



Sample Information

Patient Name: 張復昌
Gender: Male
ID No.: F120802462
History No.: 49942407
Age: 52

Ordering Doctor: DOC6490L 徐蒹葭
Ordering REQ.: 0CUMSRZ
Signing in Date: 2023/12/14

Path No.: M112-00325
MP No.: F23091
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-60278A
Percentage of tumor cells: 20%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	BRAF p.(V600E) c.1799T>A	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	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: 11.94%	dabrafenib ^{1,2} dabrafenib + trametinib ^{1,2} trametinib ^{1,2} vemurafenib	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} bevacizumab + chemotherapy BRAF inhibitor + MEK inhibitor dabrafenib + MEK inhibitor encorafenib encorafenib + panitumumab ipilimumab + nivolumab selumetinib	2

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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.

Variant Details

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	11.94%	NM_004333.6	missense	1969
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.25%	NM_213647.3	missense	2000
RET	p.(L769=)	c.2307G>T	.	chr10:43613843	99.95%	NM_020975.6	synonymous	1998
MAP2K2	p.(V64=)	c.192C>T	.	chr19:4117528	49.85%	NM_030662.4	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 BRAF³. 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 fusions⁴. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I⁴. 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 loop¹¹. 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}.

Biomarker Descriptions (continued)

Potential relevance: Vemurafenib²⁰ (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 insensitive⁴. BRAF kinase inhibitors including dabrafenib²¹ (2013) and encorafenib²² (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib²² is approved in combination with cetuximab²³ (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 alterations⁴. Trametinib²⁴ (2013) and binimetinib²⁵ (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/cobimetinib²⁶ (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017) with a BRAF V600E mutation. The PD-L1 antibody, atezolizumab²⁷, has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. In 2018, binimetinib²⁸ was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib²⁹ was granted fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. The FDA granted fast track designation (2022) to the pan-RAF inhibitor, KIN-2787³⁰, for the treatment of BRAF class II or III alteration-positive malignant or unresectable melanoma. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma³¹. 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)^{32,33,34,35,36,37,38}. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported¹⁹.

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*
dabrafenib + trametinib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
dabrafenib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
trametinib	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
vemurafenib	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
binimetinib + encorafenib	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
cetuximab + encorafenib	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
cobimetinib + vemurafenib	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
atezolizumab + cobimetinib + vemurafenib	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
encorafenib	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
encorafenib + panitumumab	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
selumetinib	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
bevacizumab + CAPOX	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
bevacizumab + FOLFOX	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
bevacizumab + FOLFOXIRI	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
BRAF inhibitor + MEK inhibitor	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

* 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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
dabrafenib + MEK inhibitor	✕	✕	✕	○	✕
ipilimumab + nivolumab	✕	✕	✕	○	✕
binimetinib, encorafenib	✕	✕	✕	✕	● (II)
binimetinib	✕	✕	✕	✕	● (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 2023-09-13. For the most up-to-date information, search www.fda.gov.

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

☒ dabrafenib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Solid Tumor, Thyroid Gland Anaplastic Carcinoma

Label as of: 2023-08-31

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.
- the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

Limitations of Use: TAFINLAR® is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition. TAFINLAR® is not indicated for treatment of patients with wildtype BRAF solid tumors.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202806s027lbl.pdf

BRAF p.(V600E) c.1799T>A (continued)**① trametinib, dabrafenib + trametinib**

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Solid Tumor, Thyroid Gland Anaplastic Carcinoma

Label as of: 2023-08-31

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-naïve 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.
- the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on overall 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).
- the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

Limitations of Use: MEKINIST® is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204114s029lbl.pdf

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

○ atezolizumab + cobimetinib + vemurafenib

Cancer type: Melanoma

Label as of: 2023-05-12

Variant class: BRAF V600E mutation

Indications and usage:

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

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 $\geq 1\%$ 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 $\geq 50\%$ of tumor cells [TC $\geq 50\%$] or PD-L1 stained tumor-infiltrating immune cells [IC] covering $\geq 10\%$ of the tumor area [IC $\geq 10\%$]), 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 adult patients with unresectable or metastatic HCC who have not received prior systemic therapy.

Melanoma

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

Alveolar Soft Part Sarcoma (ASPS)

- for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761034s049s051lbl.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)

○ binimetinib + encorafenib, cetuximab + encorafenib

Cancer type: Colorectal Cancer, Melanoma

Label as of: 2022-02-11

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/2022/210496s013lbl.pdf

○ cetuximab + encorafenib

Cancer type: Colorectal Cancer

Label as of: 2021-09-24

Variant class: BRAF V600E mutation

Indications and usage:

Erbix® 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)**○ cobimetinib + vemurafenib**

Cancer type: Melanoma

Label as of: 2023-05-31

Variant class: BRAF V600E mutation

Indications and usage:

COTELLIC® is a kinase inhibitor indicated:

- For the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.
- As a single agent for the treatment of adult patients with histiocytic neoplasms.

Reference:https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/206192s006lbl.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

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 2023-09-01. For the most up-to-date information, search www.nccn.org. For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

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

☒ dabrafenib

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, Biomarker discovered prior to first line therapy (First-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

☒ 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, Biomarker discovered prior to first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

☒ 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, Biomarker discovered prior to first line therapy (First-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]

BRAF p.(V600E) c.1799T>A (continued)**○ 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 2.2023]**○ 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 4.2023]**○ cobimetinib + vemurafenib****Cancer type:** Circumscribed Astrocytic Gliomas**Variant class:** BRAF V600E mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Recurrent, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]**○ cobimetinib + vemurafenib****Cancer type:** Ganglioglioma (Grade 1),
Pilocytic Astrocytoma (Grade 1), Pleomorphic
Xanthoastrocytoma (Grade 2,3)**Variant class:** BRAF V600E mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- WHO CNS Tumor Grade II (Adjuvant therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

BRAF p.(V600E) c.1799T>A (continued)**○ cobimetinib + vemurafenib**

Cancer type: Glioblastoma IDH-wildtype (Grade 4) **Variant class:** BRAF V600E mutation

Other criteria: IDH wild type

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- WHO CNS Tumor Grade IV; Recurrent, Progression (Recurrence therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

○ dabrafenib + trametinib

Cancer type: Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Biliary Tract Cancers [Version 2.2023]

○ 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); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

○ dabrafenib + trametinib

Cancer type: Circumscribed Astrocytic Gliomas **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Recurrent, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

BRAF p.(V600E) c.1799T>A (continued)**○ dabrafenib + trametinib**

Cancer type: Ganglioglioma (Grade 1),
Pilocytic Astrocytoma (Grade 1), Pleomorphic
Xanthoastrocytoma (Grade 2,3)

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- WHO CNS Tumor Grade II (Adjuvant therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

○ dabrafenib + trametinib

Cancer type: Glioblastoma IDH-wildtype (Grade 4) **Variant class:** BRAF V600E mutation

Other criteria: IDH wild type

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- WHO CNS Tumor Grade IV; Recurrent, Progression (Recurrence therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

○ dabrafenib + trametinib

Cancer type: Esophageal Cancer,
Gastroesophageal Junction Adenocarcinoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma, Squamous Cell; Unresectable, Locally Advanced, Recurrent, Metastatic, Progression (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2023]

○ dabrafenib + trametinib

Cancer type: Gastric Cancer

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2023]

BRAF p.(V600E) c.1799T>A (continued)**○ dabrafenib + trametinib**

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Resectable (Neoadjuvant therapy); Useful in certain circumstances
- Unresectable, Progression, Metastatic (First-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Gastrointestinal Stromal Tumor [Version 1.2023]

○ dabrafenib + trametinib

Cancer type: Head and Neck Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2023]

○ dabrafenib + trametinib

Cancer type: Large Cell Neuroendocrine Carcinoma, Mixed Neuroendocrine Non-Neuroendocrine Neoplasm **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Extrapulmonary, Poorly Differentiated; Progression, Unresectable, Metastatic, Local, Regional (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 1.2023]

○ dabrafenib + trametinib

Cancer type: Extrapulmonary Small Cell Neuroendocrine Carcinoma **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Poorly Differentiated; Progression, Unresectable, Metastatic, Local, Regional (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 1.2023]

BRAF p.(V600E) c.1799T>A (continued)**○ dabrafenib + trametinib****Cancer type:** Ovarian Cancer**Variant class:** BRAF V600E mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Low-Grade Serous Carcinoma; Recurrent (Recurrence therapy)
- Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent, Persistent (Recurrence therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 2.2023]**○ dabrafenib + trametinib****Cancer type:** Pancreatic Cancer**Variant class:** BRAF V600E mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Adenocarcinoma; Metastatic, Locally Advanced, Recurrent (Subsequent therapy); Other recommended intervention, Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2023]**○ dabrafenib + trametinib****Cancer type:** Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma**Variant class:** BRAF V600E mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Locally Recurrent, Advanced, Metastatic, Radioactive Iodine Ablation refractory, Unresectable, Persistent (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 4.2023]**○ 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 (Line of therapy not specified); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 4.2023]

BRAF p.(V600E) c.1799T>A (continued)**○ 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 2.2023]

○ 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 4.2023]

○ selumetinib

Cancer type: Circumscribed Astrocytic Gliomas

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Recurrent, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

○ 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); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2023]

○ dabrafenib + trametinib

Cancer type: Pancreatic Cancer

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

- Adenocarcinoma; Metastatic (First-line therapy); Other recommended intervention, Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2023]

BRAF p.(V600E) c.1799T>A (continued)**○ 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); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2023]

○ 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); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2023]

○ 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); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2023]

○ dabrafenib + trametinib

Cancer type: Cutaneous Melanoma

Variant class: BRAF V600 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

- Stage III; Resectable (Adjuvant therapy); Preferred intervention
- Recurrent, Resectable (Adjuvant therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2023]

○ 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 2.2023]

BRAF p.(V600E) c.1799T>A (continued)**○ 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 2.2023]

○ dabrafenib

Cancer type: Cutaneous Melanoma

Variant class: BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Metastatic, Unresectable (First-line therapy); Other recommended intervention
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2023]

○ 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 2.2023]

○ 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 2.2023]

BRAF p.(V600E) c.1799T>A (continued)**○ encorafenib****Cancer type:** Cutaneous Melanoma**Variant class:** BRAF V600 mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Metastatic, Unresectable (First-line therapy); Other recommended intervention
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2023]**○ vemurafenib****Cancer type:** Cutaneous Melanoma**Variant class:** BRAF V600 mutation**NCCN Recommendation category:** 2A**Population segment (Line of therapy):**

- Metastatic, Unresectable (First-line therapy); Other recommended intervention
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2023]**○ 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 2.2023]**○ 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 2.2023]**○ 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 2.2023]

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 2023-09-13. For the most up-to-date information, search www.ema.europa.eu/ema.

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

☒ dabrafenib, dabrafenib + trametinib

Cancer type: Cutaneous Melanoma, Melanoma, Non-Small Cell Lung Cancer

Label as of: 2023-09-01

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: 2023-02-27

Variant class: BRAF V600E mutation

Reference:

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

☐ binimetinib + encorafenib

Cancer type: Melanoma

Label as of: 2023-09-12

Variant class: BRAF V600E mutation

Reference:

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

☐ binimetinib + encorafenib, cetuximab + encorafenib

Cancer type: Colorectal Cancer, Melanoma

Label as of: 2022-08-05

Variant class: BRAF V600E mutation

Reference:

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

☐ cobimetinib + vemurafenib

Cancer type: Melanoma

Label as of: 2023-03-06

Variant class: BRAF V600E mutation

Reference:

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

☐ vemurafenib

Cancer type: Melanoma

Label as of: 2023-07-18

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 2023-09-01. For the most up-to-date information, search www.esmo.org.

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

☒ 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; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 2
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 2

Reference: ESMO Clinical Practice Guidelines - ESMO-Oncogene-addicted Metastatic Non-Small-Cell Lung Cancer [Annals of Oncology (2023), doi: <https://doi.org/10.1016/j.annonc.2022.12.009> (Published)]

☐ cetuximab + encorafenib

Cancer type: Colorectal Cancer

Variant class: BRAF V600E mutation

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

Population segment (Line of therapy):

- Stage IV; Unresectable, Progression (Third-line therapy); ESMO-MCBS v1.1 score: 4
- Stage IV; Unresectable, Progression (Second-line therapy); ESMO-MCBS v1.1 score: 4

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

☐ dabrafenib + trametinib

Cancer type: Cholangiocarcinoma

Variant class: BRAF V600E mutation

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

Population segment (Line of therapy):

- Advanced, Metastatic, Progression (Second-line therapy); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Biliary Cancer [Ann Oncol (2023), doi: <https://doi.org/10.1016/j.annonc.2022.10.506>]

☐ bevacizumab + FOLFOXIRI

Cancer type: Colorectal Cancer

Variant class: BRAF V600E mutation

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

Population segment (Line of therapy):

- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 2

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

BRAF p.(V600E) c.1799T>A (continued)**○ bevacizumab + CAPOX****Cancer type:** Colorectal Cancer**Variant class:** BRAF V600E mutation**ESMO Level of Evidence/Grade of Recommendation:** II / B**Population segment (Line of therapy):**

- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 1

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]**○ bevacizumab + FOLFOX****Cancer type:** Colorectal Cancer**Variant class:** BRAF V600E mutation**ESMO Level of Evidence/Grade of Recommendation:** II / B**Population segment (Line of therapy):**

- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 1

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]**○ dabrafenib + trametinib****Cancer type:** Thyroid Gland Anaplastic Carcinoma**Variant class:** BRAF V600E mutation**ESMO Level of Evidence/Grade of Recommendation:** IV / B**Population segment (Line of therapy):**

- Locally Advanced, Metastatic, Unresectable (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Ann Oncol. 2022; <https://doi.org/10.1016/j.annonc.2022.04.009>]**○ 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 [Ann Oncol (2021), doi: <https://doi.org/10.1016/j.annonc.2021.09.005>]

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

○ 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]

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

○ 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]

○ bevacizumab + CAPOX

Cancer type: Colorectal Cancer

Variant class: BRAF mutation

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

Population segment (Line of therapy):

- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 1

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

○ bevacizumab + FOLFOX

Cancer type: Colorectal Cancer

Variant class: BRAF mutation

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

Population segment (Line of therapy):

- Stage IV; Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 1

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); <https://doi.org/10.1016/j.annonc.2022.10.003> (published)]

BRAF p.(V600E) c.1799T>A (continued)**○ 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> (Published)]

Clinical Trials in Taiwan region:

Clinical Trials Summary

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

NCT ID	Title	Phase
NCT05195632	Multicenter, Open-label, Phase II Study With a Safety Lead-in Part Investigating the Efficacy, Safety and Pharmacokinetics of Encorafenib and Binimetinib Combination in BRAF V600E Mutated Chinese Patients With Metastatic Non-Small Cell Lung Cancer Who Are BRAF- and MEK Inhibitor Treatment-naive	II
NCT04913285	A Phase I/II b Open-label, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of KIN-2787 in Participants With BRAF and/or NRAS Mutation-positive 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 2023-09-13. 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>

plixorafenib

Cancer type: Solid Tumor

Variant class: BRAF V600 mutation

Supporting Statement:

The FDA has granted Fast Track Designation to a novel small molecule inhibitor, plixorafenib (PLX-8394), for the treatment of patients with cancers harboring BRAF Class 1 (V600) and Class 2 (including fusions) alterations who have exhausted prior therapies.

Reference:

<https://fore.bio/fore-biotherapeutics-announces-fast-track-designation-granted-by-fda-to-fore8394-for-the-treatment-of-cancers-harboring-braf-class-1-and-class-2-alterations/>

Current ESMO Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

ESMO information is current as of 2023-09-01. 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]

References

1. Cheng et al. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. *Mod. Pathol.* 2018 Jan;31(1):24-38. PMID: 29148538
2. Alrabadi et al. Detection of driver mutations in BRAF can aid in diagnosis and early treatment of dedifferentiated metastatic melanoma. *Mod. Pathol.* 2019 Mar;32(3):330-337. PMID: 30315274
3. Quan et al. The association between BRAF mutation class and clinical features in BRAF-mutant Chinese non-small cell lung cancer patients. *Journal of Translational Medicine*, 29 Aug 2019, 17(1):298. PMID: 31470866
4. Yao et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. *Nature*. 2017 Aug 10;548(7666):234-238. PMID: 28783719
5. Bracht et al. BRAF Mutations Classes I, II, and III in NSCLC Patients Included in the SLLIP Trial: The Need for a New Pre-Clinical Treatment Rationale. *Cancers (Basel)*. 2019 Sep 17;11(9). PMID: 31533235
6. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014 Oct 23;159(3):676-90. PMID: 25417114
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2012 May;2(5):401-4. PMID: 22588877
8. Donna et al. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012 Jul 18;487(7407):330-7. PMID: 22810696
9. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
10. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat. Genet.* 2013 Oct;45(10):1113-20. PMID: 24071849
11. Wan et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell*. 2004 Mar 19;116(6):855-67. PMID: 15035987
12. Tiacci et al. BRAF mutations in hairy-cell leukemia. *N. Engl. J. Med.* 2011 Jun 16;364(24):2305-15. PMID: 21663470
13. Diamond et al. Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms. *Cancer Discov.* 2016 Feb;6(2):154-65. doi: 10.1158/2159-8290.CD-15-0913. Epub 2015 Nov 13. PMID: 26566875
14. Imielinski et al. Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma. *J Clin Invest.* 2014 Apr;124(4):1582-6. doi: 10.1172/JCI72763. Epub 2014 Feb 24. PMID: 24569458
15. Ciampi et al. Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. *J. Clin. Invest.* 2005 Jan;115(1):94-101. PMID: 15630448
16. Palanisamy et al. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. *Nat. Med.* 2010 Jul;16(7):793-8. PMID: 20526349
17. Jones et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. *Cancer Res.* 2008 Nov 1;68(21):8673-7. PMID: 18974108
18. Cin et al. Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma. *Acta Neuropathol.* 2011 Jun;121(6):763-74. doi: 10.1007/s00401-011-0817-z. Epub 2011 Mar 20. PMID: 21424530
19. Ross et al. The distribution of BRAF gene fusions in solid tumors and response to targeted therapy. *Int. J. Cancer.* 2016 Feb 15;138(4):881-90. PMID: 26314551
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202806s027lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210496s013lbl.pdf
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
24. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204114s029lbl.pdf
25. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210498s001lbl.pdf
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/206192s006lbl.pdf
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761034s049s051lbl.pdf
28. <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>
29. <https://biomed-valley.com/news/#press-releases>
30. <https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food>

References (continued)

31. Kulkarni et al. BRAF Fusion as a Novel Mechanism of Acquired Resistance to Vemurafenib in BRAFV600E Mutant Melanoma. *Clin. Cancer Res.* 2017 Sep 15;23(18):5631-5638. PMID: 28539463
32. Johnson et al. Acquired BRAF inhibitor resistance: A multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. *Eur. J. Cancer.* 2015 Dec;51(18):2792-9. PMID: 26608120
33. Nazarian et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. *Nature.* 2010 Dec 16;468(7326):973-7. doi: 10.1038/nature09626. Epub 2010 Nov 24. PMID: 21107323
34. Rizos et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. *Clin. Cancer Res.* 2014 Apr 1;20(7):1965-77. PMID: 24463458
35. Shi et al. A novel AKT1 mutant amplifies an adaptive melanoma response to BRAF inhibition. *Cancer Discov.* 2014 Jan;4(1):69-79. PMID: 24265152
36. Van et al. The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. *Cancer Discov.* 2014 Jan;4(1):94-109. doi: 10.1158/2159-8290.CD-13-0617. Epub 2013 Nov 21. PMID: 24265153
37. Villanueva et al. Concurrent MEK2 mutation and BRAF amplification confer resistance to BRAF and MEK inhibitors in melanoma. *Cell Rep.* 2013 Sep 26;4(6):1090-9. PMID: 24055054
38. Shi et al. Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. *Cancer Discov.* 2014 Jan;4(1):80-93. PMID: 24265155