Taipei Veterans General Hospital

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Sample Information

Patient Name: 許又文
Gender: Female
ID No.: C221342893
History No.: 44468384
Age: 29

Ordering Doctor: DOC1654E 林庭安
Ordering REQ.: 0BBDFWC
Signing in Date: 2021/01/21

Path No.: S110-98096
MP No.: F21005
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-01592A
Percentage of tumor cells: 60%
Note:

Sample Cancer Type: Melanoma

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Report Highlights

2 Relevant Biomarkers
11 Therapies Available
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Relevant Melanoma Variants

Gene	Finding
BRAF	***BRAF p.(V600E) c.1799T>A***
KIT	Not detected
NTRK1	Not detected
NTRK2	Not detected
NTRK3	Not 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: 47.06%	**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 ipilimumab + nivolumab	**binimetinib + encorafenib** [1, 2] **cetuximab + encorafenib** [1, 2] **dabrafenib** [1, 2] **dabrafenib + trametinib** [1, 2] **trametinib** [1, 2] encorafenib + panitumumab vemurafenib	57
IIC	*MYC amplification* MYC proto-oncogene, bHLH transcription factor	None	None	3

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

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	47.06%	NM_004333.4	missense	1987
BRCA1	p.(=)	c.5373G>A	.	chr17:41203102	63.13%	NM_007300.3	synonymous	1999

Copy Number Variations

Gene	Locus	Copy Number
MYC	chr8:128748885	5.13

Biomarker Descriptions

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

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

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

Biomarker Descriptions (continued)

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 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 (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[23] (2013) and binimetinib[24] (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 and trametinib (2015) and vemurafenib and cobimetinib[25] (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 ERK inhibitor ulixertinib[26] was 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 amplification, alternative splice transcripts, and BRAF fusions are suggested mechanisms of resistance to BRAF targeted therapy in melanoma[27,28,29,30]. Other mechanisms of resistance include activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2) as well as activation of PI3K signaling[29,31,32,33,34]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[19].

MYC (MYC proto-oncogene, bHLH transcription factor)

Background: The MYC gene encodes the MYC proto-oncogene (c-MYC), a basic helix-loop-helix transcription factor that regulates the expression of numerous genes that control cell cycle progression, apoptosis, metabolic pathways, and cellular transformation[35,36,37,38]. MYC is part of the MYC oncogene family that includes related transcription factors MYCN and MYCL that regulate transcription in 10-15% of promoter regions[39]. MYC functions as a heterodimer in complex with the transcription factor MAX[36,40].

Alterations and prevalence: Recurrent somatic alterations are observed in both solid and hematological cancers. Recurrent somatic mutations in MYC, including codon T58, are infrequent and hypothesized to increase the stability of the MYC protein[41,42]. MYC gene amplification is particularly common in diverse solid tumors. MYC amplification is observed in 30% of serous ovarian cancer, 20% of uterine serous carcinoma, 15% of esophageal and breast cancers, and is common (1-10%) in numerous other cancer types[7,43,44]. MYC is the target of the t(8;14)(q24;32) chromosomal translocation in Burkitt's lymphoma that places MYC coding sequences adjacent to immunoglobulin region regulatory sequences, which results in increased MYC expression[45,46].

Potential relevance: Currently, no therapies are approved for MYC aberrations. Due to the high frequency of somatic MYC alterations in cancer, many approaches are being investigated in clinical trials including strategies to disrupt complex formation with MAX, including inhibition of MYC expression and synthetic lethality associated with MYC overexpression[35,47,48,49].

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	◑	◑	◑	✖	✖
binimetinib + encorafenib	◑	●	◑	●	✖
cetuximab + encorafenib	◑	○	◑	✖	✖
trametinib	◑	✖	◑	✖	✖
vemurafenib	●	◑	●	✖	● (II)

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

Relevant Therapy Summary (continued)

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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cobimetinib + vemurafenib	●	●	●	●	● (II)
atezolizumab + cobimetinib + vemurafenib	●	✖	✖	✖	✖
encorafenib + panitumumab	✖	○	✖	✖	✖
BRAF inhibitor + MEK inhibitor	✖	✖	✖	●	✖
ipilimumab + nivolumab	✖	✖	✖	●	✖
bempegaldesleukin, nivolumab	✖	✖	✖	✖	● (III)
dabrafenib, trametinib, ipilimumab, nivolumab	✖	✖	✖	✖	● (III)
relatlimab, nivolumab	✖	✖	✖	✖	● (II/III)
sargramostim, nivolumab, ipilimumab	✖	✖	✖	✖	● (II/III)
atezolizumab, cobimetinib, vemurafenib	✖	✖	✖	✖	● (II)
binimetinib, encorafenib	✖	✖	✖	✖	● (II)
buparlisib	✖	✖	✖	✖	● (II)
cobimetinib, atezolizumab, vemurafenib	✖	✖	✖	✖	● (II)
cobimetinib, vemurafenib	✖	✖	✖	✖	● (II)
dabrafenib + pembrolizumab + trametinib	✖	✖	✖	✖	● (II)
dabrafenib, nivolumab, trametinib	✖	✖	✖	✖	● (II)
dabrafenib, pembrolizumab, trametinib	✖	✖	✖	✖	● (II)
dabrafenib, trametinib	✖	✖	✖	✖	● (II)
dabrafenib, trametinib, spartalizumab	✖	✖	✖	✖	● (II)
IMM-101, nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
immunostimulant, pembrolizumab	✖	✖	✖	✖	● (II)
ipilimumab, binimetinib, nivolumab, encorafenib	✖	✖	✖	✖	● (II)
ipilimumab, nivolumab, encorafenib, binimetinib, dabrafenib, trametinib	✖	✖	✖	✖	● (II)
LXH254 , LTT-462, trametinib, ribociclib	✖	✖	✖	✖	● (II)
nivolumab, ipilimumab, radiation therapy	✖	✖	✖	✖	● (II)
vemurafenib, cobimetinib	✖	✖	✖	✖	● (II)
vemurafenib, cobimetinib, atezolizumab	✖	✖	✖	✖	● (II)
vemurafenib, cobimetinib, ipilimumab, nivolumab	✖	✖	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
vemurafenib, cobimetinib, surgical intervention, radiation therapy	✖	✖	✖	✖	● (II)
vemurafenib, dabrafenib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
bemcentinib, dabrafenib, pembrolizumab, trametinib	✖	✖	✖	✖	● (I/II)
dabrafenib, trametinib, antimalarial	✖	✖	✖	✖	● (I/II)
dabrafenib, trametinib, navitoclax	✖	✖	✖	✖	● (I/II)
HH-2710	✖	✖	✖	✖	● (I/II)
lacnotuzumab, trametinib, dabrafenib	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
vorinostat	✖	✖	✖	✖	● (I/II)
ABM-1310	✖	✖	✖	✖	● (I)
BGB-3245	✖	✖	✖	✖	● (I)
CART-GD2, vemurafenib	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
E6201	✖	✖	✖	✖	● (I)
HL-085, vemurafenib	✖	✖	✖	✖	● (I)
itacitinib, dabrafenib, trametinib	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
JSI-1187, dabrafenib	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
MLN-2480	✖	✖	✖	✖	● (I)
RG-7461, pembrolizumab	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	✖	✖	● (I)
RX208	✖	✖	✖	✖	● (I)
TQ-B3233	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

MYC amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
berzosertib	✖	✖	✖	✖	● (II)
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
BMS-986158	✖	✖	✖	✖	● (I)

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

Relevant Therapy Details

Current FDA Information

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

FDA information is current as of 2020-11-18. For the most up-to-date information, search www.fda.gov.

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

◑ binimetinib + encorafenib, cetuximab + encorafenib

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

Indications and usage:

BRAFTOVI® is a kinase inhibitor indicated:

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

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

Reference:

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

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

dabrafenib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Thyroid Gland Anaplastic Carcinoma **Label as of:** 2020-04-09 **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/2020/202806s015lbl.pdf

trametinib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Thyroid Gland Anaplastic Carcinoma **Label as of:** 2020-06-23 **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/2020/204114s016lbl.pdf

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

atezolizumab + cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2020-11-10 **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, or
  - have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.

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).

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/2020/761034s020lbl.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

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

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 2020-11-02. 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: Melanoma **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Melanoma; Brain metastases; Use active agents against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2020]

● cobimetinib + vemurafenib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Melanoma; Brain metastases; Use active agents against primary tumor (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2020]

● binimetinib + encorafenib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma (First-line therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

● cobimetinib + vemurafenib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma (First-line therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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

dabrafenib + trametinib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Cutaneous Melanoma; Stage III clinically positive nodes (Adjuvant therapy) (Preferred)
- Cutaneous Melanoma; Nodal recurrence; No previous lymph node dissection (Adjuvant therapy) (Preferred)
- Cutaneous Melanoma; Disease limited to nodal recurrence; After complete resection (Adjuvant therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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dabrafenib + trametinib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma (First-line therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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binimetinib + encorafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy (Second-line or subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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cobimetinib + vemurafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma (First-line therapy) (Other recommended regimen)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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

cobimetinib + vemurafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy (Second-line or subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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dabrafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF-inhibitor monotherapy with dabrafenib or vemurafenib are recommended options, especially when checkpoint immunotherapy is not appropriate (First, second-line or subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Cutaneous Melanoma; Stage IIIA-D sentinel node positive (Adjuvant therapy) (Preferred)
- Cutaneous Melanoma; Stage III clinical satellite/in-transit; No evidence of disease following resection (Adjuvant therapy) (Preferred)
- Cutaneous Melanoma; Local satellite/in-transit recurrence; No evidence of disease following resection (Adjuvant therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy (Second-line or subsequent therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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

vemurafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF-inhibitor monotherapy with dabrafenib or vemurafenib are recommended options, especially when checkpoint immunotherapy is not appropriate (First, second-line or subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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binimetinib + encorafenib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Resectable Distant Metastatic Cutaneous Melanoma; No evidence of disease (Adjuvant therapy) (Other recommended regimen)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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cobimetinib + vemurafenib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Resectable Distant Metastatic Cutaneous Melanoma; No evidence of disease (Adjuvant therapy) (Other recommended regimen)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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dabrafenib + trametinib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Resectable Distant Metastatic Cutaneous Melanoma; No evidence of disease (Adjuvant therapy) (Other recommended regimen)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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 Colon Cancer; Previous adjuvant FOLFOX/CAPEOX within past 12 months (Primary therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2020]

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cetuximab + encorafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Metachronous Metastatic Rectal Cancer; Previous adjuvant FOLFOX/CAPEOX within past 12 months (Primary therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy (Subsequent therapy)

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

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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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease (First-line therapy) (Other Recommended)

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

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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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease (First-line therapy) (Preferred)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease (Subsequent therapy)

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

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

dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Thyroid Gland Anaplastic Carcinoma; Metastatic (Not specified) (Preferred)

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

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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 Colon Cancer; Previous adjuvant FOLFOX/CAPEOX within past 12 months (Primary therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2020]

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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 Rectal Cancer; Previous adjuvant FOLFOX/CAPEOX within past 12 months (Primary therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy (Subsequent therapy)

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

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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, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease (First-line therapy) (Other Recommended)

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

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

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):

- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; Unresectable locoregional recurrent/persistent disease; Progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate (Not specified)
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; CNS or soft tissue or bone metastases; Progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate (Not specified)

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

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):

- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; Unresectable locoregional recurrent/persistent disease; Progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate (Not specified)
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; CNS or soft tissue or bone metastases; Progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate (Not specified)

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

Current EMA Information

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

EMA information is current as of 2020-11-18. For the most up-to-date information, search www.ema.europa.eu/ema.

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

◑ binimetinib + encorafenib, cetuximab + encorafenib

Cancer type: Colorectal Cancer, Melanoma **Label as of:** 2020-06-16 **Variant class:** BRAF V600E mutation

Reference:

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

◑ dabrafenib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer **Label as of:** 2020-01-17 **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:** 2020-08-18 **Variant class:** BRAF V600E mutation

Reference:

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

● binimetinib + encorafenib

Cancer type: Melanoma **Label as of:** 2019-10-04 **Variant class:** BRAF V600E mutation

Reference:

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

● cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2020-07-07 **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:** 2020-01-30 **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 2020-11-02. For the most up-to-date information, search www.esmo.org.

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

● BRAF inhibitor + MEK inhibitor

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

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

Population segment (Line of therapy):
- Cutaneous Melanoma; Unresectable stage III and IV; First-line immunotherapy is not safe (First-line therapy)
- Cutaneous Melanoma; asymptomatic brain metastases (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: Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Cutaneous Melanoma; After surgical resection; Stage IIIA (SN >1mm), IIIB and IIIC (Adjuvant therapy) (Preferred)

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

● binimetinib + encorafenib

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

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

Population segment (Line of therapy):
- Cutaneous Melanoma; Unresectable stage III and IV (First or 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: Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Cutaneous Melanoma; Unresectable stage III and IV (First or 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: Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Cutaneous Melanoma; Unresectable stage III and IV (First or 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: Melanoma **Variant class:** BRAF V600 mutation

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

Population segment (Line of therapy):
- Cutaneous Melanoma; Unresectable stage III and IV; Asymptomatic brain metastases (First-line therapy) (Preferred)

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

○ 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 or Unresectable Thyroid Gland Anaplastic Carcinoma (First-line therapy)

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

○ 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; ESMO-Magnitude of Clinical Benefit Scale Version 1.1 Score: 2 (First or second-line therapy)

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.]

Clinical Trials Summary

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

NCT ID	Title	Phase
NCT03898908	Phase II, Multicentre Clinical Trial to Evaluate the Activity of Encorafenib and Binimetinib Administered Before Local Treatment in Patients With BRAF Mutant Melanoma Metastatic to the Brain.	II
NCT02858921	A Phase II, Randomised, Open Label Study of Neoadjuvant Dabrafenib, Trametinib and / or Pembrolizumab in BRAF V600 Mutant Resectable Stage IIIB/C Melanoma	II
NCT02231775	Neoadjuvant and Adjuvant Dabrafenib and Trametinib in Patients With Clinical Stage III Melanoma (Combi-Neo)	II
NCT04310397	Altering Adjuvant Therapy Based on Pathologic Response to Neoadjuvant Dabrafenib and Trametinib (ALTER-PATH NeoDT)	II
NCT03235245	Combination of Targeted Therapy (Encorafenib and Binimetinib) Followed by Combination of Immunotherapy (Ipilimumab and Nivolumab) vs Immediate Combination of Immunotherapy in Patients With Unresectable or Metastatic Melanoma With BRAF V600 Mutation : an EORTC Randomized Phase II Study (EBIN)	II
NCT02968303	Phase II Study With COmbination of Vemurafenib With Cobimetinib in B-RAF V600E/K Mutated Melanoma Patients to Normalize LDH and Optimize Nivolumab and Ipilimumab therapy	II
NCT01989585	Phase I/II Study of Dabrafenib, Trametinib, and Navitoclax in BRAF Mutant Melanoma (Phase I and II) and Other Solid Tumors (Phase I Only)	I/II
NCT03455764	A Phase I/II Study of MCS110 With BRAF/MEK Inhibition in Patients With Melanoma After Progression on BRAF/MEK Inhibition	I/II
NCT02836548	HDAC Inhibitor Vorinostat in Resistant BRAF V600 Mutated Advanced Melanoma	I/II
NCT04190628	A Phase I, First-In-Human, Multicenter, Open-Label Study of ABM-1310, Administered Orally in Adult Patients With Advanced Solid Tumors	I
No NCT ID	Phase I Study of Safety and Immune Effects of an Escalating Dose of Autologous GD2 Chimeric Antigen Receptor-Expressing Peripheral Blood T cells in Patients with Metastatic Melanoma	I
NCT03272464	Phase I Study of INCB039110 in Combination With Dabrafenib and Trametinib in Patients With BRAF-mutant Melanoma and Other Solid Tumors	I
NCT02224781	DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial	III
NCT03554083	Neoadjuvant Therapy for Patients With High Risk Stage III Melanoma: A Pilot Clinical Trial	II
NCT03911869	A Phase II, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With BRAFV600-mutant Melanoma Brain Metastasis	II
NCT02452294	An Open-label, Uncontrolled, Single Arm Phase II Trial of Buparlisib in Patients With Metastatic Melanoma With Brain Metastases Not Eligible for Surgery or Radiosurgery	II
NCT02036086	A Pilot Study of the Neo-adjuvant Use of Vemurafenib Plus Cobimetinib (GDC-0973) in Patients With BRAF Mutant Melanoma With Palpable Lymph Node Metastases	II
NCT03625141	A Phase II Two Cohort Study Evaluating the Safety and Efficacy of Cobimetinib Plus Atezolizumab in BRAFV600 Wild-type Melanoma With Central Nervous System Metastases and Cobimetinib Plus Atezolizumab and Vemurafenib in BRAFV600 Mutation-positive Melanoma With Central Nervous System Metastases.	II
NCT03430947	An Open-Label Phase II Multicenter Study Of Vemurafenib (Zelboraf) Plus Cobimetinib (Cotellic) After Radiosurgery In Patients With Active BRAF-V600-Mutant Melanoma Brain Metastases	II

Clinical Trials Summary (continued)

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

NCT ID	Title	Phase
NCT03149029	A Phase II Trial of Abbreviated MAPK Targeted Therapy Plus Pembrolizumab in Patients With Unresectable or Metastatic Melanoma	II
No NCT ID	A Non-Intervention MultiCenter Study of the Combination Tafinlar (Dabrafenib) and Mekinist (Trametinib) in the Treatment of Malignant Melanoma	II
NCT04417621	A Randomized, Open-label, Multi-arm, Two-part, Phase II Study to Assess Efficacy and Safety of Multiple LXH254 Combinations in Patients With Previously Treated Unresectable or Metastatic BRAFV600 or NRAS Mutant Melanoma	II
NCT03224208	VECODUE A Phase II Trial of Vemurafenib Plus Cobimetinib in Patients Treated With Prior First-line Systemic Immunotherapy for Inoperable Locally Advanced or Metastatic Melanoma	II
NCT02303951	Neoadjuvant Treatment With the Combination of Vemurafenib, Cobimetinib and Atezolizumab in Limited Metastasis of Malignant Melanoma (AJCC Stage IIIC/IV) and Integrated Biomarker Study: a Single Armed, Two Cohort, Phase II EADO Trial NEO-VC	II
NCT03514901	An Evaluation of the Efficacy Beyond Progression of Vemurafenib Combined With Cobimetinib Associated With Local Treatment Compared to Second-line Treatment in Patients With BRAFV600 Mutation-positive Metastatic Melanoma in Focal Progression With First-line Combined Vemurafenib and Cobimetinib.	II
NCT03754179	A lead-in Phase I Followed by a Phase II Clinical Trial on the Combination of Dabrafenib, Trametinib and the Autophagy Inhibitor Hydroxychloroquine in BRAF/MEK Inhibitor-pretreated Patients With Advanced BRAF V600 Mutant Melanoma	I/II
NCT04249843	A First-in-Human, Phase Ia/Ib, Open Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor BGB-3245 in Patients With Advanced or Refractory Tumors	I
NCT03284502	A Phase Ib, Open-label, Multicenter, Dose Escalation Study of the Safety, Tolerability, and Pharmacokinetics of Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors	I
NCT03543969	Pilot Study of Adaptive BRAF-MEK Inhibitor Therapy for Advanced BRAF Mutant Melanoma	I
NCT04418167	A Phase I Study of ERK1/2 Inhibitor JSI-1187 Administered as Monotherapy and in Combination With Dabrafenib for the Treatment of Advanced Solid Tumors With MAPK Pathway Mutations	I
NCT03635983	A Phase III, Randomized, Open-label Study of NKTR-214 Combined With Nivolumab Versus Nivolumab in Participants With Previously Untreated Unresectable or Metastatic Melanoma.	III
NCT03470922	A Randomized, Double-Blind Phase II/III Study of Relatlimab Combined With Nivolumab Versus Nivolumab in Participants With Previously Untreated Metastatic or Unresectable Melanoma	II/III
NCT03711188	A Study of the Safety and Efficacy of IMM-101 in Combination With Checkpoint Inhibitor Therapy in Patients With Advanced Melanoma	II
NCT02339571	Randomized Phase II/III Study of Nivolumab Plus Ipilimumab Plus Sargramostim Versus Nivolumab Plus Ipilimumab in Patients With Unresectable Stage III or Stage IV Melanoma	II/III
NCT02910700	A Phase II Study of the TRIplet Combination of Dabrafenib, Nivolumab, and Trametinib in Patients With Metastatic Melanoma (TRIDeNT)	II
NCT03563729	Efficacy Of Immunotherapy In Melanoma Patients With Brain Metastases Treated With Steroids	II
NCT02872259	A Phase Ib/II Randomised Open Label Study of BGB324 in Combination With Pembrolizumab or Dabrafenib/Trametinib Compared to Pembrolizumab or Dabrafenib/Trametinib Alone, in Patients With Advanced Non-resectable (Stage IIIc) or Metastatic (Stage IV) Melanoma.	I/II

Clinical Trials Summary (continued)

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

NCT ID	Title	Phase
NCT03332589	A Phase I Study Of E6201 For The Treatment Of Central Nervous System Metastases (CNS) From BRAF Or MEK-Mutated Metastatic Melanoma	I
NCT03453034	To Study the Pharmacokinetic Characteristics of TQ-B233 in the Human Body, Recommend a Reasonable Regimen for Subsequent Research	I
NCT04079166	A Phase II Combination Study of SCIB1 with Pembrolizumab in Patients with Stage III or Stage IV Metastatic Melanoma	II
NCT03340129	A Phase II, Open Label, Single Arm Study of Ipilimumab and Nivolumab With Salvage Radiotherapy in Patients With Melanoma Brain Metastases	II
NCT03875079	An Open-Label, Multicenter, Phase Ib Study To Evaluate Safety And Therapeutic Activity Of RO6874281, An Immunocytokine, Consisting Of Interleukin-2 Variant (IL-2v) Targeting Fibroblast Activation Protein-? (FAP), In Combination With Pembrolizumab (Anti-PD-1), In Participants With Advanced Or Metastatic Melanoma	I
NCT03905148	A Phase Ib, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of a RAF Dimer Inhibitor BGB-283 in Combination With MEK Inhibitor PD-0325901 in Patients With Advanced or Refractory Solid Tumors	I/II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
No NCT ID	Phase I study of the safety, tolerability, pharmacokinetics and preliminary efficacy of RX208 in patients with advanced malignant solid tumors	I
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT03220035	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase II Subprotocol of Vemurafenib in Patients With Tumors Harboring Braf V600 Mutations	II
NCT03781219	A Phase I, Single Arm, Dose Escalation Study to Evaluate Safety, Pharmacokinetics and Preliminary Efficacy of HL-085 Plus Vemurafenib in Patients With BRAF V600 Mutant Advanced Solid Tumor	I
NCT03239015	Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event	II
NCT04045496	A Phase I, Multi-Center, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Evidence of Antitumor Activity of JAB-3312 in Adult Patients With Advanced Solid Tumors	I
NCT02407509	A Phase I Trial of RO5126766 (a Dual RAF/MEK Inhibitor) Exploring Intermittent, Oral Dosing Regimens in Patients With Solid Tumours or Multiple Myeloma, With an Expansion to Explore Intermittent Dosing in Combination With Everolimus	I
NCT04198818	A First-in-Human, Open Label, Phase I/II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HH2710 in Patients With Advanced Tumors	I/II
NCT03429803	A Phase I Study of TAK-580 (MLN2480) for Children With Low-Grade Gliomas and Other RAS/RAF/MEK/ERK Pathway Activated Tumors	I
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	I
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT02857270	A Phase I Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	I

Clinical Trials Summary (continued)

MYC amplification

NCT ID	Title	Phase
NCT03718091	A Phase II Study of M6620 (VX-970) in Selected Solid Tumors	II
NCT03838042	INFORM2 Exploratory Multinational Phase I/II Combination Study of Nivolumab and Entinostat in Children and Adolescents with Refractory High-risk Malignancies	I/II
NCT03936465	Phase I Study of the Bromodomain (BRD) and Extra-Terminal Domain (BET) Inhibitor BMS-986158 in Pediatric Cancer	I

Alerts Informed By Public Data Sources

Current NCCN Information

Contraindicated Not recommended Resistance

NCCN information is current as of 2020-11-02. 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: 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 4.2020]

dabrafenib + trametinib

Cancer type: 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 4.2020]

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

cetuximab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2020]

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cetuximab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor."

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

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panitumumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2020]

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panitumumab

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

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor."

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

Current ESMO Information

Contraindicated Not recommended Resistance

ESMO information is current as of 2020-11-02. For the most up-to-date information, search www.esmo.org.

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

vemurafenib

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

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

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

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

Signatures

Testing Personnel:

2021.01.22
14:12:49 +08'00'

Laboratory Supervisor:

2021.01.22
14:13:03 +08'00'

Pathologist:

2021.01.22
14:13:16 +08'00'

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