Taipei Veterans General Hospital

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Sample Information

Patient Name: 陳美珠
Gender: Female
ID No.: N201285332
History No.: 19344480
Age: 72

Ordering Doctor: DOC1242E 劉峻宇
Ordering REQ.: 0BPXHYT
Signing in Date: 2021/12/17

Path No.: S110-94850
MP No.: F21109
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-93021A
Percentage of tumor cells: 80%

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

Note:

Sample Cancer Type: Thyroid Cancer

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Relevant Thyroid Cancer Variants

Gene	Finding
BRAF	***BRAF p.(V600E) c.1799T>A***
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).The content of this report has not been evaluated or approved by the FDA or other regulatory agencies.

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: 15.71% **Prognostic significance:** ATA-DTC Risk: Low to Intermediate **Diagnostic significance:** None	**dabrafenib** [1] **dabrafenib + trametinib** [1] **trametinib** [1] 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] BRAF inhibitor + MEK inhibitor dabrafenib + MEK inhibitor dabrafenib + pembrolizumab + trametinib encorafenib encorafenib + panitumumab ipilimumab + nivolumab selumetinib	0

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.

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	15.71%	NM_004333.6	missense	1961
FGFR3	p.(G90del)	c.268_270delGGG	.	chr4:1801137	43.01%	NM_000142.4	nonframeshift Deletion	1916
FGFR3	p.(Q92Sfs*6)	c.274delC	.	chr4:1801141	48.23%	NM_000142.4	frameshift Deletion	1916

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

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Biomarker Descriptions (continued)

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 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].

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	◑	◑	○	◑	✖
dabrafenib	◑	◑	○	✖	✖
trametinib	◑	✖	○	✖	✖
vemurafenib	○	◑	○	✖	✖
binimetinib + encorafenib	○	○	○	○	✖
cobimetinib + vemurafenib	○	○	○	○	✖
cetuximab + encorafenib	○	○	○	✖	✖
atezolizumab + cobimetinib + vemurafenib	○	✖	✖	✖	✖
dabrafenib + pembrolizumab + trametinib	✖	○	✖	✖	✖
encorafenib	✖	○	✖	✖	✖
encorafenib + panitumumab	✖	○	✖	✖	✖
selumetinib	✖	○	✖	✖	✖
BRAF inhibitor + MEK inhibitor	✖	✖	✖	○	✖

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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	✖	✖	✖	○	✖

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 2021-10-13. 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, 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

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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

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

atezolizumab + cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2021-04-13 **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)

- 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®

Triple-Negative Breast Cancer (TNBC)

- in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitations of Use: TECENTRIQ® is not indicated for use in combination with paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic TNBC.

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/2021/761034s041lbl.pdf

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

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

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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

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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

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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

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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

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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 2021-10-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

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

● 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 2.2021]

● 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 2.2021]

● 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 2.2021]

○ 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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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

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]

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

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]

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

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]

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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 6.2021]

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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]

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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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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

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 6.2021]

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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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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):
- 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):
- 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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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

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]

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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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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

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]

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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]

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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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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 2021-10-13. For the most up-to-date information, search www.ema.europa.eu/ema.

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

○ 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

○ binimetinib + encorafenib, cetuximab + encorafenib

Cancer type: Colorectal Cancer, Melanoma **Label as of:** 2021-09-07 **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:** 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:** 2021-09-13 **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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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 2021-10-01. For the most up-to-date information, search www.esmo.org.

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

● 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]

○ 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.]

○ 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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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.]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

Prognostic Details

Current ESMO Information

ESMO information is current as of 2021-10-01. For the most up-to-date information, search www.esmo.org.

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

Prognostic significance: ATA-DTC Risk: Low to Intermediate

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

Summary:

- Estimated risk of recurrence: Low (<=5%); only if the tumour is <1 cm
- Estimated risk of recurrence: Intermediate (6% - 20%); Intrathyroidal tumour measuring <4 cm or Multifocal papillary microcarcinoma with extrathyroidal extension

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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

Clinical Trials in Taiwan region:

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-10-13. 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

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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-10-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

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]

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2021-10-01. 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]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

Signatures

Testing Personnel:

2021.12.20
08:34:44 +08'00'

Laboratory Supervisor:

2021.12.20
08:34:56 +08'00'

Pathologist:

2021.12.20
08:35:09 +08'00'

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.11(003).

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