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Sample Information

Patient Name: 劉秋香
Gender: Female
ID No.: J201224023
History No.: 46864022
Age: 65

Ordering Doctor: DOC2683L 張世慶
Ordering REQ.: 0BEJKWK
Signing in Date: 2021/04/07

Path No.: S110-98531
MP No.: TM21004
Assay: Oncomine Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S110-10869I
Percentage of tumor cells: 40%
Note:

Sample Cancer Type: Colorectal Cancer

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Relevant Colorectal Cancer Variants

Gene	Finding
BRAF	Not detected
KRAS	***KRAS p.(G12V) c.35G>T***
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 Frequency: 34.15%	None	**alpelisib + hormone therapy** [1, 2]	18
IA	*KRAS p.(G12V) c.35G>T* KRAS proto-oncogene, GTPase Allele Frequency: 34.54%	None	cabozantinib	42
IIC	*TP53 p.(?) c.672+1G>T* tumor protein p53 Allele Frequency: 58.28%	None	None	10
	Tumor Mutational Burden 10.0 Mut/Mb measured	**pembrolizumab** [1]	pembrolizumab	17

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Alerts informed by public data sources: ⊘ Contraindicated, Resistance

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

Public data sources included in alerts: 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 Frequency	Transcript	Variant Effect	Coverage
PIK3CA	p.(E545K)	c.1633G>A	COSM763	chr3:178936091	34.15%	NM_006218.3	missense	2000
KRAS	p.(G12V)	c.35G>T	COSM520	chr12:25398284	34.54%	NM_033360.3	missense	1737
TP53	p.(?)	c.672+1G>T	.	chr17:7578176	58.28%	NM_000546.5	unknown	755
MUTYH	p.(=)	c.343A>C	.	chr1:45799090	12.20%	NM_001128425.1	synonymous	1426
DPYD	p.(=)	c.2049C>G	.	chr1:97839126	12.47%	NM_000110.3	synonymous	1612
PDE4DIP	p.(=)	c.3708A>G	.	chr1:144881488	22.15%	NM_001198834.3	synonymous	2000
DDR2	p.(S311N)	c.932G>A	.	chr1:162731077	53.43%	NM_006182.2	missense	1999
PBX1	p.(S379G)	c.1135A>G	.	chr1:164790798	16.75%	NM_002585.3	missense	1522
ABL2	p.(G727E)	c.2180G>A	.	chr1:179078177	3.92%	NM_005158.4	missense	102
RNASEL	p.(K326R)	c.977A>G	.	chr1:182554965	46.20%	NM_021133.3	missense	2000
PIK3C2B	p.(=)	c.2556G>A	.	chr1:204415206	46.42%	NM_002646.3	synonymous	1999
NCOA1	p.(=)	c.1332A>C	.	chr2:24929671	10.53%	NM_003743.4	synonymous	1995
EML4	p.(S914G)	c.2740A>G	.	chr2:42557141	16.01%	NM_019063.4	missense	1999
LRP1B	p.(A2094S)	c.6280G>T	.	chr2:141459732	50.23%	NM_018557.2	missense	1999
LRP1B	p.(=)	c.66C>T	.	chr2:142888233	50.50%	NM_018557.2	synonymous	1994

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
PAX3	p.(G24V)	c.71G>T	.	chr2:223163264	50.43%	NM_181459.3	missense	928
LTF	p.(T389A)	c.1165A>G	.	chr3:46490401	48.20%	NM_002343.5	missense	888
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	99.87%	NM_002343.5	nonframeshift Insertion	743
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.95%	NM_006206.5	synonymous	1971
IL7R	p.(N176T)	c.527A>C	.	chr5:35871305	12.50%	NM_002185.4	missense	2000
FLT4	p.(S762R)	c.2286C>A	.	chr5:180047889	51.87%	NM_182925.4	missense	1203
FOXP4	p.(V398D)	c.1193T>A	.	chr6:41557744	49.20%	NM_001012426.1	missense	1998
PKHD1	p.(D220G)	c.659A>G	.	chr6:51935812	16.50%	NM_138694.3	missense	2000
CARD11	p.(K1145R)	c.3434A>G	.	chr7:2946303	12.28%	NM_032415.5	missense	1230
KMT2C	p.(Q3792K)	c.11374C>A	.	chr7:151859288	49.77%	NM_170606.2	missense	1981
TET1	p.(?)	c.-96A>C	.	chr10:70332000	4.61%	NM_030625.2	unknown	760
NUP98	p.(=)	c.969A>G	.	chr11:3784249	43.14%	NM_016320.4	synonymous	1998
ADAMTS20	p.(=)	c.1359A>G	.	chr12:43860463	49.83%	NM_025003.4	synonymous	865
ERBB3	p.(R1127H)	c.3380G>A	.	chr12:56495023	49.54%	NM_001982.3	missense	1728
FLT1	p.(A1024E)	c.3071C>A	.	chr13:28895703	35.10%	NM_002019.4	missense	1037
LAMP1	p.(=)	c.1083T>A	.	chr13:113976011	16.98%	NM_005561.3	synonymous	1997
NIN	p.(=)	c.399G>A	.	chr14:51259466	49.70%	NM_020921.3	synonymous	1996
LTK	p.(P227L)	c.680C>T	.	chr15:41803754	20.48%	NM_002344.5	missense	542
MMP2	p.(R500H)	c.1499G>A	.	chr16:55530864	50.00%	NM_004530.5	missense	1998
MMP2	p.(S544T)	c.1630T>A	.	chr16:55532221	19.29%	NM_004530.5	missense	1996
CDH11	p.(D311G)	c.932A>G	.	chr16:65022127	17.69%	NM_001797.3	missense	1509
CDH5	p.(I517T)	c.1550_1551delTCinsCT	.	chr16:66432423	47.23%	NM_001795.4	missense	1971
FANCA	p.(K701E)	c.2101A>G	.	chr16:89838136	47.02%	NM_000135.3	missense	1999
ERBB2	p.(S633P)	c.1897T>C	.	chr17:37873732	8.36%	NM_004448.3	missense	1997
CD79B	p.(Q111H)	c.333A>C	.	chr17:62007534	11.61%	NM_001039933.2	missense	1998
RNF213	p.(P4250T)	c.12748C>A	.	chr17:78346531	47.49%	NM_001256071.2	missense	1996
RNF213	p.(=)	c.13731G>C	.	chr17:78354721	48.42%	NM_001256071.2	synonymous	1999
SMAD4	p.(S227fs)	c.678_679insC	.	chr18:48584503	55.15%	NM_005359.5	frameshift Insertion	1554
DCC	p.(=)	c.360T>C	.	chr18:50278692	4.17%	NM_005215.3	synonymous	1343
TCF3	p.(S483G)	c.1447A>G	.	chr19:1619113	47.30%	NM_001136139.3	missense	1279
TCF3	p.(G431S)	c.1291_1293delGGCinsAGT	.	chr19:1619348	49.94%	NM_001136139.3	missense	831

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
TCF3	p.(G103S)	c.307G>A	.	chr19:1627417	51.95%	NM_001136139.3	missense	1407
AXL	p.(K651T)	c.1952A>C	.	chr19:41759529	8.10%	NM_021913.4	missense	1692
MYH9	p.(=)	c.1458C>T	.	chr22:36710286	5.17%	NM_002473.5	synonymous	58
MYH9	p.(=)	c.1455C>T	.	chr22:36710289	6.78%	NM_002473.5	synonymous	59
SSX1	p.(M40T)	c.119T>C	.	chrX:48117230	45.02%	NM_005635.3	missense	753

Biomarker Descriptions

KRAS (KRAS proto-oncogene, GTPase)

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

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

Potential relevance: Currently, no therapies are approved for KRAS aberrations. However, the KRAS G12C inhibitor, sotorasib (AMG 510)[9], was granted fast track (2019) and breakthrough (2020) therapy designation for previously treated non-small cell lung cancer (NSCLC) patients with KRAS G12C mutations[10]. Additionally, onvansertib[11] was granted fast track designation (2020) for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab[12] and panitumumab[13], are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[8]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[14].

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[15]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[16,17]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[16]. 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[18,19]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[18,19,20,21]. 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[22,23,24].

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[4,7]. Activating mutations in PIK3CA commonly cluster in two regions corresponding to the exon 9 helical (codons E542/E545) and exon 20 kinase (codon H1047) domains, each having distinct mechanisms of activation[25,26,27]. 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[4,7].

Potential relevance: The PI3K inhibitor, alpelisib[28], 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[29]. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations[29]. However, alpelisib did not improve response when administered

Biomarker Descriptions (continued)

with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[30]. Case studies with MTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[31,32].

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[33]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[34,35].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[4,7,36,37,38,39]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[4,7]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[40,41,42,43].

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[44]. The FDA has granted fast track designation (2019) to the p53 reactivator, APR-246 alone,[45] and breakthrough designation[46] (2020) in combination with azacitidine for myelodysplastic syndrome (MDS) and acute myeloid leukemia patients (AML) harboring a TP53 mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[47,48]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), chronic lymphocytic leukemia (CLL),[49,50,51,52]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[53]. 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[54].

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[55]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[56,57,58,59,60]. 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[61,62,63,64].

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[65]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[62,65]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[62,65]. 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)[62,65,66]. 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[65,67,68]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[69,70,71,72].

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[73] 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[70,74,75]. 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 (pembroluzimab vs. chemotherapy),

Biomarker Descriptions (continued)

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[76]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[77]. 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, and germ cell tumors with high TMB[78,79,80,81,82,83]. 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[84,85,86,87].

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)
GDC-0077	✖	✖	✖	✖	● (II)
ipatasertib	✖	✖	✖	✖	● (II)
paxalisib	✖	✖	✖	✖	● (II)
samotolisib	✖	✖	✖	✖	● (II)
sirolimus	✖	✖	✖	✖	● (II)
temsirolimus	✖	✖	✖	✖	● (II)
copanlisib, nivolumab, ipilimumab	✖	✖	✖	✖	● (I/II)
ipatasertib, atezolizumab	✖	✖	✖	✖	● (I/II)
TAS-117, futibatinib	✖	✖	✖	✖	● (I/II)
telaglenastat, chemotherapy	✖	✖	✖	✖	● (I/II)
copanlisib, olaparib, durvalumab	✖	✖	✖	✖	● (I)
gedatolisib + palbociclib	✖	✖	✖	✖	● (I)
HH-CYH33, olaparib	✖	✖	✖	✖	● (I)
paxalisib, radiation therapy	✖	✖	✖	✖	● (I)

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	✖	✖	○	✖
apatinib, chemotherapy	✖	✖	✖	✖	● (IV)
bevacizumab, chemotherapy	✖	✖	✖	✖	● (III)

* 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.(G12V) c.35G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
avelumab	✖	✖	✖	✖	● (II)
binimetinib, palbociclib	✖	✖	✖	✖	● (II)
cetuximab, chemotherapy	✖	✖	✖	✖	● (II)
nivolumab, chemotherapy, bevacizumab	✖	✖	✖	✖	● (II)
panitumumab, trametinib	✖	✖	✖	✖	● (II)
pembrolizumab, chemotherapy	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
ulixertinib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
avelumab, binimetinib, talazoparib	✖	✖	✖	✖	● (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)
SX-682, nivolumab	✖	✖	✖	✖	● (I/II)
telaglenastat, palbociclib	✖	✖	✖	✖	● (I/II)
AZD-0364	✖	✖	✖	✖	● (I)
BBP-398	✖	✖	✖	✖	● (I)
BGB-3245	✖	✖	✖	✖	● (I)
BI-1701963, chemotherapy	✖	✖	✖	✖	● (I)
chemotherapy, binimetinib	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
COM701, nivolumab	✖	✖	✖	✖	● (I)
DAY-101	✖	✖	✖	✖	● (I)
eftozanermin alfa, chemotherapy, bevacizumab	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (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.(G12V) c.35G>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
JSI-1187	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
neratinib, trametinib	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RMC-4630, pembrolizumab	✖	✖	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	✖	✖	● (I)
TAK 659, chemotherapy	✖	✖	✖	✖	● (I)
TNO-155, ribociclib	✖	✖	✖	✖	● (I)
trametinib, ruxolitinib	✖	✖	✖	✖	● (I)
ulixertinib, antimalarial	✖	✖	✖	✖	● (I)

TP53 p.(?) c.672+1G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
BAY-1895344	✖	✖	✖	✖	● (I/II)
eprenetapopt, pembrolizumab	✖	✖	✖	✖	● (I/II)
xevinapant, nivolumab	✖	✖	✖	✖	● (I/II)
BAY-1895344, niraparib	✖	✖	✖	✖	● (I)
HWH-340	✖	✖	✖	✖	● (I)
talazoparib, palbociclib, axitinib, crizotinib	✖	✖	✖	✖	● (I)

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	○	✖	✖	● (II)
atezolizumab	✖	✖	✖	✖	● (II)
atezolizumab + chemotherapy	✖	✖	✖	✖	● (II)
atezolizumab, nivolumab, ipilimumab	✖	✖	✖	✖	● (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*
durvalumab, tremelimumab	✖	✖	✖	✖	● (II)
ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab	✖	✖	✖	✖	● (II)
nivolumab	✖	✖	✖	✖	● (II)
pembrolizumab, chemotherapy	✖	✖	✖	✖	● (II)
pembrolizumab, ipilimumab + nivolumab	✖	✖	✖	✖	● (II)
chemotherapy, tremelimumab, durvalumab	✖	✖	✖	✖	● (I/II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BAY1905254	✖	✖	✖	✖	● (I)
pembrolizumab, targinine	✖	✖	✖	✖	● (I)

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

Relevant Therapy Details

Current FDA Information

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

FDA information is current as of 2021-02-17. 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:** 2020-11-13 **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]
- 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.

Tumor Mutational Burden (continued)

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

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

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

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

Gastric Cancer

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

Esophageal Cancer

- for the treatment of patients with 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)

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

Triple-Negative Breast Cancer (TNBC)

- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.[2]

Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.[3]

[1]This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

[2]This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Tumor Mutational Burden (continued)

[3]This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s088lbl.pdf

Current NCCN Information

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

NCCN information is current as of 2021-02-01. 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 activating mutation

Other criteria: ERBB2 negative, Hormone receptor positive

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Stage IV; Recurrent, Invasive (Second-line therapy); Preferred intervention

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

Tumor Mutational Burden

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

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

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

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

○ pembrolizumab

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

NCCN Recommendation category: 2A

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

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

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: 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 1.2021]

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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 (Third-line therapy); Useful in certain circumstances

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

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pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Locally Recurrent, Advanced, Metastatic (Line of therapy not specified)

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

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pembrolizumab

Cancer type: Thyroid Gland Medullary Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Locally Recurrent, Unresectable, Symptomatic, Progression, Distant Metastases, Asymptomatic (Line of therapy not specified); Useful in certain circumstances

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

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Thyroid Gland Anaplastic Carcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 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):
- Recurrent, Metastatic (Line of therapy not specified); Useful in certain circumstances
- Uterine Sarcoma; Recurrent, Metastatic (Line of therapy not specified); Useful in certain circumstances

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

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pembrolizumab

Cancer type: Ewing Sarcoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2B

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

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

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 2021-02-17. 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:** 2021-02-16 **Variant class:** PIK3CA E545K mutation

Other criteria: ERBB2 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 2021-02-01. 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 A, Luminal B; Advanced (Line of therapy not specified); ESMO-MCBS v1.1 score: 3

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.(G12V) c.35G>T

○ 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 (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.(G12V) c.35G>T + 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
NCT02688881	Study to Evaluate the Safety and Efficacy of Sirolimus, in Subject With Refractory Solid Tumors	II
NCT04317105	A Phase I/II Biomarker Driven Combination Trial of Copanlisib and Immune Checkpoint Inhibitors in Patients With Advanced Solid Tumors	I/II

Clinical Trials Summary (continued)

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

NCT ID	Title	Phase
NCT04586335	Open Label, Phase Ib Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Clinical Activity of CYH33, an Oral a-specific PI3K Inhibitor in Combination With Olaparib, an Oral PARP Inhibitor in Patients With Advanced Solid Tumors.	I
NCT04632992	MyTACTIC: An Open-Label Phase II Study Evaluating Targeted Therapies in Patients Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response	II
NCT03673787	Ice-CAP: A Phase I Trial of Ipatasertib in Combination With Atezolizumab in Patients With Advanced Solid Tumours With PI3K Pathway Hyperactivation	I/II
NCT03239015	Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event	II
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	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 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
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
No NCT ID	Phase I/II Study of TAS-117 In Combination With TAS-120 In Patients With Advanced Solid Tumors	I/II
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	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

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

NCT ID	Title	Phase
NCT03981614	Combination of MEK Inhibitor Binimetinib and CDK4/6 Inhibitor Palbociclib in KRAS and NRAS Mutant Metastatic Colorectal Cancers	II
NCT04627142	A Phase I Open-label Dose Escalation Trial of BI 1701963 in Combination With Irinotecan in KRAS Mutation Positive Patients With Unresectable Locally Advanced or Metastatic Colorectal Cancer	I
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

Clinical Trials Summary (continued)

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

NCT ID	Title	Phase
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
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
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
No NCT ID	Exploratory Study Of Apatinib For Advanced Colorectal Cancer	IV
NCT04189055	Cetuximab as Salvage herapy in Patients with Neo Wild-type RAS/RAF Metastatic Colorectal Cancer. A Proof-of-concept Study	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
NCT03965845	A Phase Ib/II, Open Label, Dose Escalation and Expansion Study of the Glutaminase Inhibitor Telaglenastat (CB-839) in Combination With CDK4/6 Inhibitor Palbociclib in Patients With Advanced or Metastatic Solid Tumors	I/II
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
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
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
NCT04145297	A Phase I Trial of Ulixertinib (BVD-523) and Hydroxychloroquine in Patients With Advanced MAPK-Mutated Gastrointestinal Adenocarcinomas	I
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
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
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
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

Clinical Trials Summary (continued)

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

NCT ID	Title	Phase
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
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
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
NCT04599140	Phase Ib/II Trial of SX-682 in Combination With Nivolumab for Refractory RAS Mutated (RAS) Microsatellite Stable (MSS) Metastatic Colorectal Cancer (mCRC) (STOPTRAFFIC-1)	I/II
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
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
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	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
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
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT04305249	A Phase I, Open-Label, Multi-Center Dose Finding Study to Investigate the Safety, Pharmacokinetics, and Preliminary Efficacy of ATG-017 Monotherapy in Patients With Advanced Solid Tumors and Hematological Malignancies	I
NCT04528836	A Phase I/IB First-in-Human Study of the SHP2 Inhibitor BBP-398 (Formerly Known as IACS-15509) in Patients With Advanced Solid Tumors	I

Clinical Trials Summary (continued)

TP53 p.(?) c.672+1G>T

NCT ID	Title	Phase
NCT03188965	An Open-label, First-in-human, Dose-escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Maximum Tolerated Dose and / or Recommended Phase II Dose of the ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas	I/II
NCT04122625	A Dose-optimization, Exploratory Phase Ib/II Study to Assess Safety and Efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) Mimetic Debio 1143, When Given in Combination With the Anti-PD-1 Antibody Nivolumab in Patients With Specific Solid Tumors Who Have Progressed During or Immediately After Anti-PD-1/PD-L1 Treatment	I/II
NCT04383938	Study of APR-246 in Combination With Pembrolizumab in Subjects With Solid Tumor Malignancies	I/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
NCT02401347	A Phase II Clinical Trial of the PARP Inhibitor Talazoparib in BRCA1 and BRCA2 Wild Type Patients With Advanced Triple Negative Breast Cancer and Homologous Recombination Deficiency or Advanced HER2 Negative Breast Cancer or Other Solid Tumors With a Mutation in Homologous Recombination Pathway Genes Talazoparib Beyond BRCA (TBB) Trial	II
NCT03415659	A Phase I, Open-label, Single-center, Single/Multiple-dose, Dose-escalation/Dose-expansion Clinical Study on Tolerance and Pharmacokinetics of HWH340 Tablet in Patients With Advanced Solid Tumors	I
NCT03233204	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase 2 Subprotocol of Olaparib in Patients With Tumors Harboring Defects in DNA Damage Repair Genes	II
NCT04267939	An Open-label Phase Ib Study to Determine the Maximum Tolerated and/or Recommended Phase II Dose of the ATR Inhibitor BAY 1895344 in Combination With PARP Inhibitor Niraparib, in Patients With Recurrent Advanced Solid Tumors and Ovarian Cancer	I
NCT04693468	Modular Phase IB Hypothesis-Testing, Biomarker-Driven, Talazoparib Combination Trial (TalaCom)	I

Tumor Mutational Burden

NCT ID	Title	Phase
NCT03767075	Basket of Baskets: A Modular, Open-label, Phase II, Multicentre Study To Evaluate Targeted Agents in Molecularly Selected Populations With Advanced Solid Tumours	II
NCT04185831	MEGALiT - a Multicenter, Basket and Umbrella Explorative Trial on the Efficacy and Safety of Molecular Profile Selected Commercially Available Targeted Anti-cancer Drugs in Patients With Advanced Cancers Progressive on Standard Therapy	II
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT04632992	MyTACTIC: An Open-Label Phase II Study Evaluating Targeted Therapies in Patients Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response	II
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	II
NCT02029001	A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors MOST: My own specific treatment	II

Clinical Trials Summary (continued)

Tumor Mutational Burden (continued)

NCT ID	Title	Phase
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT03668119	A Randomized, Open-Label, Phase II Study of Nivolumab in Combination With Ipilimumab or Nivolumab Monotherapy in Participants With Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)	II
No NCT ID	A Multicenter Phase II Study Of Nivolumab Monotherapy In Recurrent And/Or Metastatic Gastrointestinal Cancer Patients With High Tumor Mutation Burden (TMB-H)	II
No NCT ID	TR Accompanied with the Study Titled A Multicenter Phase II Study of Nivolumab Monotherapy in Recurrent and/or Metastatic Gastrointestinal Cancer Patients with High Tumor Mutation Burden (TMB-H).	II
NCT02628067	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)	II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT03518606	A Phase I/II Basket Trial Evaluating A Combination Of Metronomic Oral Vinorelbine Plus Anti-PD-L1/ Anti-CTLA4 ImmunothErapy In Patients With Advanced Solid Tumour	I/II
NCT03838042	INFORM2 Exploratory Multinational Phase I/II Combination Study of Nivolumab and Entinostat in Children and Adolescents with Refractory High-risk Malignancies	I/II
NCT03666273	An Open-label, Phase I, First-in-human, Dose Escalation and Expansion Study to Evaluate the Safety, Tolerability, Maximum Tolerated or Administered Dose, Pharmacokinetics, Pharmacodynamics and Tumor Response Profile of the ILDR2 Function-blocking Antibody BAY1905254 in Patients With Advanced Solid Tumors	I
NCT03236935	Phase Ib Trial of L-NMMA in Combination With Pembrolizumab in Patients With Melanoma, Non-Small Cell Lung Cancer, Head and Neck Squamous Cell Carcinoma, Classical Hodgkin Lymphoma, Urothelial Carcinoma, Cervical Cancer, Esophageal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Primary Mediastinal Large B-cell Lymphoma, Renal Cell Carcinoma, Small Cell Lung Cancer, Microsatellite Instability-High/Mismatch Repair Deficient Cancer, or for the Treatment of Adult Patients With Unresectable or Metastatic Tumor Mutational Burden-High Solid Tumors	I

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-02-17. For the most up-to-date information, search www.fda.gov.

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

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2020-11-10 **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/2020/125084s275lbl.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

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

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 2021-02-01. 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.(G12V) c.35G>T

cetuximab

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

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

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 2.2021]

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 1.2021]

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 2.2021]

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

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 1.2021]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2021-02-17. For the most up-to-date information, search www.ema.europa.eu/ema.

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

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 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 Breakthrough Fast Track

ESMO information is current as of 2021-02-01. For the most up-to-date information, search www.esmo.org.

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

cetuximab

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

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

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

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

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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

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.(G12V) c.35G>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:

2021.04.14
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Laboratory Supervisor:

2021.04.14
12:12:20 +08'00'

Pathologist:

2021.04.14
12:12:34 +08'00'

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