human, Phase I/Ib, Open-label, Multicenter Study of Bifunctional EGFR/TGFß Fusion Protein BCA101 Alone and in Combination With Pembrolizumab in Patients With EGFR-Driven Advanced Solid Tumors	I
NCT04111458	A Phase I Open-label Dose Escalation Trial of BI 1701963 as Monotherapy and in Combination With Trametinib in Patients With KRAS Mutated Advanced or Metastatic Solid Tumours	I
NCT04418167	A Phase I Study of ERK1/2 Inhibitor JSI-1187 Administered as Monotherapy and in Combination With Dabrafenib for the Treatment of Advanced Solid Tumors With MAPK Pathway Mutations	I

Clinical Trials Summary (continued)

KRAS p.(G12D) c.35G>A (continued)

NCT ID	Title	Phase
NCT03065387	Phase I Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib, or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/ Amplification, or HER3/4 Mutation or KRAS Mutation	I
NCT04418661	A Phase I, Open-label, Multicenter, Safety Study of SAR442720 in Combination With Pembrolizumab in Patients With Advanced Malignancies	I
NCT02407509	A Phase I Trial of RO5126766 (a Dual RAF/MEK Inhibitor) Exploring Intermittent, Oral Dosing Regimens in Patients With Solid Tumours or Multiple Myeloma, With an Expansion to Explore Intermittent Dosing in Combination With Everolimus	I
NCT03756818	A Phase I Study of TAK-659 and Paclitaxel in Patients With Advanced Solid Tumors	I
NCT04303403	Phase Ib Study Evaluating Safety and Tolerability of Combination Trametinib and Ruxolitinib in Patients with Advanced RAS Mutant Colorectal Cancer and Pancreatic Adenocarcinoma	I
NCT03429803	A Phase I Study of TAK-580 (MLN2480) for Children With Low-Grade Gliomas and Other RAS/RAF/ MEK/ERK Pathway Activated Tumors	I
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	I
NCT02607813	A Phase I Dose Finding Study of Oral LXH254 in Adult Patients With Advanced Solid Tumors Harboring MAPK Pathway Alterations	I

CREBBP p.(R1446C) c.4336C>T

NCT ID	Title	Phase
NCT03568656	An Open-label Phase I/IIa Study to Evaluate the Safety and Efficacy of CCS1477 as Monotherapy and in Combination, in Patients With Advanced Solid/Metastatic Tumours.	I/II

Tumor Mutational Burden

NCT ID	Title	Phase
NCT03767075	Basket of Baskets: A Modular, Open-label, Phase II, Multicentre Study To Evaluate Targeted Agents in Molecularly Selected Populations With Advanced Solid Tumours	II
NCT02029001	A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors MOST: My own specific treatment	II
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT03668119	A Randomized, Open-Label, Phase II Study of Nivolumab in Combination With Ipilimumab or Nivolumab Monotherapy in Participants With Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)	II

Clinical Trials Summary (continued)

Tumor Mutational Burden (continued)

NCT ID	Title	Phase
No NCT ID	A Multicenter Phase II Study Of Nivolumab Monotherapy In Recurrent And/Or Metastatic Gastrointestinal Cancer Patients With High Tumor Mutation Burden (TMB-H)	II
No NCT ID	TR Accompanied with the Study Titled A Multicenter Phase II Study of Nivolumab Monotherapy in Recurrent and/or Metastatic Gastrointestinal Cancer Patients with High Tumor Mutation Burden (TMB-H).	II
NCT02628067	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)	II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT03838042	INFORM2 Exploratory Multinational Phase I/II Combination Study of Nivolumab and Entinostat in Children and Adolescents with Refractory High-risk Malignancies	I/II
NCT02992964	Pilot Study of Nivolumab in Pediatric Patients With Hypermutant Cancers	I/II
NCT03666273	An Open-label, Phase I, First-in-human, Dose Escalation and Expansion Study to Evaluate the Safety, Tolerability, Maximum Tolerated or Administered Dose, Pharmacokinetics, Pharmacodynamics and Tumor Response Profile of the ILDR2 Function-blocking Antibody BAY1905254 in Patients With Advanced Solid Tumors	I
NCT04087018	A Phase Ib Study to Evaluate the Safety and Clinical Activity of AB122 in Biomarker-Selected Participants With Advanced Solid Tumors	I

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance

FDA information is current as of 2020-10-14. For the most up-to-date information, search www.fda.gov.

KRAS p.(G12D) c.35G>A

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2019-04-23 **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.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125084s273lbl.pdf

panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2017-06-29 **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/2017/125147s207lbl.pdf

Current NCCN Information

Contraindicated Not recommended Resistance

NCCN information is current as of 2020-10-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

KRAS p.(G12D) c.35G>A

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 4.2020]

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 6.2020]

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 4.2020]

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 6.2020]

Current EMA Information

Contraindicated Not recommended Resistance

EMA information is current as of 2020-10-14. For the most up-to-date information, search www.ema.europa.eu/ema.

KRAS p.(G12D) c.35G>A

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2020-01-30 **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:** 2020-01-24 **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

ESMO information is current as of 2020-10-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12D) c.35G>A

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)]

KRAS p.(G12D) c.35G>A (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)]

⊘ 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)]

KRAS p.(G12D) c.35G>A (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:

2020.12.03
10:23:39 +08'00'

Laboratory Supervisor:

2020.12.03
10:23:56 +08'00'

Pathologist:

2020.12.03
10:24:09 +08'00'

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