Taipei Veterans General Hospital

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Sample Information

Patient Name: 沈馨潦
Gender: Female
ID No.: K220988187
History No.: 43898915
Age: 59

Ordering Doctor: DOC6483L 王品軒
Ordering REQ.: 0CRNDNW
Signing in Date: 2023/10/04

Path No.: M112-00260
MP No.: F23072
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S112-48479A+B
Percentage of tumor cells: 20%

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

Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

Table of Contents	Page

Report Highlights

2 Relevant Biomarkers
27 Therapies Available
13 Clinical Trials

Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	***BRAF p.(V600E) c.1799T>A***	NTRK2	None detected
EGFR	***EGFR p.(L858R) c.2573T>G, EGFR amplification***	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*BRAF p.(V600E) c.1799T>A* B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 16.39%	**dabrafenib** [1, 2] **dabrafenib + trametinib** [1, 2] **trametinib** [1, 2] vemurafenib	**atezolizumab + cobimetinib + vemurafenib** [1] **binimetinib + encorafenib** [1, 2] **cetuximab + encorafenib** [1, 2] **cobimetinib + vemurafenib** [1, 2] **dabrafenib** [1, 2] **dabrafenib + trametinib** [1, 2] **trametinib** [1, 2] **vemurafenib** [1, 2] bevacizumab + chemotherapy BRAF inhibitor + MEK inhibitor dabrafenib + MEK inhibitor encorafenib encorafenib + panitumumab ipilimumab + nivolumab selumetinib	1
IA	*EGFR p.(L858R) c.2573T>G* epidermal growth factor receptor Allele Frequency: 49.87%	**afatinib** [1, 2] **bevacizumab* + erlotinib** [2] **dacomitinib** [1, 2] **erlotinib** [1, 2] **erlotinib + ramucirumab** [1, 2] **gefitinib** [1, 2] **osimertinib** [1, 2] atezolizumab + bevacizumab + chemotherapy gefitinib + chemotherapy	None	12

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.
*** Includes biosimilars/generics**

Prevalent cancer biomarkers without relevant evidence based on included data sources

CDK4 amplification, EGFR amplification

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
EGFR	p.(L858R)	c.2573T>G	COSM6224	chr7:55259515	49.87%	NM_005228.5	missense	1995
BRAF	p.(V600E)	c.1799T>A	COSM476	chr7:140453136	16.39%	NM_004333.6	missense	1934
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.65%	NM_213647.3	missense	2000

Copy Number Variations

Gene	Locus	Copy Number
EGFR	chr7:55198956	6.7
CDK4	chr12:58142052	160.7

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 melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[15,16,17,18,19]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain leading to constitutive kinase activation[5,15,17].

Potential relevance: Vemurafenib[20] (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive[4]. BRAF kinase inhibitors including dabrafenib[21] (2013) and encorafenib[22] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[22] is approved in combination with cetuximab[23] (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations[4]. Trametinib[24] (2013) and binimetinib[25] (2018) were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC. The combinations of dabrafenib/trametinib (2015) and vemurafenib/cobimetinib[26] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017) with a BRAF V600E mutation. The PD-L1 antibody, atezolizumab[27], has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. In 2018, binimetinib[28] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib[29] was granted fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. The FDA granted fast track designation (2022) to the pan-RAF inhibitor, KIN-2787[30], for the treatment of BRAF class II or III alteration-positive malignant or unresectable melanoma. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma[31]. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification and alternative splice transcripts as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)[32,33,34,35,36,37,38]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[19].

CDK4 (cyclin dependent kinase 4)

Background: The CDK4 gene encodes the cyclin-dependent kinase 4 protein, a homologue of CDK6. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle[39,40]. CDK4 kinase is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression[41]. Germline mutations in CDK4 are associated with familial melanoma[42,43,44].

Alterations and prevalence: Recurrent somatic mutations of CDK4 codon K22 and R24 are observed in melanoma (1-2%) and lung cancer (approximately 0.1%). Codons K22 and R24 are necessary for binding and inhibition by p16/CDKN2A[45,46,47]. CDK4 is recurrently amplified in several cancer types, most notably in sarcomas (15-20%), glioma (10-15%), adrenocortical carcinoma (5%), lung adenocarcinoma (5%), and melanoma (3%)[7,9,10,48].

Potential relevance: Currently, no therapies are approved for CDK4 aberrations. Amplification of region 12q14-15, which includes CDK4, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/welldifferentiated liposarcoma (ALT/WDLS)[49]. Small molecule inhibitors targeting CDK4/6 including palbociclib (2015), abemaciclib (2017), and ribociclib (2017), are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

Biomarker Descriptions (continued)

EGFR (epidermal growth factor receptor)

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the ERBB/human epidermal growth factor receptor (HER) family. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[50]. EGFR ligand induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways. Activation of these pathways promote cell proliferation, differentiation, and survival[51,52].

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations[7,9,10,53]. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21[54]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer. A second group of less prevalent activating mutations include E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[55,56,57,58]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[59]. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V and are primarily observed in glioblastoma[48,54]. Amplification of EGFR is observed in several cancer types including 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma[7,9,10,48,60]. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma[61,62,63].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[64] (2004) and gefitinib[65] (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations. Second-generation TKIs afatinib[66] (2013) and dacomitinib[67] (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies[68,69,70,71]. However, in 2021, the irreversible tyrosine kinase inhibitor, mobocertinib[72]was FDA approved for the treatment of NSCLC with EGFR exon 20 insertion mutations. Additionally, in 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitors, CLN-081 (TPC-064)[73] and sunvozertinib[74], for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance[75]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[54]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M. Osimertinib[76] (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance. In this case, resistance is associated with the C797S mutation and occurs in 22-44% of cases[75]. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa[77]. T790M and C797S can occur in either cis or trans allelic orientation[77]. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs[77]. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone[77,78]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[77]. Fourth-generation TKIs are in development to overcome acquired C797S and T790M resistance mutations after osimertinib treatment. EGFR targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The bispecific antibody, amivantamab[79], targeting EGFR and MET was approved (2021) for NSCLC tumors harboring EGFR exon 20 insertion mutations. CPO301[80] received a fast track designation (2023) from the FDA for EGFR mutations in patients with metastatic NSCLC who are relapsed/refractory or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors including osimertinib. The Oncoprex immunogene therapy quaratusugene ozeplasmid[81] in combination with osimertinib received a fast track designation from the FDA (2020) for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. BDTX-189[82] was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutation.

Relevant Therapy Summary

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

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

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
dabrafenib + trametinib	◑	◑	◑	◑	✖
dabrafenib	◑	◑	◑	✖	✖
trametinib	◑	✖	◑	✖	✖
vemurafenib	○	◑	○	✖	✖
binimetinib + encorafenib	○	○	○	○	✖
cetuximab + encorafenib	○	○	○	○	✖
cobimetinib + vemurafenib	○	○	○	○	✖
atezolizumab + cobimetinib + vemurafenib	○	✖	✖	✖	✖
encorafenib	✖	○	✖	✖	✖
encorafenib + panitumumab	✖	○	✖	✖	✖
selumetinib	✖	○	✖	✖	✖
bevacizumab + CAPOX	✖	✖	✖	○	✖
bevacizumab + FOLFOX	✖	✖	✖	○	✖
bevacizumab + FOLFOXIRI	✖	✖	✖	○	✖
BRAF inhibitor + MEK inhibitor	✖	✖	✖	○	✖
dabrafenib + MEK inhibitor	✖	✖	✖	○	✖
ipilimumab + nivolumab	✖	✖	✖	○	✖
binimetinib	✖	✖	✖	✖	● (I)

EGFR p.(L858R) c.2573T>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
osimertinib	●	●	●	●	● (III)
afatinib	●	●	●	●	● (II)
dacomitinib	●	●	●	●	✖
erlotinib	●	●	●	●	✖
erlotinib + ramucirumab	●	●	●	●	✖
gefitinib	●	●	●	●	✖
bevacizumab + erlotinib	✖	●	●	●	✖
bevacizumab (Allergan) + erlotinib	✖	✖	●	✖	✖

* 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

EGFR p.(L858R) c.2573T>G (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab (Celltrion) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Mabxience) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Pfizer) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Samsung Bioepis) + erlotinib	✖	✖	●	✖	✖
bevacizumab (Stada) + erlotinib	✖	✖	●	✖	✖
atezolizumab + bevacizumab + carboplatin + paclitaxel	✖	✖	✖	●	✖
gefitinib + carboplatin + pemetrexed	✖	✖	✖	●	✖
amivantamab, lazertinib, chemotherapy	✖	✖	✖	✖	● (III)
osimertinib, chemotherapy	✖	✖	✖	✖	● (III)
patritumab deruxtecan	✖	✖	✖	✖	● (III)
savolitinib, osimertinib	✖	✖	✖	✖	● (III)
erlotinib, OBI-833	✖	✖	✖	✖	● (II)
osimertinib, savolitinib	✖	✖	✖	✖	● (II)
chemotherapy	✖	✖	✖	✖	● (I/II)
sunvozertinib	✖	✖	✖	✖	● (I/II)
ABBV 400	✖	✖	✖	✖	● (I)
BAY-2927088	✖	✖	✖	✖	● (I)

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

Relevant Therapy Details

Current FDA Information

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

FDA information is current as of 2023-08-16. For the most up-to-date information, search www.fda.gov.

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

◑ dabrafenib, dabrafenib + trametinib

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

Label as of: 2023-05-26

Variant class: BRAF V600E mutation

Indications and usage:

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

TAFINLAR® is indicated, in combination with trametinib, for:

- the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
- the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.
- the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202806s026lbl.pdf

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

trametinib, dabrafenib + trametinib

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

Label as of: 2023-05-26

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.
- the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204114s028lbl.pdf

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

atezolizumab + cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2023-05-12 **Variant class:** BRAF V600E mutation

Indications and usage:

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

Non-Small Cell Lung Cancer (NSCLC)

- as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test.
- for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 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®.

Small Cell Lung Cancer (SCLC)

- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Hepatocellular Carcinoma (HCC)

- in combination with bevacizumab for the treatment of adult patients with unresectable or metastatic HCC who have not received prior systemic therapy.

Melanoma

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

Alveolar Soft Part Sarcoma (ASPS)

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

Reference:

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

binimetinib + encorafenib

Cancer type: Melanoma **Label as of:** 2019-01-23 **Variant class:** BRAF V600E mutation

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

Reference:

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

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

binimetinib + encorafenib, cetuximab + encorafenib

Cancer type: Colorectal Cancer, Melanoma **Label as of:** 2022-02-11 **Variant class:** BRAF V600E mutation

Indications and usage:

BRAFTOVI® is a kinase inhibitor indicated:

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

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210496s013lbl.pdf

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cetuximab + encorafenib

Cancer type: Colorectal Cancer **Label as of:** 2021-09-24 **Variant class:** BRAF V600E mutation

Indications and usage:

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved test

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: Erbitux® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf

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

○ cobimetinib + vemurafenib

Cancer type: Melanoma **Label as of:** 2023-05-31 **Variant class:** BRAF V600E mutation

Indications and usage:

COTELLIC® is a kinase inhibitor indicated:

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

Reference:

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

○ vemurafenib

Cancer type: Melanoma **Label as of:** 2020-05-18 **Variant class:** BRAF V600E mutation

Indications and usage:

- ZELBORAF® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
- ZELBORAF® is indicated for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation.

Limitation of Use: ZELBORAF® is not indicated for treatment of patients with wild-type BRAF melanoma.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf

EGFR p.(L858R) c.2573T>G

● afatinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-04-07 **Variant class:** EGFR L858R mutation

Indications and usage:

GILOTRIF® is a kinase inhibitor indicated for:

- First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test.

Limitations of Use: Safety and efficacy of GILOTRIF® were not established in patients whose tumors have resistant EGFR mutations

- Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf

EGFR p.(L858R) c.2573T>G (continued)

dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2020-12-18 **Variant class:** EGFR L858R mutation

Indications and usage:
VIZIMPRO® is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf

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erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2016-10-18 **Variant class:** EGFR L858R mutation

Indications and usage:

TARCEVA® is a kinase inhibitor indicated for:

- The treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen.
- First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.

Limitations of Use:

- Safety and efficacy of TARCEVA® have not been established in patients with NSCLC whose tumors have other EGFR mutations.
- TARCEVA® is not recommended for use in combination with platinum-based chemotherapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf

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erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-03-22 **Variant class:** EGFR L858R mutation

Indications and usage:

CYRAMZA® is a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist indicated:

- as a single agent or in combination with paclitaxel, for treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
- in combination with erlotinib, for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.
- in combination with docetaxel, for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA®.
- in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- as a single agent, for the treatment of hepatocellular carcinoma in patients who have an alpha fetoprotein of ≥400 ng/mL and have been treated with sorafenib.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125477s042lbl.pdf

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EGFR p.(L858R) c.2573T>G (continued)

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2021-05-05 **Variant class:** EGFR L858R mutation

Indications and usage:

IRESSA® is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Limitation of Use: Safety and efficacy of IRESSA® have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf

osimertinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-06-21 **Variant class:** EGFR L858R mutation

Indications and usage:

TAGRISSO® is a kinase inhibitor indicated for:

- as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test
- the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208065Orig1s028lbl.pdf

Current NCCN Information

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

NCCN information is current as of 2023-08-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

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

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

● dabrafenib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Useful in certain circumstances

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

● dabrafenib + trametinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

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

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

● vemurafenib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Useful in certain circumstances

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

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

cetuximab + encorafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metachronous Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

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

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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 (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2023]

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cobimetinib + vemurafenib

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

NCCN Recommendation category: 2A

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

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

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cobimetinib + vemurafenib

Cancer type: Ganglioglioma (Grade 1), Pilocytic Astrocytoma (Grade 1), Pleomorphic Xanthoastrocytoma (Grade 2,3) **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade II (Adjuvant therapy); Useful in certain circumstances

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

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

cobimetinib + vemurafenib

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

Other criteria: IDH wild type

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade IV; Recurrent, Progression (Recurrence therapy); Useful in certain circumstances

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Progression (Subsequent therapy); Useful in certain circumstances

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Brain Metastases (Line of therapy not specified); Preferred intervention

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

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

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

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

dabrafenib + trametinib

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

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade II (Adjuvant therapy); Useful in certain circumstances

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

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dabrafenib + trametinib

Cancer type: Glioblastoma IDH-wildtype (Grade 4)

Variant class: BRAF V600E mutation

Other criteria: IDH wild type

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade IV; Recurrent, Progression (Recurrence therapy); Useful in certain circumstances

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

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dabrafenib + trametinib

Cancer type: Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 2.2023]

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dabrafenib + trametinib

Cancer type: Gastric Cancer

Variant class: BRAF V600E mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 1.2023]

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

dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Resectable (Neoadjuvant therapy); Useful in certain circumstances
- Unresectable, Progression, Metastatic (First-line therapy); Useful in certain circumstances

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

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

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Extrapulmonary, Poorly Differentiated; Progression, Unresectable, Metastatic (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 2.2022]

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Poorly Differentiated; Progression, Unresectable, Metastatic (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Neuroendocrine and Adrenal Tumors [Version 2.2022]

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

dabrafenib + trametinib

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

NCCN Recommendation category: 2A

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

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma; Metastatic, Locally Advanced, Recurrent (Subsequent therapy); Other recommended intervention, Useful in certain circumstances

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

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dabrafenib + trametinib

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma **Variant class:** BRAF V600E mutation

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2023]

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVA, Stage IVB; Local, Unresectable, Regional (Neoadjuvant therapy); Consider
- Stage IVC; Metastatic (Line of therapy not specified); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2023]

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

encorafenib + panitumumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metachronous Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

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

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encorafenib + panitumumab

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Metachronous Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 4.2023]

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selumetinib

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

NCCN Recommendation category: 2A

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

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

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cobimetinib + vemurafenib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Brain Metastases (Line of therapy not specified); Preferred intervention

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Adenocarcinoma; Metastatic (First-line therapy); Other recommended intervention, Useful in certain circumstances

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

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

○ binimetinib + encorafenib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Other recommended intervention

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

○ cobimetinib + vemurafenib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Other recommended intervention

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

○ dabrafenib + trametinib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Other recommended intervention

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

○ dabrafenib + trametinib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Stage III; Resectable (Adjuvant therapy); Preferred intervention
- Recurrent, Resectable (Adjuvant therapy); Preferred intervention

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

○ binimetinib + encorafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

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

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

cobimetinib + vemurafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

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

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dabrafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Other recommended intervention
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IIIA, Stage IIIB, Stage IIIC, Stage IIID (Adjuvant therapy); Preferred intervention
- Stage III; Resectable (Adjuvant therapy); Preferred intervention
- Locally Recurrent, Resectable (Adjuvant therapy); Preferred intervention

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

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

encorafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Other recommended intervention
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

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

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vemurafenib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic, Unresectable (First-line therapy); Other recommended intervention
- Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Preferred intervention

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

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binimetinib + encorafenib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Resectable, Distant Metastases (Adjuvant therapy); Other recommended intervention

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

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cobimetinib + vemurafenib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Resectable, Distant Metastases (Adjuvant therapy); Other recommended intervention

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

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dabrafenib + trametinib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Resectable, Distant Metastases (Adjuvant therapy); Other recommended intervention

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

EGFR p.(L858R) c.2573T>G

afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention

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

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dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention

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

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erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention

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

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gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention

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

EGFR p.(L858R) c.2573T>G (continued)

osimertinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Preferred intervention

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

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afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

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

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afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

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

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bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-squamous Cell; Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention
- Non-squamous Cell; Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

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

EGFR p.(L858R) c.2573T>G (continued)

bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Non-squamous Cell; Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

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

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dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

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

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dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

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

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erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

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

EGFR p.(L858R) c.2573T>G (continued)

erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

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

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erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered prior to first line therapy (First-line therapy); Other recommended intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

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

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erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

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

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gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy)

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

EGFR p.(L858R) c.2573T>G (continued)

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

Other criteria: EGFR T790M mutation negative

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Symptomatic, Asymptomatic (Subsequent therapy)

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

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osimertinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Brain Metastases, Leptomeningeal Metastases (Line of therapy not specified); Preferred intervention

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

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osimertinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IB , Stage IIA, Stage IIB, Stage IIIA, Stage IIIB; Resected (Adjuvant therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Biomarker discovered during first line therapy (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Asymptomatic, Symptomatic (Subsequent therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Leptomeningeal Metastases, Progression (Subsequent therapy); Consider

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

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erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Leptomeningeal Metastases (Line of therapy not specified); Other recommended intervention

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

EGFR p.(L858R) c.2573T>G (continued)

afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFRi sensitizing mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Brain Metastases (Line of therapy not specified); Other recommended intervention

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

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFRi sensitizing mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Brain Metastases (Line of therapy not specified); Other recommended intervention

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

Current EMA Information

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

EMA information is current as of 2023-08-16. For the most up-to-date information, search www.ema.europa.eu/ema.

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

◑ dabrafenib, dabrafenib + trametinib

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

Label as of: 2023-02-27

Variant class: BRAF V600E mutation

Reference:

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

◑ trametinib, dabrafenib + trametinib

Cancer type: Melanoma, Non-Small Cell Lung Cancer

Label as of: 2023-02-27

Variant class: BRAF V600E mutation

Reference:

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

○ binimetinib + encorafenib

Cancer type: Melanoma

Label as of: 2022-01-26

Variant class: BRAF V600E mutation

Reference:

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

○ binimetinib + encorafenib, cetuximab + encorafenib

Cancer type: Colorectal Cancer, Melanoma

Label as of: 2022-08-05

Variant class: BRAF V600E mutation

Reference:

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

○ cobimetinib + vemurafenib

Cancer type: Melanoma

Label as of: 2023-03-06

Variant class: BRAF V600E mutation

Reference:

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

○ vemurafenib

Cancer type: Melanoma

Label as of: 2023-07-18

Variant class: BRAF V600E mutation

Reference:

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

EGFR p.(L858R) c.2573T>G

afatinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-06-21 **Variant class:** EGFR L858R mutation

Reference:

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

bevacizumab (Allergan) + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-01-05 **Variant class:** EGFR L858R mutation

Reference:

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

bevacizumab (Celltrion) + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-05-10 **Variant class:** EGFR L858R mutation

Reference:

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

bevacizumab (Mabxience) + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-07-26 **Variant class:** EGFR L858R mutation

Reference:

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

bevacizumab (Pfizer) + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-01-05 **Variant class:** EGFR L858R mutation

Reference:

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

bevacizumab (Samsung Bioepis) + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-04-11 **Variant class:** EGFR L858R mutation

Reference:

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

bevacizumab (Samsung Bioepis) + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-04-11 **Variant class:** EGFR L858R mutation

Reference:

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

EGFR p.(L858R) c.2573T>G (continued)

bevacizumab (Stada) + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-07-14 **Variant class:** EGFR L858R mutation

Reference:

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

bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-12-15 **Variant class:** EGFR L858R mutation

Reference:

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

bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-03-17 **Variant class:** EGFR L858R mutation

Reference:

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

dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2021-07-21 **Variant class:** EGFR L858R mutation

Reference:

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

erlotinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-05-16 **Variant class:** EGFR L858R mutation

Reference:

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

erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2022-12-13 **Variant class:** EGFR L858R mutation

Other criteria: EGFR T790M mutation negative

Reference:

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

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-07-27 **Variant class:** EGFR L858R mutation

Reference:

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

EGFR p.(L858R) c.2573T>G (continued)

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-07-17 **Variant class:** EGFR L858R mutation

Reference:

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

osimertinib

Cancer type: Non-Small Cell Lung Cancer **Label as of:** 2023-08-11 **Variant class:** EGFR L858R mutation

Reference:

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

Current ESMO Information

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

ESMO information is current as of 2023-08-01. For the most up-to-date information, search www.esmo.org.

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

● dabrafenib + trametinib

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

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

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

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

○ cetuximab + encorafenib

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

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

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

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

○ dabrafenib + trametinib

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

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

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

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

○ bevacizumab + FOLFOXIRI

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

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

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

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

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

bevacizumab + CAPOX

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

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

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

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

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bevacizumab + FOLFOX

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

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

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

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

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dabrafenib + trametinib

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

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

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Thyroid Cancer [Ann Oncol. 2022; https://doi.org/10.1016/j.annonc.2022.04.009]

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dabrafenib + MEK inhibitor

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

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

Population segment (Line of therapy):
- Advanced, Metastatic (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-EUROCAN-Gastrointestinal Stromal Tumours [Ann Oncol (2021), doi: https://doi.org/10.1016/j.annonc.2021.09.005.]

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

BRAF inhibitor + MEK inhibitor

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

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

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy)
- Asymptomatic, Metastatic (Line of therapy not specified)

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

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dabrafenib + trametinib

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

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

Population segment (Line of therapy):
- Stage IIIA, Stage IIIB, Stage IIIC; Resectable (Adjuvant therapy); ESMO-MCBS v1.1 score: A

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

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binimetinib + encorafenib

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

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

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy, Second-line therapy)

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

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cobimetinib + vemurafenib

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

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

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy, Second-line therapy)

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

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

dabrafenib + trametinib

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

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

Population segment (Line of therapy):
- Stage III, Stage IV; Unresectable (First-line therapy, Second-line therapy)

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

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ipilimumab + nivolumab

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

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

Population segment (Line of therapy):
- Stage III, Stage IV; Asymptomatic, Brain Metastases, Metastatic, Unresectable (First-line therapy)

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

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bevacizumab + CAPOX

Cancer type: Colorectal Cancer **Variant class:** BRAF mutation

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

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

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

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bevacizumab + FOLFOX

Cancer type: Colorectal Cancer **Variant class:** BRAF mutation

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

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

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

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

○ ipilimumab + nivolumab

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

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

Population segment (Line of therapy):
- Asymptomatic, Brain Metastases (First-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-EANO-ESMO Brain Metastasis from Solid Tumours [Ann Oncol (2021), https://doi.org/10.1016/j.annonc.2021.07.016 (Published)]

EGFR p.(L858R) c.2573T>G

● osimertinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IB , Stage IIA, Stage IIB, Stage IIIA; Resected (Adjuvant therapy); ESMO-MCBS v1.1 score: A

Reference: ESMO Clinical Practice Guidelines - ESMO-Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer [Ann Oncol (2017) 28 (suppl 4): iv1–iv21. (eUpdate: 01 September 2021, 04 May 2020)]

● osimertinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 4

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

● afatinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 5

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

EGFR p.(L858R) c.2573T>G (continued)

bevacizumab + erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 2

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

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dacomitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 3

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

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erlotinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 4

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

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erlotinib + ramucirumab

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 3

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

EGFR p.(L858R) c.2573T>G (continued)

gefitinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IV; Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 4

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

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gefitinib + carboplatin + pemetrexed

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IV; Advanced, Metastatic (First-line therapy)

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

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atezolizumab + bevacizumab + carboplatin + paclitaxel

Cancer type: Non-Small Cell Lung Cancer **Variant class:** EGFR L858R mutation

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

Population segment (Line of therapy):
- Stage IV; Advanced, Metastatic, Progression (Subsequent therapy); ESMO-MCBS v1.1 score: 3

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

Clinical Trials in Taiwan region:

Clinical Trials Summary

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

NCT ID	Title	Phase
NCT04913285	A Phase I/I b Open-label, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of KIN-2787 in Participants With BRAF and/or NRAS Mutation-positive Solid Tumors.	I

EGFR p.(L858R) c.2573T>G

NCT ID	Title	Phase
NCT04988295	A Phase III, Open-Label, Randomized Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure	III
NCT05120349	A Phase III, Double-blind, Randomised, Placebo-Controlled, International Study to Assess the Efficacy and Safety of Adjuvant Osimertinib Versus Placebo in Participants With EGFR Mutation-positive Stage IA2-IA3 Non-small Cell Lung Cancer, Following Complete Tumour Resection	III
NCT04351555	A Phase III, Randomised, Controlled, Multi-center, 3-Arm Study of Neoadjuvant Osimertinib as Monotherapy or in Combination With Chemotherapy Versus Standard of Care Chemotherapy Alone for the Treatment of Patients With Epidermal Growth Factor Receptor Mutation Positive, Resectable Non-small Cell Lung Cancer	III
NCT05338970	HERTHENA–Lung02: Phase III, Randomized, Open-label Study of Patritumab Deruxtecan Versus Platinum-Based Chemotherapy in Metastatic or Locally Advanced Non-Small Cell Lung Cancer (NSCLC) With Epidermal Growth Factor Receptor (EGFRm) Mutation After Failure treatment with epidermal growth factor (EGFR) tyrosine kinase inhibitors (TKIs)	III
NCT05261399	A Phase III, Randomised, Open-Label Study of Savolitinib in Combination With Osimertinib Versus Platinum-Based Doublet Chemotherapy in Participants With EGFR Mutated, MET-Overexpressed and/or Amplified, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Progressed on Treatment With Osimertinib (SAFFRON).	III
NCT05215548	A Phase II Study of Primary Tumor Resection for Stage IV Non-small-cell Lung Cancer Without Progression After First-line Epidermal Growth Factor Receptor-tyrosine Kinase Inhibitor	II
NCT05442060	A Randomized, Open-Label, Phase 2 Study to Evaluate OBI-833/OBI-821 in Combination With First-Line Erlotinib in Patients With EGFR-Mutated, Globo H-Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer	II
NCT03778229	A Phase II Study Assessing the Efficacy of Osimertinib in Combination With Savolitinib in Patients With EGFRm+ and MET+, Locally Advanced or Metastatic Non Small Cell Lung Cancer Who Have Progressed Following Treatment With Osimertinib.	II
NCT05099172	An Open Label, First-in-human Study of BAY 2927088 in Participants With Advanced Non-small Cell Lung Cancer (NSCLC) Harboring an EGFR and/or HER2 Mutation	I
NCT05241873	Phase I/II Study of BLU-451 in Advanced Cancers With EGFR Exon 20 Insertion Mutations	I/II
NCT03974022	A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 Mutation	I/II
NCT05029882	A Phase I First in Human Study Evaluating Safety, Pharmacokinetics and Efficacy of ABBV-400 in Adult Subjects With Advanced Solid Tumors	I

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2023-08-16. For the most up-to-date information, search www.fda.gov.

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

binimetinib + cetuximab + encorafenib

Cancer type: Colorectal Cancer

Variant class: BRAF V600E mutation

Supporting Statement:
The FDA has granted Breakthrough Designation to the MEK inhibitor, binimetinib, in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer.

Reference:

https://markets.businessinsider.com/news/stocks/array-biopharma-receives-fda-breakthrough-therapy-designation-for-braftovi-in-combination-with-mektovi-and-cetuximab-for-brafv600e-mutant-metastatic-colorectal-cancer-1027437791

plixorafenib

Cancer type: Solid Tumor

Variant class: BRAF V600 mutation

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

Reference:

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

EGFR p.(L858R) c.2573T>G

patritumab deruxtecan

Cancer type: Non-Small Cell Lung Cancer

Variant class: EGFR L858R mutation or EGFRi sensitizing mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy Designation to a potential first-in-class HER3 directed antibody-drug conjugate, patritumab deruxtecan, for metastatic or locally advanced, EGFR-mutant non-small cell lung cancer.

Reference:

https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-status-to-patritumab-deruxtecan-for-egfr-metastatic-nsclc

EGFR p.(L858R) c.2573T>G (continued)

CPO-301

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

Supporting Statement:
The FDA has granted Fast Track Designation to a first-in-class antibody drug conjugate, CPO301, for EGFR mutations in patients with metastatic non-small cell lung cancer (NSCLC) who are relapsed/refractory to or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors including Osimertinib.

Reference:

http://iis.aastocks.com/20230612/10770455-0.PDF

osimertinib + quaratusugene ozeplasmid

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

Supporting Statement:
The FDA has granted Fast Track Designation to the immunogene therapy, quaratusugene ozeplasmid, in combination with EGFR inhibitor osimertinib for the treatment of EGFR mutations in non-small cell lung cancer (NSCLC) patients that progressed after treatment with osimertinib alone.

Reference:

https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2023-08-01. For the most up-to-date information, search www.esmo.org.

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

vemurafenib

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

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

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

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

References

1. Cheng et al. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. Mod. Pathol. 2018 Jan;31(1):24-38. PMID: 29148538
2. Alrabadi et al. Detection of driver mutations in BRAF can aid in diagnosis and early treatment of dedifferentiated metastatic melanoma. Mod. Pathol. 2019 Mar;32(3):330-337. PMID: 30315274
3. Quan et al. The association between BRAF mutation class and clinical features in BRAF-mutant Chinese non-small cell lung cancer patients. Journal of Translational Medicine, 29 Aug 2019, 17(1):298. PMID: 31470866
4. Yao et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. Nature. 2017 Aug 10;548(7666):234-238. PMID: 28783719
5. Bracht et al. BRAF Mutations Classes I, II, and III in NSCLC Patients Included in the SLLIP Trial: The Need for a New Pre-Clinical Treatment Rationale. Cancers (Basel). 2019 Sep 17;11(9). PMID: 31533235
6. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014 Oct 23;159(3):676-90. PMID: 25417114
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
8. Donna et al. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7. PMID: 22810696
9. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
10. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
11. Wan et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell. 2004 Mar 19;116(6):855-67. PMID: 15035987
12. Tiacci et al. BRAF mutations in hairy-cell leukemia. N. Engl. J. Med. 2011 Jun 16;364(24):2305-15. PMID: 21663470
13. Diamond et al. Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms. Cancer Discov. 2016 Feb;6(2):154-65. doi: 10.1158/2159-8290.CD-15-0913. Epub 2015 Nov 13. PMID: 26566875
14. Imielinski et al. Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma. J Clin Invest. 2014 Apr;124(4):1582-6. doi: 10.1172/JCI72763. Epub 2014 Feb 24. PMID: 24569458
15. Ciampi et al. Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. J. Clin. Invest. 2005 Jan;115(1):94-101. PMID: 15630448
16. Palanisamy et al. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. Nat. Med. 2010 Jul;16(7):793-8. PMID: 20526349
17. Jones et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res. 2008 Nov 1;68(21):8673-7. PMID: 18974108
18. Cin et al. Oncogenic FAM131B-BRAF fusion resulting from 7q34 deletion comprises an alternative mechanism of MAPK pathway activation in pilocytic astrocytoma. Acta Neuropathol. 2011 Jun;121(6):763-74. doi: 10.1007/s00401-011-0817-z. Epub 2011 Mar 20. PMID: 21424530
19. Ross et al. The distribution of BRAF gene fusions in solid tumors and response to targeted therapy. Int. J. Cancer. 2016 Feb 15;138(4):881-90. PMID: 26314551
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202806s026lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210496s013lbl.pdf
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf
24. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204114s028lbl.pdf
25. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210498s001lbl.pdf
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/206192s006lbl.pdf
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761034s049s051lbl.pdf
28. https://markets.businessinsider.com/news/stocks/array-biopharma-receives-fda-breakthrough-therapy-designation-for-braftovi-in-combination-with-mektovi-and-cetuximab-for-brafv600e-mutant-metastatic-colorectal-cancer-1027437791
29. https://biomed-valley.com/news/#press-releases
30. https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food

References (continued)

31. Kulkarni et al. BRAF Fusion as a Novel Mechanism of Acquired Resistance to Vemurafenib in BRAFV600E Mutant Melanoma. Clin. Cancer Res. 2017 Sep 15;23(18):5631-5638. PMID: 28539463
32. Johnson et al. Acquired BRAF inhibitor resistance: A multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. Eur. J. Cancer. 2015 Dec;51(18):2792-9. PMID: 26608120
33. Nazarian et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. Nature. 2010 Dec 16;468(7326):973-7. doi: 10.1038/nature09626. Epub 2010 Nov 24. PMID: 21107323
34. Rizos et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. Clin. Cancer Res. 2014 Apr 1;20(7):1965-77. PMID: 24463458
35. Shi et al. A novel AKT1 mutant amplifies an adaptive melanoma response to BRAF inhibition. Cancer Discov. 2014 Jan;4(1):69-79. PMID: 24265152
36. Van et al. The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. Cancer Discov. 2014 Jan;4(1):94-109. doi: 10.1158/2159-8290.CD-13-0617. Epub 2013 Nov 21. PMID: 24265153
37. Villanueva et al. Concurrent MEK2 mutation and BRAF amplification confer resistance to BRAF and MEK inhibitors in melanoma. Cell Rep. 2013 Sep 26;4(6):1090-9. PMID: 24055054
38. Shi et al. Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. Cancer Discov. 2014 Jan;4(1):80-93. PMID: 24265155
39. Malumbres et al. Cell cycle, CDKs and cancer: a changing paradigm. Nat. Rev. Cancer. 2009 Mar;9(3):153-66. PMID: 19238148
40. Sherr et al. Targeting CDK4 and CDK6: From Discovery to Therapy. Cancer Discov. 2016 Apr;6(4):353-67. PMID: 26658964
41. Weinberg. The retinoblastoma protein and cell cycle control. Cell. 1995 May 5;81(3):323-30. PMID: 7736585
42. Rane et al. Germ line transmission of the Cdk4(R24C) mutation facilitates tumorigenesis and escape from cellular senescence. Mol. Cell. Biol. 2002 Jan;22(2):644-56. PMID: 11756559
43. Zuo et al. Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. Nat. Genet. 1996 Jan;12(1):97-9. PMID: 8528263
44. Molven et al. A large Norwegian family with inherited malignant melanoma, multiple atypical nevi, and CDK4 mutation. Genes Chromosomes Cancer. 2005 Sep;44(1):10-8. PMID: 15880589
45. Ceha et al. Several noncontiguous domains of CDK4 are involved in binding to the P16 tumor suppressor protein. Biochem. Biophys. Res. Commun. 1998 Aug 19;249(2):550-5. PMID: 9712735
46. Tsao et al. Novel mutations in the p16/CDKN2A binding region of the cyclin-dependent kinase-4 gene. Cancer Res. 1998 Jan 1;58(1):109-13. PMID: 9426066
47. Sotillo et al. Invasive melanoma in Cdk4-targeted mice. Proc. Natl. Acad. Sci. U.S.A. 2001 Nov 6;98(23):13312-7. PMID: 11606789
48. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
49. NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 2.2023]
50. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science. 1985 Sep 6;229(4717):974-6. PMID: 2992089
51. Zhixiang. ErbB Receptors and Cancer. Methods Mol. Biol. 2017;1652:3-35. PMID: 28791631
52. Gutierrez et al. HER2: biology, detection, and clinical implications. Arch. Pathol. Lab. Med. 2011 Jan;135(1):55-62. PMID: 21204711
53. Pines et al. Oncogenic mutant forms of EGFR: lessons in signal transduction and targets for cancer therapy. FEBS Lett. 2010 Jun 18;584(12):2699-706. PMID: 20388509
54. da et al. EGFR mutations and lung cancer. Annu Rev Pathol. 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
55. Arcila et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol. Cancer Ther. 2013 Feb;12(2):220-9. PMID: 23371856
56. Kobayashi et al. EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs. Clin Cancer Res. 2015 Dec 1;21(23):5305-13. doi: 10.1158/1078-0432.CCR-15-1046. Epub 2015 Jul 23. PMID: 26206867
57. Yasuda et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. Sci Transl Med. 2013 Dec 18;5(216):216ra177. PMID: 24353160
58. Chiu et al. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment Response in Advanced Lung Adenocarcinomas with G719X/L861Q/S768I Mutations. J Thorac Oncol. 2015 May;10(5):793-9. PMID: 25668120
59. Karachaliou et al. KRAS mutations in lung cancer. Clin Lung Cancer. 2013 May;14(3):205-14. PMID: 23122493

References (continued)

60. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
61. Mitsudomi et al. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. FEBS J. 2010 Jan;277(2):301-8. PMID: 19922469
62. Gazdar. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene. 2009 Aug;28 Suppl 1:S24-31. PMID: 19680293
63. Gan et al. The EGFRvIII variant in glioblastoma multiforme. J Clin Neurosci. 2009 Jun;16(6):748-54. PMID: 19324552
64. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf
65. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf
66. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf
67. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf
68. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2023]
69. Naidoo et al. Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. Cancer. 2015 Sep 15;121(18):3212-3220. PMID: 26096453
70. Vyse et al. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther. 2019;4:5. PMID: 30854234
71. Yi et al. A comparison of epidermal growth factor receptor mutation testing methods in different tissue types in non-small cell lung cancer. Int J Mol Med. 2014 Aug;34(2):464-74. PMID: 24891042
72. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215310s002lbl.pdf
73. https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncologys
74. https://www.prnewswire.com/news-releases/fda-grants-breakthrough-therapy-designation-for-dizal-pharmaceuticals-dzd9008-in-patients-with-locally-advanced-or-metastatic-non-small-cell-lung-cancer-harboring-egfr-exon20-insertion-301469692.html
75. Madic et al. EGFR C797S, EGFR T790M and EGFR sensitizing mutations in non-small cell lung cancer revealed by six-color crystal digital PCR. Oncotarget. 2018 Dec 21;9(100):37393-37406. PMID: 30647840
76. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208065Orig1s028lbl.pdf
77. Niederst et al. The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies. Clin. Cancer Res. 2015 Sep 1;21(17):3924-33. PMID: 25964297
78. Wang et al. Lung Adenocarcinoma Harboring EGFR T790M and In Trans C797S Responds to Combination Therapy of First- and Third-Generation EGFR TKIs and Shifts Allelic Configuration at Resistance. J Thorac Oncol. 2017 Nov;12(11):1723-1727. PMID: 28662863
79. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761210s002lbl.pdf
80. http://iis.aastocks.com/20230612/10770455-0.PDF
81. https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/
82. https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda