Taipei Veterans General Hospital

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Sample Information

Patient Name: 陳英志
Gender: Male
ID No.: G120132439
History No.: 33469088
Age: 58

Ordering Doctor: DOC3177H 李彥融
Ordering REQ.: 0AUZQCV
Signing in Date: 2020/08/20

Path No.: S109-99887
MP No.: F20058
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S109-25674A
Percentage of tumor cells: 60%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Report Highlights

1 Relevant Biomarkers
10 Therapies Available
19 Clinical Trials

Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	Not detected
BRAF	***BRAF p.(V600E) c.1799T>A***	NTRK2	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected
MET	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: 33.37%	**dabrafenib + trametinib** [1, 2] **dabrafenib** [1, 2] **trametinib** [1, 2]	**dabrafenib + trametinib** [1, 2] **dabrafenib** [1, 2] **trametinib** [1, 2]	19

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

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
		vemurafenib	**binimetinib + encorafenib** [1, 2] **cetuximab + encorafenib** [1] **cobimetinib + vemurafenib** [1, 2] **vemurafenib** [1, 2] encorafenib + panitumumab BRAF inhibitor + MEK inhibitor ipilimumab + nivolumab	

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

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
BRAF	p.(V600E)	c.1799T>A	COSM476	chr7:140453136	33.37%	NM_004333.4	missense	1975
JAK1	p.(=)	c.2199A>G	.	chr1:65310489	47.87%	NM_002227.3	synonymous	1991
ALK	p.(D1529E)	c.4587C>G	.	chr2:29416366	99.80%	NM_004304.4	missense	1997
ALK	p.(I1461V)	c.4381A>G	.	chr2:29416572	99.80%	NM_004304.4	missense	1999
ALK	p.(=)	c.3375C>A	.	chr2:29445458	99.80%	NM_004304.4	synonymous	1991
FGFR3	p.(=)	c.1953G>A	.	chr4:1807894	99.75%	NM_000142.4	synonymous	1997
PDGFRA	p.(=)	c.1701A>G	.	chr4:55141055	99.95%	NM_006206.5	synonymous	1997
KIT	p.(=)	c.1578G>C	.	chr4:55593421	28.35%	NM_000222.2	synonymous	2000
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.15%	NM_213647.2	missense	2000
EGFR	p.(=)	c.2361G>A	.	chr7:55249063	99.50%	NM_005228.4	synonymous	1998
RET	p.(=)	c.2307G>T	.	chr10:43613843	49.10%	NM_020975.4	synonymous	1998

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].

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)[3,4,5,6,7]. The most recurrent somatic BRAF mutation across diverse cancer types is V600E in exon 15, which results in constitutive kinase activity by relieving negative regulatory inhibition[8]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer and prevalent in histiocytic neoplasms[9,10,11].

Biomarker Descriptions (continued)

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[8]. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer[4,7]. Chromosomal translocations generating BRAF fusions are observed with a diverse range of partner genes. 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[12,13,14,15,16]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal autoinhibitory domain leading to constitutive kinase activation[12,14].

Potential relevance: Vemurafenib[17] (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation. Subsequently, BRAF kinase inhibitors including dabrafenib[18] (2013) and encorafenib[19] (2018) were approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[19] 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, several MEK inhibitors have been approved for patients harboring BRAF alterations. Trametinib[20] (2013) and binimetinib[21] (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[22] (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. BRAF amplification, alternative splice transcripts, and BRAF fusions are suggested mechanisms of resistance to BRAF targeted therapy in melanoma[23,24,25,26]. Other mechanisms of resistance include activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2) as well as activation of PI3K signaling[25,27,28,29,30]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[16].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
dabrafenib + trametinib	◑	◑	◑	◑	✖
dabrafenib	◑	◑	◑	✖	✖
trametinib	◑	✖	◑	✖	✖
vemurafenib	○	◑	○	✖	● (II)
cobimetinib + vemurafenib	○	○	○	○	● (II)
binimetinib + encorafenib	○	○	○	○	✖
cetuximab + encorafenib	○	○	✖	✖	✖
encorafenib + panitumumab	✖	○	✖	✖	✖
BRAF inhibitor + MEK inhibitor	✖	✖	✖	○	✖
ipilimumab + nivolumab	✖	✖	✖	○	✖
dabrafenib, trametinib	✖	✖	✖	✖	● (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 ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
encorafenib, binimetinib	✖	✖	✖	✖	● (II)
targeted therapy, chemotherapy	✖	✖	✖	✖	● (II)
vemurafenib, cobimetinib	✖	✖	✖	✖	● (II)
ASTX029	✖	✖	✖	✖	● (I/II)
CBT-502, anlotinib hydrochloride	✖	✖	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	✖	✖	● (I/II)
BGB-3245	✖	✖	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	✖	✖	● (I)
HL-085, vemurafenib	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
LXH254	✖	✖	✖	✖	● (I)
LXH254 , LTT-462, trametinib, ribociclib	✖	✖	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	✖	✖	● (I)
RMC-4630	✖	✖	✖	✖	● (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 ⊘ Contraindicated ⛔ Not recommended 🛡 Resistance

FDA information is current as of 2020-05-26. 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:** 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

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:** 2020-04-09 **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/2020/204114s014lbl.pdf

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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)

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:** 2017-11-06 **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/2017/202429s016lbl.pdf

Current NCCN Information

In this cancer type | In other cancer type | In this cancer type and other cancer types | Contraindicated | Not recommended | Resistance

NCCN information is current as of 2020-05-01. 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

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; BRAF V600E mutation discovered prior to first-line systemic therapy; If dabrafenib + trametinib is not tolerated (First-line therapy) (Other Recommended)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

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; BRAF V600E mutation discovered prior to or during first-line systemic therapy (First-line therapy) (Preferred)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Progression after first-line systemic therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

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; BRAF V600E mutation discovered prior to first-line systemic therapy; If dabrafenib + trametinib is not tolerated (First-line therapy) (Other Recommended)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [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 3.2020]

○ 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 4.2020]

○ 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 2.2020]

○ 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; Stage IVC (Systemic therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2019]

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

○ encorafenib + panitumumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Metachronous Metastatic 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 3.2020]

○ 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 4.2020]

○ 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 2.2020]

○ 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 if clinically needed for early response)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 3.2020]

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

○ 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 if clinically needed for early response)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 3.2020]

○ 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 if clinically needed for early response)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 3.2020]

○ 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 3.2020]

○ 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 3.2020]

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

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 3.2020]

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 3.2020]

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 3.2020]

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 3.2020]

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

○ 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 3.2020]

○ 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 3.2020]

○ 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; Iodine#refractory 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 metastases or iodine#refractory 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 2.2019]

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

vemurafenib

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

Variant class: BRAF mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; Iodine#refractory 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 metastases or iodine#refractory 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 2.2019]

EGFR tyrosine kinase inhibitor

Cancer type: Non-Small Cell Lung Cancer

Variant class: BRAF mutation

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

- "Non-responsiveness to EGFR TKI therapy is associated with KRAS and BRAF mutations and ALK or ROS1 gene fusions."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2020]

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 3.2020]

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 4.2020]

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

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 3.2020]

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 4.2020]

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 3.2020]

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 3.2020]

Current EMA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⛔ Not recommended 🛡 Resistance

EMA information is current as of 2020-05-26. For the most up-to-date information, search www.ema.europa.eu/ema.

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

◑ 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:** 2020-02-04 **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:** 2019-10-30 **Variant class:** BRAF V600E mutation

Reference:

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

○ binimetinib + encorafenib

Cancer type: Melanoma **Label as of:** 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:** 2019-08-20 **Variant class:** BRAF V600E mutation

Reference:

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

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

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 ⊘ Contraindicated ⛔ Not recommended 🛡 Resistance

ESMO information is current as of 2020-05-01. For the most up-to-date information, search www.esmo.org.

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

● dabrafenib + trametinib

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

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

Population segment (Line of therapy):
- Stage IV; 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 [Ann Oncol (2018) 29 (suppl 4): iv192–iv237; https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer]

○ 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]

○ 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/mdz41]

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

○ 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/mdz41]

○ 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/mdz41]

○ 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/mdz41]

○ 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/mdz41]

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

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/mdz41]

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/mdz41]

Signatures

Testing Personnel:

2020.08.25
08:21:57 +08'00'

Laboratory Supervisor:

2020.08.25
09:04:45 +08'00'

Pathologist:

2020.08.25
09:05:32 +08'00'

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