



Sample Information

Patient Name: 簡鐘阿蘭

Gender: Female

ID No.: F203031505

History No.: 23797537

Age: 71

Ordering Doctor: DOC3109L 邱昭華

Ordering REQ.: D55JEND

Signing in Date: 2020/06/04

Path No.: S109-99535

MP No.: F20027

Assay: Oncomine Focus Assay

Sample Type: FFPE

Block No.: S109-75773A

Percentage of tumor cells: 50%

Note:

Sample Cancer Type: Thyroid Cancer

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Report Highlights

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 15 Therapies Available
 17 Clinical Trials

Relevant Thyroid Cancer Findings

Gene	Finding
BRAF	BRAF p.(V600E) c.1799T>A
NTRK1	Not detected
NTRK2	Not detected
NTRK3	Not detected

Relevant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
BRAF p.(V600E) c.1799T>A B-Raf proto-oncogene, serine/threonine kinase Tier: IA Allele Frequency: 26.02%	dabrafenib + trametinib ¹ dabrafenib ¹ trametinib ¹	dabrafenib + trametinib ^{1,2} dabrafenib ^{1,2} trametinib ^{1,2}	17

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

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



Relevant Biomarkers (continued)

■ Indicated ■ Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
	■ vemurafenib	■ binimetinib + encorafenib ^{1, 2} ■ cobimetinib + vemurafenib ^{1, 2} ■ vemurafenib ^{1, 2} ■ binimetinib + cetuximab + encorafenib ■ binimetinib + encorafenib + panitumumab ■ cetuximab + dabrafenib + trametinib ■ cetuximab + encorafenib ■ dabrafenib + panitumumab + trametinib ■ encorafenib + panitumumab ■ panitumumab + vemurafenib + chemotherapy ■ BRAF inhibitor + MEK inhibitor ■ ipilimumab + nivolumab	

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

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

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	26.02%	NM_004333.4	missense	1987
FGFR4	p.(=)	c.483A>G	.	chr5:176517985	9.48%	NM_213647.2	synonymous	1508

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, differentiation, and survival¹.

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)^{2,3,4,5,6}. 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 inhibition⁷. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer and prevalent in histiocytic neoplasms^{8,9,10}. 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 loop⁷. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer^{3,6}. Chromosomal translocations generating BRAF fusions with a range of partner genes are uncommon



Biomarker Descriptions (continued)

(about 0.5%) but have been described in melanoma that lack V600 mutations, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types^{11,12,13,14,15}. BRAF fusions retain the kinase domain but lack the autoinhibitory N-terminal domain of BRAF^{11,13}.

Potential relevance: Vemurafenib¹⁶ (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 dabrafenib¹⁷ (2013) and encorafenib¹⁸ (2018) were approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Due to the tight coupling of RAF and MEK, several MEK inhibitors have been approved for patients harboring BRAF alterations. Trametinib¹⁹ (2013) and binimetinib²⁰ (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 cobimetinib²¹ (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^{22,23,24,25}. Other mechanisms of resistance include activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2) as well as activation of PI3K signaling^{24,26,27,28,29}. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported¹⁵.

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	○	○	○	○	✕
binimetinib + cetuximab + encorafenib	✕	○	✕	✕	✕
binimetinib + encorafenib + panitumumab	✕	○	✕	✕	✕
cetuximab + dabrafenib + trametinib	✕	○	✕	✕	✕
cetuximab + encorafenib	✕	○	✕	✕	✕
dabrafenib + panitumumab + trametinib	✕	○	✕	✕	✕
encorafenib + panitumumab	✕	○	✕	✕	✕
panitumumab + vemurafenib + irinotecan	✕	○	✕	✕	✕
BRAF inhibitor + MEK inhibitor	✕	✕	✕	○	✕

* 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*
ipilimumab + nivolumab	✕	✕	✕	○	✕
atezolizumab, cobimetinib, vemurafenib	✕	✕	✕	✕	● (II)
dabrafenib, cobimetinib, vemurafenib	✕	✕	✕	✕	● (II)
trametinib, dabrafenib	✕	✕	✕	✕	● (II)
vemurafenib, cobimetinib	✕	✕	✕	✕	● (II)
ASTX029	✕	✕	✕	✕	● (I/II)
cobimetinib	✕	✕	✕	✕	● (I/II)
mirdametinib, lifirafenib	✕	✕	✕	✕	● (I/II)
belvarafenib + cobimetinib	✕	✕	✕	✕	● (I)
HL-085 + vemurafenib	✕	✕	✕	✕	● (I)
JAB-3312	✕	✕	✕	✕	● (I)
KO-947	✕	✕	✕	✕	● (I)
LXH254	✕	✕	✕	✕	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✕	✕	✕	✕	● (I)
RMC-4630	✕	✕	✕	✕	● (I)
RO-5126766, everolimus + RO-5126766	✕	✕	✕	✕	● (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 2020-02-28. For the most up-to-date information, search www.fda.gov.

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

① dabrafenib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Thyroid Gland Anaplastic Carcinoma
Label as of: 2019-10-06

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/2019/202806s012lbl.pdf



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

① trametinib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer, Thyroid Gland Anaplastic Carcinoma
Label as of: 2019-10-06

Variant class: BRAF V600E mutation

Indications and usage:

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

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

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204114s012lbl.pdf

○ binimetinib + encorafenib

Cancer type: Melanoma

Label as of: 2019-01-23

Variant class: BRAF V600E mutation

Indications and usage:

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

Reference:

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

○ binimetinib + encorafenib

Cancer type: Melanoma

Label as of: 2019-05-24

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.

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210496s003lbl.pdf



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

☐ cobimetinib + vemurafenib

Cancer type: Melanoma

Label as of: 2018-01-26

Variant class: BRAF V600E mutation

Indications and usage:

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

Reference:

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

☐ 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 2019-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

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

① 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]

① 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]



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; Stage IVC (Systemic therapy) (Preferred)

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

○ binimetinib + 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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

○ binimetinib + 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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2020]



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

○ binimetinib + 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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

○ binimetinib + 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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2020]



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

○ cetuximab + dabrafenib + trametinib

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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

○ cetuximab + dabrafenib + trametinib

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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2020]



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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

○ 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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2020]



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

○ 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; BRAF V600E mutation discovered prior to first-line systemic therapy if dabrafenib + trametinib is not tolerated (First-line therapy) (Other Recommended)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; BRAF V600E mutation discovered during first-line systemic therapy if dabrafenib + trametinib is not tolerated (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression after first-line systemic therapy if dabrafenib + trametinib is not tolerated (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

○ dabrafenib + panitumumab + trametinib

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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]



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

○ dabrafenib + panitumumab + trametinib

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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2020]

○ 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; BRAF V600E mutation discovered prior to first-line systemic therapy (First-line therapy) (Preferred)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; BRAF V600E mutation discovered during first-line systemic therapy; Interrupt or complete planned systemic therapy, including maintenance therapy (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression after first-line systemic therapy (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]



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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

○ 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; Previous oxaliplatin based therapy without irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous treatment with oxaliplatin and irinotecan (Subsequent therapy)
- Advanced or Metastatic Rectal Cancer; Progression after initial therapy; Previous fluoropyrimidine without irinotecan or oxaliplatin (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2020]



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

○ panitumumab + vemurafenib + irinotecan

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; Previous oxaliplatin based therapy without irinotecan; If neither cetuximab or panitumumab was previously given (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous irinotecan based therapy without oxaliplatin; If neither cetuximab or panitumumab was previously given (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Progression after initial therapy; Previous FOLFOXIRI; If neither cetuximab or panitumumab was previously given (Subsequent therapy)
- Advanced or Metastatic Colon Cancer; Following fluoropyrimidine without irinotecan or oxaliplatin; If neither cetuximab or panitumumab previously given (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2020]

○ 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; BRAF V600E mutation discovered prior to first-line systemic therapy if dabrafenib + trametinib is not tolerated (First-line therapy) (Other Recommended)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; BRAF V600E mutation discovered during first-line systemic therapy if dabrafenib + trametinib is not tolerated (First-line therapy)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Progression after first-line systemic therapy if dabrafenib + trametinib is not tolerated (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [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 1.2020]



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 1.2020]

☐ 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)
- Resectable or Recurrent Cutaneous Melanoma (Adjuvant therapy) (Preferred)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 1.2020]

☐ 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 1.2020]

☐ 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 1.2020]



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 (Second-line or subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 1.2020]

☐ dabrafenib + trametinib

Cancer type: Melanoma

Variant class: BRAF V600 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

- Recurrent Resectable Cutaneous Melanoma (Adjuvant 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 1.2020]

☐ 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 (Second-line or subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 1.2020]

☐ 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 1.2020]



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 1.2020]

☐ 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 1.2020]

☒ 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 1.2020]

☒ 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 1.2020]



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

EGFR tyrosine kinase inhibitor

Cancer type: Non-Small Cell Lung Cancer

Variant class: BRAF V600E mutation

Summary:

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

- "EGFR TKI therapy is not effective in patients with KRAS mutations, BRAF V600E mutations, ALK gene rearrangements, or ROS1 rearrangements."

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 2.2020]

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 1.2020]

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 1.2020]

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 1.2020]



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

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 1.2020]



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 2020-02-28. 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: 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

☐ 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



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 2019-11-01. 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 or Unresectable Thyroid Gland Anaplastic Carcinoma (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Annals of Oncology (2019): mdz400, <https://doi.org/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 (2019), mdz411, <https://doi.org/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 (2019), mdz411, <https://doi.org/10.1093/annonc/mdz411>]



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

○ 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 (2019), mdz411, <https://doi.org/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 (2019), mdz411, <https://doi.org/10.1093/annonc/mdz411>]

○ 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 (2019), mdz411, <https://doi.org/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; 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>]



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 (2019), mdz411, <https://doi.org/10.1093/annonc/mdz411>]

🗨️ vemurafenib

Cancer type: Melanoma

Variant class: BRAF V600 mutation

Summary:

NCCN 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 (2019), mdz411, <https://doi.org/10.1093/annonc/mdz411>]

Signatures

Testing Personnel:

Laboratory Supervisor:

Pathologist:



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