Taipei Veterans General Hospital

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Sample Information

Patient Name: 李莊伯
Gender: Male
ID No.: F102756298
History No.: 21654115
Age: 67

Ordering Doctor: DOC1322F 趙毅
Ordering REQ.: H4221GP
Signing in Date: 2022/01/27

Path No.: S111-98297
MP No.: TM22001
Assay: Tumor Mutation Load Assay
Sample Type: FFPE
Block No.: S111-00160B
Percentage of tumor cells: 60%

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

Note:

Sample Cancer Type: Colorectal Cancer

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Relevant Colorectal Cancer Variants

Gene	Finding
BRAF	***BRAF p.(V600E) c.1799T>A***
KRAS	None detected
NRAS	None detected
NTRK1	None detected
NTRK3	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*BRAF p.(V600E) c.1799T>A* B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 24.61% **Prognostic significance:** ESMO: Very poor **Diagnostic significance:** None	**binimetinib + encorafenib** [1, 2] **cetuximab + encorafenib** [1, 2] encorafenib + panitumumab	**atezolizumab + cobimetinib + vemurafenib** [1] **binimetinib + encorafenib** [1, 2] **cetuximab + encorafenib** [1, 2] **cobimetinib + vemurafenib** [1, 2] **dabrafenib** [1, 2] **dabrafenib + trametinib** [1, 2] **trametinib** [1, 2] **vemurafenib** [1, 2] BRAF inhibitor + MEK inhibitor dabrafenib + MEK inhibitor dabrafenib + pembrolizumab + trametinib encorafenib ipilimumab + nivolumab selumetinib	0
IA	*Tumor Mutational Burden* 9.17 Mut/Mb measured **Prognostic significance:** None **Diagnostic significance:** None	**pembrolizumab** [1]	pembrolizumab	2

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

TP53 p.(C176Y) c.527G>A

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

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
BRAF	p.(V600E)	c.1799T>A	COSM476	chr7:140453136	24.61%	NM_004333.6	missense	1991
TP53	p.(C176Y)	c.527G>A	COSM10687	chr17:7578403	36.12%	NM_000546.5	missense	1999
MTOR	p.(T1834_T1837del)	c.5490_5501delTGCCGCCACCAC	.	chr1:11190697	46.39%	NM_004958.4	nonframeshift Deletion	1248
PDE4DIP	p.(R870W)	c.2608C>T	.	chr1:144904704	50.65%	NM_001198834.4	missense	1998
MSH2	p.(L787P)	c.2360T>C	.	chr2:47705560	3.28%	NM_000251.3	missense	61
MSH2	p.(A789=)	c.2367C>T	.	chr2:47705567	3.23%	NM_000251.3	synonymous	62
BCL11A	p.(T722M)	c.2165C>T	.	chr2:60687882	7.66%	NM_022893.4	missense	1998
ERCC3	p.(?)	c.-51G>A	.	chr2:128051708	38.03%	NM_000122.2	unknown	1023
LRP1B	p.(H3952R)	c.11855A>G	.	chr2:141108403	48.84%	NM_018557.3	missense	1468

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
LTF	p.(R23dup)	c.68_69insAAG	.	chr3:46501284	99.59%	NM_002343.6	nonframeshift Insertion	488
FOXP1	p.(?)	c.-76920G>T	.	chr3:71179826	50.61%	NM_001244815.2	unknown	1569
GATA2	p.(T160=)	c.480C>T	.	chr3:128204961	47.45%	NM_032638.5	synonymous	2000
GATA2	p.(R67=)	c.201G>A	.	chr3:128205674	49.62%	NM_032638.5	synonymous	1997
PIK3CB	p.(R153L)	c.458G>T	.	chr3:138461563	48.17%	NM_006219.3	missense	1995
PDGFRA	p.(P567=)	c.1701A>G	.	chr4:55141055	99.84%	NM_006206.6	synonymous	1838
KDR	p.(G152=)	c.456G>A	.	chr4:55981481	48.56%	NM_002253.3	synonymous	1182
ADGRL3	p.(G1116V)	c.3347G>T	.	chr4:62897288	18.35%	NM_015236.6	missense	1248
FGFR4	p.(I197T)	c.590T>C	.	chr5:176518092	47.00%	NM_213647.3	missense	1998
PKHD1	p.(V1287G)	c.3860T>G	.	chr6:51890748	48.77%	NM_138694.4	missense	1997
FOXO3	p.(R222W)	c.664C>T	.	chr6:108984700	23.90%	NM_001455.4	missense	2000
ROS1	p.(Q1326=)	c.3978A>G	.	chr6:117677955	49.00%	NM_002944.2	synonymous	2000
SYNE1	p.(K4121S)	c.12362_12363delAG insGT	.	chr6:152658141	48.84%	NM_182961.4	missense	1728
SYNE1	p.(K4121R)	c.12362A>G	.	chr6:152658142	48.55%	NM_182961.4	missense	1728
SAMD9	p.(K1097del)	c.3286_3288delAAG	.	chr7:92732122	57.25%	NM_001193307.1	nonframeshift Deletion	1186
EPHB4	p.(L721=)	c.2161C>T	.	chr7:100405160	29.34%	NM_004444.5	synonymous	1997
MET	p.(E549D)	c.1647G>C	.	chr7:116381025	25.58%	NM_001127500.3	missense	1294
SMO	p.(R261H)	c.782G>A	.	chr7:128845485	49.55%	NM_005631.5	missense	1671
KMT2C	p.(E531=)	c.1593G>A	.	chr7:151949052	51.61%	NM_170606.3	synonymous	1339
TET1	p.(E1044D)	c.3132A>T	.	chr10:70405618	13.98%	NM_030625.3	missense	1896
BMPR1A	p.(*533G)	c.1597T>G	.	chr10:88683474	24.70%	NM_004329.3	stoploss	1640
WT1	p.(Y233=)	c.699C>T	.	chr11:32450128	27.19%	NM_024426.6	synonymous	1280
EXT2	p.(?)	c.-36C>T	.	chr11:44117767	55.81%	NM_000401.3	unknown	353
BIRC2	p.(S349=)	c.1047T>C	.	chr11:102239107	48.57%	NM_001256166.2	synonymous	1997
CBL	p.(P666L)	c.1997C>T	.	chr11:119158617	21.35%	NM_005188.4	missense	2000
EP400	p.(T1170=)	c.3510C>T	.	chr12:132497622	67.12%	NM_015409.5	synonymous	1998
LAMP1	p.(G187Efs*38)	c.556_557delCGinsA	.	chr13:113965176	100.00%	NM_005561.4	frameshift Block Substitution	1997
TGM7	p.(T393N)	c.1178C>A	.	chr15:43574215	46.24%	NM_052955.3	missense	1501
ERCC4	p.(G912R)	c.2734G>A	.	chr16:14042187	50.33%	NM_005236.3	missense	1987
ITGB3	p.(E654Kfs*15)	c.1960delG	.	chr17:45377889	53.50%	NM_000212.3	frameshift Deletion	1886

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
CD79B	p.(?)	c.-19C>T	.	chr17:62009640	24.07%	NM_001039933.3	unknown	1998
CDH2	p.(R808Q)	c.2423G>A	.	chr18:25543412	26.61%	NM_001792.5	missense	1999
BCL2	p.(A42Pfs*54)	c.124delG	.	chr18:60985775	52.43%	NM_000633.2	frameshift Deletion	267
BCL2	p.(P40Rfs*112)	c.119_127delCGGGGGCCGinsGGGGCCA	.	chr18:60985773	43.45%	NM_000633.2	frameshift Block Substitution	267
KEAP1	p.(G571V)	c.1712G>T	.	chr19:10597491	11.11%	NM_203500.2	missense	1999
AXL	p.(R499C)	c.1495C>T	.	chr19:41749570	37.85%	NM_021913.5	missense	2000
CIC	p.(V679=)	c.2037C>T	.	chr19:42794957	60.00%	NM_015125.4	synonymous	500
PTPRT	p.(S1247=)	c.3741C>G	.	chr20:40730794	47.77%	NM_133170.4	synonymous	1999
MYH9	p.(D1708=)	c.5124C>T	.	chr22:36681937	35.50%	NM_002473.6	synonymous	2000

Biomarker Descriptions

BRAF (B-Raf proto-oncogene, serine/threonine kinase)

Background: The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1 (CRAF). BRAF is among the most commonly mutated kinases in cancer. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, dedifferentiation, and survival[1,2]. BRAF mutations are categorized into three distinct functional classes namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF[3]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[3,4,5].

Alterations and prevalence: Recurrent somatic mutations in BRAF are observed in 40-60% of melanoma and thyroid cancer, approximately 10% of colorectal cancer, and about 2% of non-small cell lung cancer (NSCLC)[6,7,8,9,10]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[4,11]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R/, G464V/E/, and BRAF fusions[4]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[4]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer, and prevalent in histiocytic neoplasms[12,13,14]. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11 as well as additional codons flanking V600 in the activation loop[11]. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer[7,10]. BRAF fusions are mutually exclusive to BRAF V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[15,16,17,18,19]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain leading to constitutive kinase activation[5,15,17].

Potential relevance: Vemurafenib[20] (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive[4]. BRAF kinase inhibitors including dabrafenib[21] (2013) and encorafenib[22] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[22] is approved in combination with cetuximab[23] (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations[4]. Trametinib[24] (2013) and binimetinib[25] (2018) were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC. The combinations of dabrafenib/trametinib (2015) and vemurafenib/cobimetinib[26] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017) with a BRAF V600E mutation. The PD-L1 antibody, atezolizumab[27], has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. The pan-RAF kinase inhibitor DAY-101 was granted breakthrough therapy designation (2020) by the FDA for pediatric patients with advanced low-grade glioma harboring

Biomarker Descriptions (continued)

activating RAF alterations[28]. The ERK inhibitor ulixertinib[29] was also granted a fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma[30]. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification and alternative splice transcripts as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)[31,32,33,34,35,36,37]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[19].

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[38]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[39,40].

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%)[7,10,41,42,43,44]. 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[7,10]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[45,46,47,48].

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[49]. The FDA has granted fast track designation (2019) to the p53 reactivator, eprenetapopt,[50] and breakthrough designation[51] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[52,53]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), chronic lymphocytic leukemia (CLL),[54,55,56,57]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[58]. 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[59].

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[60]. Errors in DNA repair, including mutations in the POLE gene and in mismatch repair (MMR) genes, are associated with increased TMB[61,62,63,64,65]. 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[66,67,68,69].

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[70]. Certain childhood cancers, leukemia, glioblastoma, and neuroblastoma typically have low mutation burden and median TMB values <1 mut/Mb[67,70]. In comparison, cancers that experience genotoxic insults including skin cancer and lung cancer have higher median TMB values of approximately 10 mut/Mb[67,70]. 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)[67,70,71]. 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[70,72,73]. In NSCLC, several studies have suggested establishing a threshold between low and high TMB of 10 +/- 1 mut/Mb[74,75,76,77].

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[78] 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

Biomarker Descriptions (continued)

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[75,79,80]. In contrast, several promising previous trials failed to show an improvement in survival outcomes between high and low TMB including CheckMate 227 (ipilimumab + nivolumab vs. chemotherapy), CheckMate 026 (nivolumab vs. chemotherapy), KEYNOTE 189 (pembrolizumab vs. chemotherapy), KEYNOTE 021 (pembrolizumab vs. pembrolizumab + chemotherapy), and Lung-MAP (nivolumab + ipilimumab vs. nivolumab). In response, suggestions to combine TMB score with PD-L1 expression as a way to increase the predictive power for patient stratification have been reported[81]. Nivolumab alone or in combination with ipilimumab is recommended for use in NSCLC with evidence of high TMB[82]. Pembrolizumab is indicated for use in various cancer types with evidence of metastasis including Ewing sarcoma, salivary gland neoplasms, cervical cancer, uterine sarcoma, endometrial carcinoma, thyroid cancer, ovarian cancer, esophageal cancer, esophagogastric junction cancer, breast cancer, and germ cell tumors with high TMB[83,84,85,86,87,88,89,90,91]. 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[92,93,94,95].

Relevant Therapy Summary

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

BRAF p.(V600E) c.1799T>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cetuximab + encorafenib	◑	●	◑	✖	✖
binimetinib + encorafenib	◑	○	◑	○	✖
cobimetinib + vemurafenib	○	○	○	○	✖
dabrafenib + trametinib	○	○	○	○	✖
dabrafenib	○	○	○	✖	✖
vemurafenib	○	○	○	✖	✖
trametinib	○	✖	○	✖	✖
atezolizumab + cobimetinib + vemurafenib	○	✖	✖	✖	✖
encorafenib + panitumumab	✖	●	✖	✖	✖
dabrafenib + pembrolizumab + trametinib	✖	○	✖	✖	✖
encorafenib	✖	○	✖	✖	✖
selumetinib	✖	○	✖	✖	✖
BRAF inhibitor + MEK inhibitor	✖	✖	✖	○	✖
dabrafenib + MEK inhibitor	✖	✖	✖	○	✖
ipilimumab + nivolumab	✖	✖	✖	○	✖

Tumor Mutational Burden

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab	●	○	✖	✖	● (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*
atezolizumab	✖	✖	✖	✖	● (II)

* 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 2021-11-17. For the most up-to-date information, search www.fda.gov.

BRAF p.(V600E) c.1799T>A

◑ binimetinib + encorafenib, cetuximab + encorafenib

Cancer type: Colorectal Cancer, Melanoma **Label as of:** 2020-04-08 **Variant class:** BRAF V600E mutation

Indications and usage:

BRAFTOVI® is a kinase inhibitor indicated:

- in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.
- in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

Limitations of Use: BRAFTOVI® is not indicated for treatment of patients with wild-type BRAF melanoma or wild-type BRAF CRC.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210496s006lbl.pdf

BRAF p.(V600E) c.1799T>A (continued)

cetuximab + encorafenib

Cancer type: Colorectal Cancer **Label as of:** 2021-09-24 **Variant class:** BRAF V600E mutation

Indications and usage:

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

Head and Neck Cancer

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

Colorectal Cancer

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

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

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

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

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

Reference:

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

BRAF p.(V600E) c.1799T>A (continued)

atezolizumab + cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2021-10-15 **Variant class:** BRAF V600E mutation

Indications and usage:

TECENTRIQ® is a programmed death-ligand 1 (PD-L1) blocking antibody indicated:

Urothelial Carcinoma

- for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or
  - are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Non-Small Cell Lung Cancer (NSCLC)

- as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test.
- for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
- in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
- for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ®

Small Cell Lung Cancer (SCLC)

- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Hepatocellular Carcinoma (HCC)

- in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.

Melanoma

- in combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761034Orig1s042lbl.pdf

binimetinib + encorafenib

Cancer type: Melanoma **Label as of:** 2019-01-23 **Variant class:** BRAF V600E mutation

Indications and usage:
MEKTOVI® is a kinase inhibitor indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210498s001lbl.pdf

BRAF p.(V600E) c.1799T>A (continued)

cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2018-01-26 **Variant class:** BRAF V600E mutation

Indications and usage:

COTELLIC® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206192s002lbl.pdf

dabrafenib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Thyroid Gland Anaplastic Carcinoma **Label as of:** 2021-05-07 **Variant class:** BRAF V600E mutation

Indications and usage:

TAFINLAR® is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

TAFINLAR® is indicated, in combination with trametinib, for:

- the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
- the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.

Limitations of Use: TAFINLAR® is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF NSCLC, or wild-type BRAF ATC.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202806s017lbl.pdf

BRAF p.(V600E) c.1799T>A (continued)

trametinib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Thyroid Gland Anaplastic Carcinoma **Label as of:** 2021-05-07 **Variant class:** BRAF V600E mutation

Indications and usage:

MEKINIST® is a kinase inhibitor indicated as a single agent for the treatment of BRAF-inhibitor treatment-naive patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

MEKINIST® is indicated, in combination with dabrafenib, for:

- the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
- the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204114s018lbl.pdf

vemurafenib

Cancer type: Melanoma **Label as of:** 2020-05-18 **Variant class:** BRAF V600E mutation

Indications and usage:

- ZELBORAF® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
- ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation.

Limitation of Use: ZELBORAF® is not indicated for treatment of patients with wild-type BRAF melanoma.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf

Tumor Mutational Burden

pembrolizumab

Cancer type: Solid Tumor **Label as of:** 2021-11-17 **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®.

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

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1]

Tumor Mutational Burden (continued)

- Limitations of Use: The safety and effectiveness of KEYTRUDA® in pediatric patients with MSI-H central nervous system cancers have not been established.

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

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

Gastric Cancer

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

Esophageal Cancer

- for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

Cervical Cancer

- in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Hepatocellular Carcinoma (HCC)

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

Merkel Cell Carcinoma (MCC)

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

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of adult patients with advanced RCC.
- in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
- for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

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

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)and description of clinical benefit in the confirmatory trial

- for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.

Triple-Negative Breast Cancer (TNBC)

- for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

Tumor Mutational Burden (continued)

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

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

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.[2]

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

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s113lbl.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 2021-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

BRAF p.(V600E) c.1799T>A

● cetuximab + encorafenib

Cancer type: Colon Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metachronous Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

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

● cetuximab + encorafenib

Cancer type: Rectal Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metachronous Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

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

● encorafenib + panitumumab

Cancer type: Colon Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metachronous Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

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

● encorafenib + panitumumab

Cancer type: Rectal Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metachronous Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

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

BRAF p.(V600E) c.1799T>A (continued)

cobimetinib + vemurafenib

Cancer type: Anaplastic Astrocytoma, Anaplastic Oligoastrocytoma, Anaplastic Oligodendroglioma, Glioblastoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent (Recurrence therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

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cobimetinib + vemurafenib

Cancer type: Ganglioglioma, Pilocytic Astrocytoma, Pleomorphic Xanthoastrocytoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade I, WHO CNS Tumor Grade II (Adjuvant therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

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cobimetinib + vemurafenib

Cancer type: Ganglioglioma, Pilocytic Astrocytoma, Pleomorphic Xanthoastrocytoma, Subependymal Giant Cell Astrocytoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade I, WHO CNS Tumor Grade II; Recurrent, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

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dabrafenib + trametinib

Cancer type: Melanoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

BRAF p.(V600E) c.1799T>A (continued)

dabrafenib + trametinib

Cancer type: Anaplastic Astrocytoma, Anaplastic Oligoastrocytoma, Anaplastic Oligodendroglioma, Glioblastoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent (Recurrence therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

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dabrafenib + trametinib

Cancer type: Ganglioglioma, Pilocytic Astrocytoma, Pleomorphic Xanthoastrocytoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade I, WHO CNS Tumor Grade II (Adjuvant therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

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dabrafenib + trametinib

Cancer type: Ganglioglioma, Pilocytic Astrocytoma, Pleomorphic Xanthoastrocytoma, Subependymal Giant Cell Astrocytoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade I, WHO CNS Tumor Grade II; Recurrent, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

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dabrafenib + trametinib

Cancer type: Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2021]

BRAF p.(V600E) c.1799T>A (continued)

dabrafenib + trametinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

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dabrafenib + trametinib

Cancer type: Thyroid Gland Anaplastic Carcinoma **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVA, Stage IVB; Local, Unresectable, Regional (Neoadjuvant therapy); Consider
- Stage IVC; Metastatic (Second-line therapy); Preferred intervention, Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]

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selumetinib

Cancer type: Pilocytic Astrocytoma **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade I; Recurrent, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

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vemurafenib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 7.2021]

BRAF p.(V600E) c.1799T>A (continued)

cobimetinib + vemurafenib

Cancer type: Melanoma **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 2.2021]

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binimetinib + encorafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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cobimetinib + vemurafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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dabrafenib + trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

BRAF p.(V600E) c.1799T>A (continued)

dabrafenib + trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Stage III (Adjuvant therapy); Preferred intervention
- Recurrent (Adjuvant therapy); Preferred intervention
- Recurrent, Resectable (Adjuvant therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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binimetinib + encorafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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cobimetinib + vemurafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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dabrafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Preferred intervention
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

BRAF p.(V600E) c.1799T>A (continued)

dabrafenib + trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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dabrafenib + trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IIIA, Stage IIIB, Stage IIIC, Stage IIID (Adjuvant therapy); Preferred intervention
- Stage III; Resectable (Adjuvant therapy); Preferred intervention
- Locally Recurrent, Resectable (Adjuvant therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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encorafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Preferred intervention
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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vemurafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Preferred intervention
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

BRAF p.(V600E) c.1799T>A (continued)

binimetinib + encorafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Resectable, Distant Metastases (Adjuvant therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

---

cobimetinib + vemurafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Resectable, Distant Metastases (Adjuvant therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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dabrafenib + pembrolizumab + trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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dabrafenib + trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Resectable, Distant Metastases (Adjuvant therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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dabrafenib

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma **Variant class:** BRAF mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]

BRAF p.(V600E) c.1799T>A (continued)

vemurafenib

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma

Variant class: BRAF mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]

Tumor Mutational Burden

pembrolizumab

Cancer type: Chondrosarcoma, Ewing Sarcoma, Osteosarcoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2022]

pembrolizumab

Cancer type: Breast Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 8.2021]

pembrolizumab

Cancer type: Cervical Small Cell Neuroendocrine Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

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

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

Tumor Mutational Burden (continued)

pembrolizumab

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

NCCN Recommendation category: 2A

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

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

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pembrolizumab

Cancer type: Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Squamous Cell; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 4.2021]

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pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 5.2021]

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pembrolizumab

Cancer type: Head and Neck Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Nasopharyngeal; Recurrent, Unresectable, Metastatic (Subsequent therapy); Useful in certain circumstances
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 3.2021]

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2021]

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pembrolizumab

Cancer type: Large Cell Neuroendocrine Carcinoma, Small Cell Neuroendocrine Carcinoma

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 3.2021]

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pembrolizumab

Cancer type: Neuroendocrine Tumor

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Well Differentiated; G3; Locally Advanced, Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 3.2021]

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pembrolizumab

Cancer type: Ovarian Cancer

Variant class: Tumor Mutational Burden

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Useful in certain circumstances

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

Tumor Mutational Burden (continued)

pembrolizumab

Cancer type: Castration-Resistant Prostate Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

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

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

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pembrolizumab

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

NCCN Recommendation category: 2A

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

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

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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); Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]

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pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Persistent, Local, Distant Metastases, Regional (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]

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pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVC; Metastatic (Second-line therapy); Useful in certain circumstances, Consider

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2021]

Tumor Mutational Burden (continued)

pembrolizumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metastatic, Progression (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 4.2021]

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pembrolizumab

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 4.2021]

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pembrolizumab

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Well Differentiated; G3; Locally Advanced, Metastatic, Progression, Unresectable (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 3.2021]

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pembrolizumab

Cancer type: Castration-Resistant Prostate Cancer **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2B

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

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

Current EMA Information

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

EMA information is current as of 2021-11-17. For the most up-to-date information, search www.ema.europa.eu/ema.

BRAF p.(V600E) c.1799T>A

◑ binimetinib + encorafenib, cetuximab + encorafenib

Cancer type: Colorectal Cancer, Melanoma **Label as of:** 2021-11-09 **Variant class:** BRAF V600E mutation

Reference:

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

○ binimetinib + encorafenib

Cancer type: Melanoma **Label as of:** 2021-09-03 **Variant class:** BRAF V600E mutation

Reference:

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

○ cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2021-09-15 **Variant class:** BRAF V600E mutation

Reference:

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

○ dabrafenib, dabrafenib + trametinib

Cancer type: Cutaneous Melanoma, Melanoma, Non-Small Cell Lung Cancer **Label as of:** 2021-09-13 **Variant class:** BRAF V600E mutation

Reference:

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

○ trametinib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer **Label as of:** 2021-10-27 **Variant class:** BRAF V600E mutation

Reference:

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

○ vemurafenib

Cancer type: Melanoma **Label as of:** 2021-09-08 **Variant class:** BRAF V600E mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/zelboraf-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 2021-11-01. For the most up-to-date information, search www.esmo.org.

BRAF p.(V600E) c.1799T>A

○ dabrafenib + MEK inhibitor

Cancer type: Gastrointestinal Stromal Tumor **Variant class:** BRAF V600E mutation

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

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

Reference: ESMO Clinical Practice Guidelines - ESMO-EUROCAN-Gastrointestinal Stromal Tumours [Annals of Oncology (2021), doi: https://doi.org/10.1016/j.annonc.2021.09.005.]

○ dabrafenib + trametinib

Cancer type: Thyroid Gland Anaplastic Carcinoma **Variant class:** BRAF V600E mutation

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

Population segment (Line of therapy):
- Advanced, Unresectable (First-line therapy)

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

○ BRAF inhibitor + MEK inhibitor

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy)
- Asymptomatic, Metastatic (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz411]

○ dabrafenib + trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Stage IIIA, Stage IIIB, Stage IIIC; Resectable (Adjuvant therapy); ESMO-MCBS v1.1 score: A

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz411]

BRAF p.(V600E) c.1799T>A (continued)

binimetinib + encorafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy, Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz411]

cobimetinib + vemurafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy, Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz411]

dabrafenib + trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy, Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz411]

dabrafenib + trametinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Stage IV (First-line therapy, Second-line therapy); ESMO-MCBS v1.1 score: 2

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

BRAF p.(V600E) c.1799T>A (continued)

ipilimumab + nivolumab

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Stage III, Stage IV; Asymptomatic, Brain Metastases, Metastatic, Unresectable (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz411]

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ipilimumab + nivolumab

Cancer type: Melanoma **Variant class:** BRAF mutation

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

Population segment (Line of therapy):
- Asymptomatic, Brain Metastases (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-EANO-ESMO Brain Metastasis from Solid Tumours [Ann Oncol (2021), https://doi.org/10.1016/j.annonc.2021.07.016]

Prognostic Details

Current ESMO Information

ESMO information is current as of 2021-11-01. For the most up-to-date information, search www.esmo.org.

BRAF p.(V600E) c.1799T>A

Prognostic significance: ESMO: Very poor

Cancer type: Colorectal Cancer **Variant class:** BRAF mutation

Summary:

- ESMO™ associates the biomarker with very poor prognosis for Metastatic Colorectal Cancer

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)]

Clinical Trials in Taiwan region:

Clinical Trials Summary

Tumor Mutational Burden

NCT ID	Title	Phase
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
NCT02628067	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158).	II

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-11-17. For the most up-to-date information, search www.fda.gov.

BRAF p.(V600E) c.1799T>A

binimetinib + cetuximab + encorafenib

Cancer type: Colorectal Cancer

Variant class: BRAF V600E mutation

Supporting Statement:
The FDA has granted Breakthrough Designation to the MEK inhibitor, binimetinib, in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer.

Reference:

https://markets.businessinsider.com/news/stocks/array-biopharma-receives-fda-breakthrough-therapy-designation-for-braftovi-in-combination-with-mektovi-and-cetuximab-for-brafv600e-mutant-metastatic-colorectal-cancer-1027437791

DAY-101

Cancer type: Diffuse Astrocytoma,
Myxopapillary Ependymoma,
Oligodendroglioma, Pilocytic Astrocytoma,
Pleomorphic Xanthoastrocytoma,
Subependymal Giant Cell Astrocytoma

Variant class: RAF aberration

Supporting Statement:
The FDA has granted Breakthrough Therapy Designation to DAY-101 for activating RAF alterations in pediatric, advanced low-grade gliomas that have progressed following prior treatment or have no satisfactory alternative treatment options.

Reference:

https://ir.dayonebio.com/node/6511/pdf

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

BRAF p.(V600E) c.1799T>A

trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600E mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "Although trametinib is FDA approved for single-agent use to treat patients with unresectable or metastatic melanoma with BRAF V600E mutation, trametinib monotherapy is no longer an NCCN recommended treatment option due to relatively poor efficacy compared with BRAF inhibitor monotherapy and BRAF/MEK inhibitor combination therapy."

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

dabrafenib + trametinib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "As the COMBI-AD trial excluded patients with distant metastases, dabrafenib/trametinib is not a recommended adjuvant treatment option for resected stage IV disease."

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

Tumor Mutational Burden

pembrolizumab

Cancer type: Giant Cell Tumor of Soft Tissue **Variant class:** Tumor Mutational Burden

NCCN Recommendation category: 2A

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "NCCN does not recommend this systemic treatment for GCTB since it is not technically a malignant tumor."

Reference: NCCN Guidelines® - NCCN-Bone Cancer [Version 2.2022]

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2021-11-01. For the most up-to-date information, search www.esmo.org.

BRAF p.(V600E) c.1799T>A

vemurafenib

Cancer type: Cutaneous Melanoma **Variant class:** BRAF V600 mutation

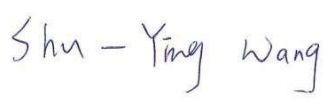
Summary:
ESMO Clinical Practice Guidelines include the following supporting statement(s):

- "Efficacy of adjuvant targeted therapy has also been recently reported. The BRIM8 study analysed vemurafenib monotherapy versus a placebo in stage IIC and stage III (AJCC 7th edition) melanoma after complete surgical resection. The study did not meet its primary end point of DFS. Therefore, BRAF inhibitor monotherapy cannot be recommended as adjuvant treatment for melanoma".

Reference: ESMO Clinical Practice Guidelines - ESMO-Cutaneous Melanoma [Annals of Oncology 30: 1884–1901. doi:10.1093/annonc/mdz411]

Signatures

Testing Personnel:



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Laboratory Supervisor:

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Pathologist:

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