| 2.04.77 | BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy | | |
|---|---|---|---|
| **Original Policy Date:** | July 6, 2012 | **Effective Date:** | September 1, 2019 |
| **Section:** | 2.0 Medicine | **Page:** | Page 1 of 25 |

## Policy Statement

Testing for *BRAF* V600 variants in tumor tissue of patients with unresectable or metastatic melanoma may be considered **medically necessary** to select patients for treatment with Food and Drug Administration-approved BRAF or MEK inhibitors.

Testing for *BRAF* V600 variants in tumor tissue of patients with resected stage III melanoma may be considered **medically necessary** to select patients for treatment with Food and Drug Administration-approved BRAF or MEK inhibitors.

Testing for *BRAF* V600 variants for all other patients with melanoma is considered **investigational**.

Testing for *BRAF* V600 variants in patients with glioma to select patients for targeted treatment is considered **investigational**.

## Policy Guidelines

**Note:** This policy does not apply to BRAF testing related to colorectal cancer (see Blue Shield of California Medical Policies: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes and KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer).

**Genetics Nomenclature Update**
The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

| Previous | Updated | Definition |
|---|---|---|
| Mutation | Disease-associated variant | Disease-associated change in the DNA sequence |
| | Variant | Change in the DNA sequence |
| | Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

| Variant Classification | Definition |
|---|---|
| Pathogenic | Disease-causing change in the DNA sequence |
| Likely pathogenic | Likely disease-causing change in the DNA sequence |
| Variant of uncertain significance | Change in DNA sequence with uncertain effects on disease |
| Likely benign | Likely benign change in the DNA sequence |

| Variant Classification | Definition |
|---|---|
| Benign | Benign change in the DNA sequence |

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

### Coding

There is a specific CPT code for BRAF Gene Mutation Testing when used to select BRAF Inhibitor Targeted Therapy:

- **81210**: BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)

## Description

BRAF and MEK inhibitors are drugs designed to target a somatic variant in the BRAF gene. The inhibitors were originally developed for patients with advanced melanoma. BRAF encodes a kinase component in the RAF-MEK-ERK signal transduction phosphorylation cascade. Mutated BRAF causes constitutive kinase activity, which is believed to promote oncogenic proliferation. Direct and specific inhibition of the mutated kinase has been shown to retard tumor growth significantly and may improve patient survival.

## Related Policies

- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

Table 1 summarizes the targeted treatments approved by the U.S. Food and Drug Administration for patients with melanoma along with the concurrently approved diagnostic tests. The combination agent encorafenib and binimetinib (Array BioPharma) is under review for the treatment of *BRAF* variant advanced, unresectable, or metastatic melanoma with a target action date of June 30, 2018. The combination agent of dabrafenib and trametinib (GlaxoSmithKline) was approved in May 2018 for adjuvant treatment of *BRAF* variant, resected, stage III melanoma; the agent had both breakthrough therapy and priority review designations.

**Table 1. FDA-Approved Targeted Treatments for Melanoma and Approved Companion Diagnostic Tests**

| Treatment | Indication | FDA Approval of Companion Diagnostic Test |
|---|---|---|
| Vemurafenib (Zelboraf®; Roche/Genentech and Plexxikon) | •2011: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600variants[33,] | •2011: cobas® 4800 BRAF V600 Mutation Test (Roche)[34,]<br>•2017: FoundationOne CDx™ (Foundation Medicine)[35,] |

| Treatment | Indication | FDA Approval of Companion Diagnostic Test |
|---|---|---|
| Dabrafenib (Tafinlar®; GlaxoSmithKline) | •2013: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E variants[14,]<br>•2014: Used in combination with trametinib to treat patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants<br>•2018: Used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants | •2013: THxID™ BRAF kit (bioMérieux)[34,]<br>•2017: FoundationOne CDx™ (Foundation Medicine)[35,] |
| Trametinib (Mekinist™; GlaxoSmithKline) | •2013: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants[16,]<br>•2014: Used in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants<br>•2018: Used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants | •2013: THxID™ BRAF kit (bioMérieux)[34,]<br>•2017: FoundationOne CDx™ (Foundation Medicine)[35,] |
| Cobimetinib (Cotellic®; Genentech) | •2015: Used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K variants[17,] | •2017: FoundationOne CDx™ (Foundation Medicine)[35,] |
| Binimetinib (Mektovi®; Array BioPharma) | •2018: Used in combination with encorafenib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation[36,] | •2013: THxID™ BRAF kit (bioMérieux)[34,] |
| Encorafenib (Bravtovi®; Array BioPharma) | •2018: Used in combination with binimetinib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation[37,] | •2013: THxID™ BRAF kit (bioMérieux)[34,] |

FDA: Food and Drug Administration.
FDA product code: OWD.

## Rationale

### Background

#### Melanoma

Overall incidence rates for melanoma have been increasing for at least 30 years; in 2017, there were more than 87100 new cases.[1,] In advanced (stage IV) melanoma, the disease has spread beyond the original area of skin and nearby lymph nodes. Although only a small proportion of cases are stage IV at diagnosis, the prognosis is extremely poor; 5-year survival is 15% to 20%.

### Treatment

#### Unresectable or Metastatic Melanoma

For several decades after its approval in 1975, cytotoxic chemotherapy with dacarbazine was considered the standard systemic therapy but has provided disappointingly low response rates of only 15% to 25% and median response duration of 5 to 6 months; less than 5% of responses are complete.[2] Temozolomide has similar efficacy and, unlike dacarbazine, has much better efficacy with central nervous system tumors. Recently immunotherapy with ipilimumab or with checkpoint inhibitors such as pembrolizumab and nivolumab has demonstrated superior efficacy to chemotherapy[2,3,4,5,6,] regardless of *BRAF* status and is now recommended as a potential first-line treatment of metastatic or unresectable melanoma.

Variants in the *BRAF* kinase gene are common in tumors of patients with advanced melanoma and result in constitutive activation of a key signaling pathway (RAF-MEK-ERK pathway) that is associated with oncogenic proliferation. In general, 50% to 70% of melanoma tumors harbor a *BRAF* variant; of these, 80% are positive for the *BRAF* V600E variant, and 16% are positive for *BRAF* V600K.[7,] Thus, 45% to 60% of advanced melanoma patients may respond to a BRAF inhibitor targeted to this mutated kinase.

Two BRAF inhibitors (vemurafenib, dabrafenib) and two MEK inhibitors (trametinib, cobimetinib) have been developed for use in patients with advanced melanoma. Vemurafenib (also known as PLX4032 and RO5185426) was developed using a fragment-based, structure-guided approach that allowed the synthesis of a compound with high potency to inhibit the *BRAF* V600E mutated kinase and with significantly lower potency to inhibit most of many other kinases tested.[8,] Preclinical studies have demonstrated that vemurafenib selectively blocked the RAF-MEK-ERK pathway in *BRAF* mutant cells[9,10,11,] and caused regression of *BRAF* mutant human melanoma xenografts in murine models.[8,] Paradoxically, preclinical studies also showed that melanoma tumors with the *BRAF* wild-type gene sequence could respond to mutant BRAF-specific inhibitors with accelerated growth,[9,10,11,] suggesting that it may be harmful to administer BRAF inhibitors to patients with *BRAF* wild-type melanoma tumors. Potentiated growth in BRAF wild-type tumors has not yet been confirmed in melanoma patients, because the supportive clinical trials were enrichment trials, enrolling only patients with tumors positive for the *BRAF* V600E variant.

Dabrafenib (also known as GSK2118436 or SB-590885) inhibits several kinases, including mutated forms of the BRAF kinase, with the greatest activity against V600E-mutated *BRAF*.[12,13,] In vitro and in vivo studies have demonstrated dabrafenib's ability to inhibit the growth of *BRAF* V600-variant melanoma cells.[14,]

Trametinib is an inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2. MEK kinases regulate the extracellular signal-related kinase, which promotes cellular proliferation. *BRAF* V600E and V600K variants result in constitutive activation of MEK1 and MEK2.[15,] Trametinib inhibits the growth of *BRAF* V600 variant-positive melanoma cells in vitro and in vivo.[16,]

Cobimetinib is a MEK1 and MEK2 inhibitor. Coadministration of cobimetinib and vemurafenib has resulted in increased apoptosis and reduced tumor growth of *BRAF* V600E tumor cells in vitro, and cobimetinib has prevented the vemurafenib-mediated growth of wild-type *BRAF* tumor cells in vivo.[17,]

**Resected Stage III Melanoma**

Wide local excision is the definitive surgical treatment of melanoma. Following surgery, patients with American Joint Committee on Cancer stage III melanoma may receive adjuvant therapy. Ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4, has been shown to prolong recurrence-free survival by approximately 25% compared with placebo at a median of 5.3 years in patients who had resected stage III disease.[18,] Nivolumab, a programmed cell death protein 1blocking antibody, has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months.[19,] Before the development of checkpoint inhibitor immunotherapy and targeted therapy, high-dose interferon alfa was an option for adjuvant treatment of stage III melanoma. Interferon alfa has demonstrated an improvement in overall survival but with numerous serious side effects.[20,]

**Glioma**

More than 79000 new cases of primary malignant and nonmalignant brain and other central nervous system tumors are expected to be diagnosed in the U. S. in 2017, the majority of which are gliomas.[21,] Gliomas encompass a heterogeneous group of tumors and classification of gliomas has changed over time. In 2016, the World Health Organization (WHO) updated its classification of gliomas based on both histopathologic appearance and molecular parameters.[22,] The classification ranges from grade I to IV, corresponding to the degree of malignancy (aggressiveness), with WHO grade I being least aggressive and grade IV being most aggressive.

**Treatment**

Low-grade gliomas are classified as WHO grade I or II and include pilocytic astrocytoma, diffuse astrocytoma, and oligodendroglioma. Surgical resection of the tumor is generally performed, although additional therapy with radiotherapy and chemotherapy following surgery is usually

required, except for pilocytic astrocytoma. The optimal timing of additional therapies is unclear. Many patients will recur following initial treatment, with a clinical course similar to high-grade glioma.

High-grade gliomas (WHO grade III/IV) include anaplastic gliomas and glioblastoma. Maximal surgical resection is the initial treatment followed by combined adjuvant chemoradiotherapy. Temozolomide, an oral alkylating agent, is considered standard systemic chemotherapy for malignant gliomas. The prognosis for patients with high-grade gliomas is poor; the 1-year survival in U.S. patients with anaplastic astrocytoma is about 63% and with glioblastoma is about 38%.[23,] There is a high frequency of *BRAF* V600E variants in several types of gliomas. For example, BRAF V600E variants have been found in 5% to 10% of pediatric diffusely infiltrating gliomas, 10% to 15% of pilocytic astrocytoma, 20% of gangliioglioma, and more than 50% of pleomorphic xanthoastrocytoma.[24,-29,] However, it may be rare in adult glioblastoma.[30,] There is considerable interest in targeted therapies that inhibit the RAF-MEK-ERK pathway, particularly in patients with high-grade and low-grade gliomas whose tumors are in locations that prevent full resection. Evidence from early-phase trials in patients with *BRAF* variant-positive melanoma with brain metastases have suggested some efficacy for brain tumor response with vemurafenib and dabrafenib.[31,32,] indicating that these agents might be potential therapies for primary brain tumors.

**Literature Review**
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Unresectable or Metastatic Melanoma**
When treatment is developed for a specific biologic target that characterizes only some patients with a particular disease, and a test is codeveloped to identify diseased patients with that target, clinical validity and clinical utility cannot be evaluated separately. Rather, clinical studies of treatment benefits; that use the test to select patients, provide evidence of both clinical validity and clinical utility. We reviewed the phase 3 clinical trials of treatments in which testing for the *BRAF* variant was required for selection into the trial. In the absence of clinical trials in which *both* patients with and without *BRAF* variants are entered into randomized controlled trials (RCTs) of novel therapies, we cannot be certain that the test has clinical utility because it is unknown whether the treatment would be effective in patients without *BRAF* variant. However, patients without *BRAF* variants have not been enrolled in clinical trials of *BRAF* inhibitors.

**Clinical Context and Test Purpose**
The purpose of testing for *BRAF* pathogenic variants in individuals with unresectable or metastatic melanoma is to inform a decision whether to treat with *BRAF* or MEK tyrosine kinase inhibitors or with other standard treatments for metastatic melanoma. At the time of the early trials of targeted therapy for metastatic melanoma, cytotoxic chemotherapy (e.g., dacarbazine, temozolomide) was widely used to treat metastatic melanoma and was therefore considered a comparator, although it was never demonstrated to improve survival. Chemotherapy is now generally used only in second- or third-line settings or not at all. The current standard treatment for patients with metastatic melanoma includes immunotherapy, which is effective in patients with and without BRAF V600 variants. Patients whose tumors contain a *BRAF* V600 pathogenic variant may receive a *BRAF* inhibitor and/or a MEK inhibitor instead of or following immunotherapy. There are no RCTs directly comparing *BRAF* and MEK inhibitors with

immunotherapy, and no prospective data on the optimal sequencing of *BRAF* and MEK inhibitors and immunotherapy for patients with a *BRAF* V600 pathogenic variant.

The question addressed in this evidence review is: Does testing for *BRAF* V600 pathogenic variants to select treatment improve the net health outcome in individuals with unresectable or metastatic melanoma?

The following PICOTS were used to select literature to inform this review:

**Patients**
The relevant population of interest are patients with stage IIIC or stage IV unresectable or metastatic melanoma.

**Interventions**
The cobas 4800 BRAF V600 test and THxID BRAF kit are companion diagnostics approved by the U.S. Food and Drug Administration (FDA) for selecting patients for treatment with FDA- approved BRAF or MEK inhibitors.

**Comparators**
The comparator of interest is the standard treatment for metastatic melanoma without genetic testing for *BRAF* variants.

**Outcomes**
The primary outcomes of interest are overall survival (OS) and progression-free survival (PFS). False-positive *BRAF* test results could lead to inappropriate treatment with *BRAF* and/or MEK inhibitors, which have not been shown to be effective in patients without *BRAF* V600 pathogenic variants, and also could lead to delay in treatment with immunotherapy.

**Timing**
Due to the poor prognosis of metastatic melanoma, demonstration of improvement in survival outcomes at six months and one year are important.

**Setting**
Patients suspected of having melanoma should be urgently referred for management by specialists. A multidisciplinary group of specialists involved in caring for patients with metastatic melanoma includes dermatologists, oncologists, and plastic surgeons.

**Study Selection Criteria**
Below are selection criteria for studies to assess whether a test is clinically valid.

a. The study population represents the population of interest. Eligibility and selection are described.
b. The test is compared with a credible reference standard.
c. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
d. Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic, area under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
e. Studies should also report reclassification of diagnostic or risk category.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid and Clinically Useful**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Vemurafenib**

The primary evidence of clinical validity and utility for the cobas 4800 BRAF V600 Mutation Test is provided by the phase 3 clinical trial of vemurafenib that enrolled patients testing positive for a V600 variant.

The BRAF Inhibitors in Melanoma 3 trial as reported by Chapman et al (2011) is summarized in Table 2. A total of 675 patients were randomized to vemurafenib (960 mg twice daily orally) or to dacarbazine (1000 mg/m$^2$ body surface area by intravenous infusion every 3 weeks) to determine whether vemurafenib would prolong the rate of OS or PFS compared with dacarbazine.[37] All enrolled patients had unresectable, previously untreated stage IIIC or IV melanoma with no active central nervous system metastases. Melanoma specimens from all patients tested positive for the *BRAF* V600E variant on the cobas 4800 BRAF V600 Mutation Test. Included were 19 patients with *BRAF* V600Kvariants and 1 with a *BRAF* V600D variant.

Tumor assessments, including computed tomography, were performed at baseline, at weeks 6 and 12, and every 9 weeks after that. Tumor responses were determined by investigators using Response Evaluation Criteria in Solid Tumors, version 1.1. Primary endpoints were the rate of OS and PFS. An interim analysis was planned at 98 deaths and a final analysis at 196 deaths; the published report is the interim analysis. The data and safety monitoring board determined that both coprimary endpoints had met prespecified stopping criteria and recommended that patients in the dacarbazine group be allowed to cross over to receive vemurafenib. At the time the trial was halted, 118 patients had died; median survival had not been reached. Results for OS strongly favored vemurafenib, with a hazard ratio (HR) of 0.37 (95% confidence interval [CI], 0.26 to 0.55). Adverse events in the vemurafenib group included grade 2 or 3 photosensitivity skin reactions in 12% of patients and cutaneous squamous cell carcinoma in 18%. The results of this trial comprised the efficacy and safety data supporting vemurafenib submission to FDA and established safety and effectiveness of the cobas 4800 BRAF V600 Mutation Test, resulting in approval of both the drug and companion test.

Final OS results from the BRAF Inhibitors in Melanoma 3 trial were reported by Chapman et al (2017).[38] Eighty-four (25%) of the 338 dacarbazine patients crossed over to vemurafenib, and overall 173 (51%) of the 338 patients in the dacarbazine group and 175 of the 337 patients (52%) in the vemurafenib group received subsequent anticancer therapies, most commonly ipilimumab. Median OS without censoring at crossover was 13.6 months (95% CI, 12.0 to 15.4) in vemurafenib vs 10.3 months (95% CI, 9.1 to 12.8 months) in dacarbazine (HR=0.81; 95% CI, 0.68 to 0.96; p=0.01).

**Table 2. Phase 3 RCTs of BRAF and MEK Inhibitors for BRAF-Positive Advanced Melanoma**

| Study/Year | FU, mo | Group | N | OS (95% CI) | PFS (95% CI), mo | ORR (95% CI) |
|---|---|---|---|---|---|---|
| **Vemurafenib** | | | | | | |
| Chapman et al (2011)[37] | 6 | Vemurafenib | 337 | 84% (78% to 89%) | 5.3[a] | 48% (42% to 55%) |
| | | Dacarbazine | 338 | 65% (56% to 73%) | 1.6[a] | 5% (3% to 9%) |
| | | Hazard ratio | | 0.37 (0.26 to 0.55) | 0.26 (0.20 to 0.33) | NA |
| | | p | | <0.001 | <0.001 | NA |
| Dabrafenib | | | | | | |

| Study/Year | FU, mo | Group | N | OS (95% CI) | PFS (95% CI), mo | ORR (95% CI) |
|---|---|---|---|---|---|---|
| Hauschild et al (2012)[39] | 4.9[a] 0-9.9[b] | Dabrafenib | 187 | 89% | 5.1[a] | 50% (42.4% to 57.1%) |
| | | Dacarbazine | 63 | 86% | 2.7[a] | 6% (1.8% to 15.5%) |
| | | Hazard ratio | | 0.61 (0.25 to 1.48) | 0.33 (0.20 to 0.54) | NA |
| | | p | | NR | <0.001 | NA |
| Trametinib | | | | | | |
| Flaherty et al (2012)[40] | 6 | Trametinib | 214 | 81% | 4.8 (4.3 to 4.9)[a] | 22% (17% to 28%) |
| | | Chemotherapy[c] | 108 | 67% | 1.5 (1.4 to 2.7)[a] | 8% (4% to 15%) |
| | | Hazard ratio | | 0.54 (0.32 to 0.92) | 0.47 (0.34 to 0.65) | NA |
| | | p | | 0.01 | <0.001 | NA |
| **Dabrafenib plus trametinib** | | | | | | |
| Long et al (2015)[41] | | Dabrafenib plus trametinib | 211 | 74% | 11.0 | NA |
| | | Dabrafenib | 212 | 68% | 8.8 | NA |
| | | Hazard ratio | | 0.71 (0.55 to 0.92) | 0.67 (0.53 to 0.84) | NA |
| | | p | | 0.01 | <0.001 | NA |
| Robert et al (2015)[42] | NR | Dabrafenib plus trametinib | 352 | 72% | 11.4 | 64% |
| | | Vemurafenib | 352 | 65% | 7.3 | 51% |
| | | Hazard ratio | | 0.69 (0.53 to 0.89) | 0.56 (0.46 to 0.69) | NA |
| | | p | | 0.005 | 0.001 | 0.001 |
| **Vemurafenib plus cobimetinib** | | | | | | |
| Ascierto et al (2016)[43] | 14[a] | Vemurafenib plus cobimetinib | 248 | 22.3% (20.3% to NE) | 12.3 (9.5 to 13.4) | 68% (61% to 73%) |
| | | Vemurafenib | 247 | 17.4% (15.0% to 19.8%) | 7.2 (5.6 to 7.5) | 45% (38% to 51%) |
| | | Hazard ratio | | 0.70 (0.55 to 0.90) | 0.58 (0.46 to 0.72) | NA |
| | | p | | 0.005 | <0.001 | <0.001 |
| **Encorafenib plus binimetinib** | | | | | | |
| Dummer et al (2018)[44] | 17[a] | Encorafenib plus binimetinib | 192 | NR | 14.9 (11.0 to 18.5) | 63% (56% to 70%) |
| | | Encorafenib | 194 | NR | 9.6 (7.5 to 14.8) | 51% (43% to 58%) |
| | | Vemurafenib | 191 | | 7.3 (5.6 to 8.2) | 40% (33% to 48%) |
| | | Hazard ratio[d] | | | 0.54 (0.41 to 0.71) | NR |
| | | p | | | <0.001 | |

CI: confidence interval; FU: follow-up; NA: not applicable; NE: not estimable; NR: not reported; ORR: objective response rate (including complete and partial responses); OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial.
[a] Median value.
[b] Range.
[c] Either intravenous dacarbazine 1000 mg/m$^2$ or intravenous paclitaxel 175 mg/m$^2$ every 3 weeks at investigator discretion.
[d] Compared encorafenib plus binimetinib with vemurafenib.

### Dabrafenib

One phase 3, open-label RCT of dabrafenib for advanced (stage IV or unresectable stage III) melanoma has been published;[39] the results of this trial are summarized in Table 2. The main

objective of this RCT was to compare the efficacy of dabrafenib with standard dacarbazine treatment in patients who had *BRAF* V600E-variant metastatic melanoma. Two hundred fifty patients were randomized 3:1 to oral dabrafenib 150 mg twice daily or to intravenous dacarbazine 1000 mg/m$^2$ every 3weeks. The primary outcome was PFS, and secondary outcomes were OS, objective response rate, and adverse events.

Median PFS for the dabrafenib and dacarbazine groups was 5.1 months and 2.7 months ($p < 0.001$), respectively. OS did not differ significantly between groups: 11% of patients in the dabrafenib group died compared with 14% in the dacarbazine group (HR = 0.61; 95% CI, 0.25 to 1.48). However, 28 (44%) patients in the dacarbazine arm crossed over at disease progression to receive dabrafenib. The objective response rate, defined as complete plus partial responses, was higher in the dabrafenib group (50%; 95% CI, 42.4% to 57.1%) than in the dacarbazine group (6%; 95% CI, 1.8% to 15.5%). Treatment-related adverse events of grade 2 or higher occurred in 53% of patients who received dabrafenib and in 44% of patients who received dacarbazine. Grade 3 and 4 adverse events were uncommon in both groups. The most common serious adverse events were cutaneous squamous cell carcinoma (7% vs none in controls); serious noninfectious, febrile drug reactions (3% grade 3 pyrexia vs none in controls); and severe hyperglycemia (> 250-500 mg/dL) requiring medical management in nondiabetic patients or change in management of diabetic patients (6% vs none in controls).

**Trametinib**

The clinical efficacy and safety of trametinib were assessed in the phase 3, open-label trial, improved survival with MEK inhibition in BRAF-mutated melanoma.[40] Patients with stage IV or unresectable stage IIIC cutaneous melanoma were randomized 2:1 to trametinib 2 mg orally once daily (n = 214) or to chemotherapy (n = 108), either dacarbazine 1000 mg/m$^2$ intravenously every 3 weeks or paclitaxel 175 mg/m$^2$ intravenously every 3 weeks at investigator discretion. Most patients (67%) were previously untreated. The primary efficacy endpoint was PFS; secondary endpoints included OS, overall response rate, and safety. Tumor assessments were performed at baseline and weeks 6, 12, 21, and 30 and then every 12 weeks.

Median PFS was 4.8 months (95% CI, 4.3 to 4.9 months) in the trametinib arm and 1.5 months (95% CI, 1.4 to 2.7 months) in the chemotherapy arm ($p < 0.001$) (see Table 2). Although median OS had not been reached at the time of the report publication, 6-month survival was statistically longer in the trametinib group than in the chemotherapy group ($p = 0.01$); 51 (47%) of 108 patients in the chemotherapy group had crossed over at disease progression to receive trametinib. Decreased ejection fraction or ventricular dysfunction was observed in 14 (7%) patients in the trametinib group; 2 patients had grade 3 cardiac events that led to permanent drug discontinuation. Twelve percent of the trametinib group and 3% of the chemotherapy grouped experienced grade 3 hypertension. Nine percent of patients in the trametinib group experienced ocular events (mostly grade 1 or 2), most commonly blurred vision (4%). The most common adverse events in the trametinib group were rash, diarrhea, peripheral edema, and fatigue; rash was grade 3 or 4 in 16 (8%) patients. Cutaneous squamous cell carcinoma was not observed during treatment.

**Combination BRAF Plus MEK Inhibitors**

**Dabrafenib and Trametinib**

The efficacy of combination dabrafenib plus trametinib treatment has been established with two, phase 3 clinical trials.[41, 42, 46] This combination agent was evaluated in the phase 3, open-label trial by Long et al (2014, 2015).[41, 46] In this trial, 4234 patients with unresectable stage IIC or stage IV melanoma with a *BRAF* V600E or V600K variant were randomized to dabrafenib plus trametinib or dabrafenib plus placebo. The primary endpoint was PFS, as reported in a first publication,[46] followed by a second publication in which longer-term OS was reported.[41]

Median PFS was 11.0 months in the dabrafenib plus trametinib group and 8.8 months in the dabrafenib-only group. The overall response rate was 67% in the dabrafenib plus trametinib group and 51% in the dabrafenib-only group. An interim OS analysis showed a statistically

significant difference using standard statistical criteria, but the difference did not cross the prespecified stopping boundary. The rate of cutaneous squamous cell carcinoma was lower in the dabrafenib plus trametinib group (2% vs 9%), whereas pyrexia occurred in more patients (51% vs 28%). In the longer-term study assessing OS, median survival was 25.1 months in the dabrafenib plus trametinib group and 18.7 months in the dabrafenib-only group.

Another phase 3 RCT, by Roberts et al (2015), compared dabrafenib plus trametinib with vemurafenib.[42] A total of 704 patients with metastatic melanoma with *BRAF* V600E or V600K variants were randomized equally. The trial was terminated at a preplanned interim OS analysis. The OS rate at 12 months was 72% for dabrafenib plus trametinib and 65% for vemurafenib ($p = 0.005$) (see Table 2). Median PFS was 11.4 months for dabrafenib plus trametinib and 7.3 months for vemurafenib ($p < 0.001$). The objective response rate was 64% for dabrafenib plus trametinib and 51% for vemurafenib ($p < 0.001$). Rates of severe adverse events were similar in both groups. Cutaneous squamous cell carcinoma and keratoacanthoma occurred in 1% of dabrafenib plus trametinib subjects and 18% of vemurafenib subjects.

**Vemurafenib Plus Cobimetinib**

A multicenter, randomized, double-blinded, placebo-controlled phase 3 trial evaluated vemurafenib plus cobimetinib in 495 patients with previously untreated, *BRAF* V600 variant-positive, unresectable or metastatic melanoma.[43] All patients received vemurafenib 960 mg orally twice daily on days 1 to 28 and were randomized 1:1 to also receive cobimetinib 60 mg once daily on days 1 to 21 or to receive placebo. The primary outcome was PFS. Analyses were done on the intention-to-treat population. Median follow-up was 14 months (see Table 2). PFS was significantly increased with vemurafenib plus cobimetinib compared with vemurafenib plus placebo (median PFS, 12.3 months vs 7.2 months; HR = 0.58; 95% CI, 0.46 to 0.72; $p < 0.001$). Median OS was 22 months for vemurafenib plus cobimetinib and 17 months for vemurafenib plus placebo (HR = 0.70; 95% CI, 0.55 to 0.90; $p = 0.005$). Serious adverse events were reported in 92 (37%) patients in the vemurafenib plus cobimetinib group and 69 (28%) patients in the vemurafenib plus placebo group. The most common serious adverse events in the vemurafenib plus cobimetinib group were pyrexia and dehydration. The most common grade 3 or 4 adverse events occurring in the vemurafenib plus cobimetinib group were γ-glutamyl transferase increase, blood creatine phosphokinase increase, and alanine transaminase.

**Encorafenib Plus Binimetinib**

Dummer et al (2018) reported on results of COLUMBUS, a phase 3 RCT comparing encorafenib, a *BRAF* inhibitor, alone or in combination with the MEK inhibitor binimetinib, with vemurafenib in patients who had advanced *BRAF* V600-variant unresectable or metastatic melanoma.[44] The COLUMBUS trial was conducted in 162 hospitals in 28 countries between 2013 and 2015; patients were randomized (1:1:1) to oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily (n = 192), oral encorafenib 300 mg once daily (n = 194), or oral vemurafenib 960 mg twice daily (n = 191). The primary outcome was PFS for encorafenib plus binimetinib vs vemurafenib. Analyses were done on the intention-to-treat population. Median follow-up was 17 months. PFS was significantly increased with encorafenib plus binimetinib compared with vemurafenib (median PFS = 14.9 months vs 7.3 months in the vemurafenib group; HR = 0.54; 95% CI, 0.41 to 0.71; $p < 0.001$; see Table 2). OS was not reported. The most common grade 3 or 4 adverse events were increased γ-glutamyltransferase (9%), increased creatine phosphokinase (7%), and hypertension (6%) in the encorafenib plus binimetinib group; palmoplantar erythrodysesthesia syndrome (14%), myalgia (10%), and arthralgia (9%) in the encorafenib group; and arthralgia (6%) in the vemurafenib group.

**BRAF Plus MEK Inhibitors vs Immunotherapy**

For patients who have *BRAF* V600 variant-positive unresectable or metastatic melanoma, guidelines have suggested that both immunotherapy and *BRAF* plus MEK inhibitors are appropriate first-line therapies. We found no RCTs directly comparing *BRAF* and MEK inhibitors with immunotherapy. Network meta-analyses providing indirect comparisons are discussed below.

Amdahl et al (2016) reported on a network meta-analysis of RCTs comparing dabrafenib plus trametinib in previously untreated patients with other first-line treatments approved by Health Canada as of February 2015 (dabrafenib, vemurafenib, trametinib, ipilimumab, dacarbazine) for submission to Canadian reimbursement authorities.[47] Seven studies (total n = 2834 patients) were included. Bayesian network meta-analyses were performed to estimate HRs for PFS and OS. The combination of dabrafenib plus trametinib was associated with prolonged PFS and OS compared with all other first-line therapies analyzed. For PFS, the HRs (95% credible interval) favoring dabrafenib plus trametinib were 0.23 (0.18 to 0.29) vs dacarbazine; 0.32 (0.24 to 0.42) vs ipilimumab plus dacarbazine; 0.52 (0.32 to 0.83) vs trametinib; 0.57 (0.48 to 0.69) vs vemurafenib; and 0.59 (0.50 to 0.71) vs dabrafenib. For OS, the HRs (95% credible interval) were 0.41 (0.29 to 0.56) vs dacarbazine; 0.52 (0.38 to 0.71) vs ipilimumab plus dacarbazine; 0.68 (0.47 to 0.95) vs trametinib; 0.69 (0.57 to 0.84) vs vemurafenib; and 0.72 (0.60 to 0.85) vs dabrafenib. Nivolumab, pembrolizumab, and cobimetinib were not approved in Canada when the analysis was conducted.

Devji et al (2017) performed a network meta-analyses comparing first-line treatments and including RCTs of treatment-naive patients in which at least 1 intervention was a *BRAF* and a MEK inhibitor or an immune checkpoint inhibitor.[48] Fifteen RCTs (total n = 6662 patients) were included. Treatments were combined into drug classes: targeted therapy (*BRAF* and/or MEK inhibitor), immunotherapy (cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4], programmed cell death protein 1 [PD-1], and/or granulocyte macrophage colony-stimulating factor), chemotherapy, and combinations of these treatments. Bayesian network meta-analyses were performed to calculate HRs for OS and PFS and odds ratios for objective response rates. The risk of bias for the included studies was low. *BRAF* plus MEK inhibition and PD-1 were both individually associated with improved OS compared with all other treatments except CTLA-4/granulocyte macrophage colony-stimulating factor; there was no significant difference in OS between *BRAF* plus MEK inhibition and PD-1 (HR = 1.02; 95% credible interval, 0.72 to 1.45). The network meta-analysis showed a significant advantage of *BRAF* plus MEK inhibition compared with all other treatment strategies for PFS and objective response rate. Chemotherapy and PD-1 had the lowest risk of serious adverse events.

Pasquali et al (2017) also compared immune checkpoint inhibitors with *BRAF* targeted therapies in a network meta-analysis that included 12 RCTs (total n = 6207 patients) reporting on anti-PD-1 antibodies, anti-CTLA-4 antibodies, *BRAF* inhibitors, and MEK inhibitors.[49] *BRAF* plus MEK inhibition was associated with longer PFS compared with *BRAF* inhibition alone and immunotherapy (*BRAF* plus MEK vs anti-CTLA-4, HR = 0.22; 95% CI, 0.12 to 0.41; *BRAF* vs MEK vs anti-PD-1 antibodies, HR = 0.38; 95% CI, 0.20 to 0.72; *BRAF* plus MEK vs *BRAF* alone, HR = 0.56; 95% CI, 0.44 to 0.70). Anti-PD-1 monoclonal antibodies were estimated to be the least toxic while the combination of anti-CTLA-4 and anti-PD-1 monoclonal antibodies was associated with the highest toxicity level.

**Section Summary: Clinical Validity and Clinical Utility**
RCTs of *BRAF* and MEK inhibitor therapy in patients selected by *BRAF* V600 variant testing have shown improvements in OS and PFS. Single-agent *BRAF* inhibitor treatment with vemurafenib and dabrafenib compared with chemotherapy has shown superior outcomes for response and PFS. Combination *BRAF* and MEK inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib have shown superior OS compared with vemurafenib alone or dabrafenib alone. There are no RCTs directly comparing *BRAF* and MEK inhibitor therapy with immunotherapy as a first-line treatment for patients with *BRAF* pathogenic variants. Network meta-analyses including indirect comparisons have suggested that *BRAF* and MEK combination therapy might prolong PFS but with higher toxicity compared with immunotherapy.

**Resected Stage III Melanoma**
As was stated, clinical validity and clinical utility are evaluated together when treatments are developed for a specific biologic target that characterizes only some patients with a particular disease, and a test is codeveloped to identify diseased patients with that target. Therefore,

phase 3 RCTs of targeted treatments are reviewed in this section in which either (1) testing for the BRAF variant was required for enrollment into the trial, or (2) RCTs in which *both* patients with and without *BRAF* variants were enrolled and treatment effects stratified by variant status are reported.

**Clinical Context and Test Purpose**
The purpose of testing for *BRAF* pathogenic variants in individuals with resected stage III melanoma is to inform a decision whether to use adjuvant treatment with *BRAF* and/or MEK tyrosine kinase inhibitors after surgical resection. Observation, as well as treatment with nivolumab or ipilimumab, are also options for resected, stage III melanoma. There are no RCTs directly comparing *BRAF* and MEK inhibitors with immunotherapy.

The question addressed in this evidence review is: Does testing for *BRAF* V600 pathogenic variants to select treatment improve the net health outcome in individuals with resected stage III melanoma?

The following PICOTS were used to select literature to inform this review:

**Patients**
The relevant population of interest are patients with stage III resected melanoma.

**Interventions**
The cobas 4800 BRAF V600 test and THxID BRAF kit are FDA-approved companion diagnostics for selecting patients for treatment with FDA-approved *BRAF* or MEK inhibitors.

**Comparators**
The comparator of interest is the standard treatment for resected stage III melanoma without genetic testing for *BRAF* variants, which includes observation, checkpoint inhibitor immunotherapy, or high-dose interferon alfa.

**Outcomes**
The primary outcome of interest is a recurrence. False-positive *BRAF* test results could lead to inappropriate treatment with *BRAF* and/or MEK inhibitors, which have not been shown to be effective in patients without *BRAF* V600 pathogenic variants, and also could lead to delay in treatment with immunotherapy.

**Timing**
The time point of interest for outcomes is at least three years.

**Setting**
Patients with resected stage III melanoma would receive care from dermatologists and oncologists.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid and Clinically Useful**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Two RCTs of *BRAF* and/or MEK inhibitors in patients with resected stage III *BRAF*-variant melanoma have been reported. Trial design characteristics are reported in Table 3; results are reported in Table 4. An appraisal of study relevance as well as design and conduct gaps are reported in Tables 5 and 6.

Long et al (2017) reported on results of COMBI-AD, a phase 3 RCT comparing adjuvant combination therapy using dabrafenib plus trametinib with placebo in 870 patients who had stage III melanoma with *BRAF* V600E or V600K variants.[50] In 2013 and 2014 when patients were being enrolled in COMBI-AD, observation was the standard of care after resection of stage III melanoma in most countries. With a median follow-up of 2.8 years, the 3-year rate of relapse-free survival was 58% in the combination group and 39% in the placebo group (HR = 0.47; 95% CI, 0.39 to 0.58; P < 0.001). OS rates at 3 years were 86% and 77%, respectively (HR = 0.57; 95% CI, 0.42 to 0.79; P < 0.001).

Maio et al (2018) reported on results of BRIM8, a phase 3 RCT comparing adjuvant vemurafenib monotherapy with placebo in 498 patients who had stage IIC, IIIA, IIIB, or IIIC *BRAF* V600 variant-positive melanoma.[51] Patients with stage IIC, IIIA, or IIIB disease were enrolled in cohort 1 (n = 314), and patients with stage IIIC disease were enrolled in cohort 2 (n = 184). As stated previously, during enrollment, observation was standard care for stage III melanoma. A hierarchical testing strategy was prespecified for the primary outcome (disease-free survival) based on the assumption that observing a biologic effect in higher risk disease (i.e., cohort 2) would suggest a treatment effect across the continuum of melanoma given the effect is already established in metastatic melanoma. In the hierarchical strategy, only a P value of 0.05 or less in cohort 2 would allow for results in cohort 1 to be considered significant. The median trial follow-up was 34 months (interquartile range, 26-42 months) in cohort 2 and 31 months (interquartile range, 26-41 months) in cohort 1. In cohort 2, median disease-free survival was 23 months (95% CI, 19 to 27 months) in the vemurafenib group and 15 months (95% CI, 11 to 36 months) in the placebo group (HR = 0.80; 95% CI, 0.54 to 1.18; P = 0.26). In cohort 1, median disease-free survival was not reached (95% CI, not estimable) in the vemurafenib group and 37 months (95% CI, 21 to not estimable) in the placebo group (HR = 0.54; 95% CI, 0.37 to 0.78); however, this result cannot be considered statistically significant because of the prespecified hierarchical testing strategy.

**Table 3. Characteristics of RCTs of BRAF and/or MEK Inhibitors for BRAF-Positive Stage III Melanoma**

| Study | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | ***BRAF* and/or MEK Inhibitor** | **Control** |
| Long et al (2017)[50]; COMBI-AD (NCT01682083) | 26 countries including U.S. | 169 | 2013-2014 | Adults with completely resected stage III melanoma with *BRAF* V600E or V600K variants:<br>• Stage IIIA: 19%<br>• Stage IIIB: 39%<br>• Stage IIIC: 41%<br>• Stage III unspecified: 1% | Dabrafenib (150 mg bid) plus trametinib (2 mg qd) for 12 mo (n=438) | Matching placebos (n=432) |
| Maio et al (2018)[51]; BRIM8 (NCT01667419) | 23 countries including U.S. | 124 | 2012-2015 | Adults with completely resected stage IIC, IIIA, or IIIB (cohort 1) or stage IIIC (cohort 2) melanoma with *BRAF* V600E or V600K variants<br>• Cohort 1:<br>o Stage IIC: 9%<br>o Stage IIIA: 24%<br>o Stage IIIB: 68%<br>• Cohort 2: | • Cohort 1: n=157<br>• Cohort 2: n=93<br>• Vemurafenib (960 mg bid) for 12 mo | • Cohort 1: n=157<br>• Cohort 2: n=91<br>• Matching placebo |

| Study | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | ***BRAF* and/or MEK Inhibitor** | **Control** |
| | | | | o Stage IIIC: 100% | | |

bid: twice daily; qd: every day; RCT: randomized controlled trial.

**Table 4. Results of RCTs of BRAF and/or MEK Inhibitors for BRAF-Positive Stage III Melanoma**

| Study | Median Recurrence-Free Survival, mo | Distant Metastasis | Death | SAEs |
|---|---|---|---|---|
| | **Recurrence or Death** | **% Over Study Period** | **% Over Study Period** | |
| Long et al (2017)[50] | | | | |
| N | 870 | 870 | 870 | 867 |
| Dabrafenib plus trametinib (95% CI) | Not yet reached (44.5 to NE) | 25% | 14% | 36% |
| Control (95% CI) | 16.6 (12.7 to 22.1) | 35% | 22% | 10% |
| TE (95% CI); p | HR=0.47 (0.39 to 0.58); <0.001 | HR=0.51 (0.40 to 0.65); <0.001 | HR=0.57 (0.42 to 0.79); <0.001 | NR |
| | **Recurrence, New Primary Melanoma, or Death** | **Median, mo** | **% at 2 Years** | |
| Maio et al (2018)[51] | | | | |
| Cohort 1 (stage IIC, IIIA, IIIB) | | | | |
| N | 314 | 314 | 314 | 494[b] |
| Vemurafenib | Not yet reached (NE) | Not yet reached (NE) | 93 (89% to 98%) | 16% |
| Control | 36.9 (21.4 to NE) | Not yet reached (NE) | 87 (81% to 92%) | 10% |
| TE (95% CI); p | HR=0.54 (0.37 to 0.78)[a] | HR=0.58 (0.37 to 0.90); 0.01 | NR | NR |
| Cohort 2 (stage IIIC) | | | | |
| N | 184 | 184 | 184 | See above[b] |
| Vemurafenib | 23.1 (18.6 to 26.5) | 37.2 (22.1 to NE) | 84% (76% to 92%) | |
| Control | 15.4 (11.1 to 35.9) | 30.7 (24.5 to NE) | 85% (78% to 93%) | |
| TE (95% CI); p | HR=0.80 (0.54 to 1.18); 0.26[a] | HR=0.91 (0.57 to 1.44); 0.68 | NR | |

CI: confidence interval; HR: hazard ratio; NE: not estimable; NR: not reported; RCT: randomized controlled trial; SAE: serious adverse event; TE: treatment effect.
[a] Hierarchical testing of cohort 2 before cohort 1 was prespecified for this outcome. Because the HR in cohort 2 was not statistically significantly different than 1, the test in cohort 1 cannot be regarded as significant.
[b] Cohorts 1 and 2 combined for safety analyses.

**Table 5. Relevance Limitations of RCTs of BRAF and/or MEK Inhibitors for BRAF-Positive Stage III Melanoma**

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Duration of FU[e] |
|---|---|---|---|---|---|
| Long et al (2017)[50] | | | 2. Trial was conducted before immunotherapy became more widely used in stage III melanoma | | |
| Maio et al (2018)[51] | | | 2. Trial was conducted before immunotherapy became more widely used in stage III melanoma | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
FU: follow-up; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

**Table 6. Study Design and Conduct Limitations of RCTs of BRAF and/or MEK Inhibitors for BRAF-Positive Stage III Melanoma**

| Study | Selection[a] | Blinding[b] | Delivery of Test[c] | Selective Reporting[d] | Data Completeness[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Long et al (2017)[50] | | | | | | |
| Maio et al (2018)[51] | | | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
RCT: randomized controlled trial.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

### Section Summary: Clinically Valid and Clinically Useful

RCTs of *BRAF* and MEK inhibitor therapy in stage III melanoma patients selected by RAF V600 variant testing have shown reductions in recurrence risk. One well-conducted RCT of combination *BRAF* and MEK inhibitor treatment with dabrafenib plus trametinib has shown superiority for recurrence risk and OS in *BRAF* variant-positive, stage III patients compared with placebo. Single-agent *BRAF* inhibitor treatment using vemurafenib compared with placebo showed numeric benefit for disease-free survival in patients with stage IIC, IIIA, or IIIB *BRAF* V600 variant-positive melanoma, but this result must be considered exploratory given the lack of statistically significant benefit in stage IIIC disease and the hierarchical statistical testing strategy. There are no RCTs directly comparing *BRAF* and MEK inhibitor therapy with immunotherapy as an adjuvant treatment for stage III patients with *BRAF* pathogenic variants.

### Glioma

When treatment is developed for a specific biologic target that characterizes only some patients with a particular disease, and a test is codeveloped to identify diseased patients with that target, clinical validity and clinical utility cannot be evaluated separately. Rather, clinical studies of treatment benefit; that use the test to select patients provide evidence of both clinical validity and clinical utility We reviewed the phase 3 clinical trials of treatments in which testing for the *BRAF* variant was required for selection into the trial. In the absence of clinical trials in which *both* patients with and without *BRAF* variants are entered into RCTs of novel therapies, we cannot be certain that the test has clinical utility because it is unknown whether the treatment would be effective in patients without *BRAF* variant. However, patients without *BRAF* variants have not been enrolled in clinical trials of *BRAF* inhibitors.

### Clinical Context and Test Purpose

The purpose of testing for *BRAF* pathogenic variants in individuals with glioma is to inform a decision whether to treat with *BRAF* or MEK inhibitors or with other standard treatments for

glioma. Standard treatment for patients with glioma includes surgical resection followed by radiotherapy and/or chemotherapy with temozolomide.

The question addressed in this evidence review is: Does testing for *BRAF* pathogenic variants to select treatment improve the net health outcome in individuals with glioma?

The following PICOTS were used to select literature to inform this review:

**Patients**
The relevant population of interest are patients with glioma, particularly patients for whom adjuvant therapy following resection is indicated or for whom resection is not possible.

**Interventions**
The intervention of interest is genetic testing for *BRAF* V600 pathogenic variants to select treatments.

**Comparators**
The comparator of interest is the standard treatment for glioma without genetic testing for *BRAF* variants.

**Outcomes**
The primary outcomes of interest are OS and PFS. False-positive *BRAF* test results could lead to inappropriate treatment with *BRAF* and/or MEK inhibitors, may not be effective in patients without *BRAF* V600 pathogenic variants, and could also lead to delay in treatment with chemotherapy.

**Timing**
For low-grade glioma, the time point of interest for survival outcomes is at least five years. Due to the poor prognosis of high-grade glioma, demonstration of improvement in survival outcomes at one year is important.

**Setting**
Patients diagnosed gliomas should be referred for treatment by specialists experienced in the management of glioma. This will likely consist of a multidisciplinary group of physicians including neurologists, neurosurgeons, oncologists, and radiation oncologists.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid and Clinically Useful**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Sorafenib**
Sorafenib is a multikinase inhibitor with potent in vitro activity against both *BRAF* wild-type and V600E variants as well as vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and *c-KIT*. Several phase 2, single-arm prospective studies have investigated the use of sorafenib in newly diagnosed and recurrent, adult and pediatric, and low- and high-grade gliomas in various combinations with other treatments. Results have not shown sorafenib

to be effective. Most studies did not report *BRAF* V600 variant status. Table 7 describes select prospective studies of sorafenib in glioma.

**Table 7. Prospective Studies of Sorafenib in Patients With Glioma**

| Study | Populations | N | Treatment(s) | Results (95% CI), mo | |
|---|---|---|---|---|---|
| | | | | Median PFS | Median OS |
| Karajannis et al (2014)[52] | Children with recurrent or progressive low-grade astrocytomas | 11 overall; 5 positive for constitutive *BRAF* activation (*KIAA-BRAF* fusion or *BRAF*-activating variant including *BRAF* V600E) | Sorafenib bid at 200 mg/m$^2$ per dose in continuous 28-d cycles | 2.8 (2.1 to 31.0)[a] | |
| Hottinger et al (2014)[53] | Adults with newly diagnosed high-grade glioma | 17; *BRAF* status not reported | 60-Gy RT plus TMZ 75 mg/m$^2$ per day and sorafenib 200 mg qd, 200 mg bid, or 400 mg bid | 7.9 (5.4 to 14.6) | 17.8 (14.7 to 25.6) |
| Galanis et al (2013)[54] | Adults with recurrent GBM | 54; *BRAF* status not reported | Bevacizumab 5 mg/kg per 2 wk plus sorafenib 200 mg qd or bid | 6-mo, 20.4% | 5.6 (4.7 to 8.2) |
| Zustovich et al (2013)[55] | Adults with recurrent GBM | 53; *BRAF* status not reported | TMZ 40 mg/m2 per day plus sorafenib 400 mg bid | 3.2 (1.8 to 4.8) | 7.4 (5.6 to 9) |
| Den et al (2013)[56] | High-grade glioma (primary or recurrent) with at least 2wk of RT | 18; *BRAF* status not reported | Sorafenib 200-400 mg bid plus:<br>• Primary disease, TMZ 75 mg/m$^2$ per day and 60-Gy RT<br>• Recurrent disease, 35 Gy in 10 fractions | | 18 (6 to undefined) |
| Peereboom et al (2013)[57] | Adults with recurrent or progressive GBM | 56; *BRAF* status not reported | Erlotinib 150 mg qd plus sorafenib 400 mg bid | 2.5 (1.8 to 3.7) | 5.7 (4.5 to 7.9) |
| Lee et al (2012)[58] | Adults with recurrent GBM or gliosarcoma | 18; *BRAF* status not reported | Sorafenib 800 mg qd plus temsirolimus 25 mg/wk | 8 wk (5-9 wks)[a] | |
| Hainsworth et al (2010)[59] | Adults with newly diagnosed GBM | 47; *BRAF* status not reported | 60-Gy RT and TMZ 75 mg/m$^2$ per day followed by TMZ 150 mg/m2 per day plus sorafenib 400 mg bid | 6 (3.7 to 7) | 12 (7.2 to 16) |

bid: twice daily; CI: confidence interval; GBM: glioblastoma multiforme; Gy: gray; OS: overall survival; PFS: progression-free survival; qd: every day: RT: radiotherapy; TMZ: temozolomide.
[a] Study terminated early.

### Vemurafenib, Dabrafenib, and Trametinib

Several case reports and small case series have suggested clinical benefit with vemurafenib, dabrafenib, and trametinib in patients with glioma and *BRAF* V600 pathogenic variants. Ongoing early-phase studies evaluating BRAF and MEK inhibitors are listed in Table 8.

Hyman et al (2015) published results of a multicenter phase 2 "basket" study of vemurafenib in *BRAF* V600 variant-positive nonmelanoma cancers.[59,] A total of 122 patients with *BRAF* V600

pathogenic variants were enrolled, including 8 patients with gliomas. The response was assessed by site investigators using Response Evaluation Criteria in Solid Tumors criteria. Of the 8 glioma patients, 2 died before the 1-month evaluation; 4 had a stable disease at 12, 6, 4, and 3 months and 2 had progressive disease at 2 and 7 months, all respectively.

**Section Summary: Clinical Validity and Clinically Useful**
Studies of sorafenib in patients with newly diagnosed and recurrent gliomas combined with various other treatments have not shown benefit, although most did not report *BRAF* V600 status. Evaluation of the BRAF and MEK inhibitors vemurafenib, dabrafenib, and trametinib in patients with gliomas have been limited to one phase 2 "basket" study (including eight patients with glioma), case reports, and small case series. Several early-phase studies are ongoing. Phase 3 clinical trials of targeted treatments are needed in which either (1) testing for the *BRAF* variant was required for selection into the trial or (2) patients with and without a *BRAF* variant are included, and testing for treatment interactions by variant status are prespecified.

**Summary of Evidence**
For individuals who have unresectable or metastatic melanoma who receive *BRAF* gene variant testing to select a treatment with BRAF or MEK inhibitor combination therapy, the evidence includes randomized trials. The relevant outcomes are OS, disease-specific survival, and test accuracy. Randomized phase 3 trials of BRAF inhibitor therapy in patients selected on the basis of *BRAF* variant testing have shown improvements in OS and progression-free survival. Single-agent BRAF inhibitor treatment compared with nontargeted treatments have shown superior outcomes for most endpoints. Combination BRAF and MEK inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib have shown superior OS compared with vemurafenib or dabrafenib alone. Data showing treatment effects in patients without BRAF variants do not exist; therefore, *BRAF* variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have resected stage III melanoma who receive *BRAF* gene variant testing to select a treatment with BRAF or MEK inhibitors, the evidence includes randomized trials. The relevant outcomes are OS, disease-specific survival, and test accuracy. One randomized phase 3 trial of BRAF and MEK combination therapy with dabrafenib plus trametinib in patients selected by *BRAF* variant testing has shown improvements in recurrence-free survival and OS compared with placebo. One randomized phase 3 trial of vemurafenib monotherapy did not find statistically significant differences in disease-free survival in patients with stage IIIC disease. In patients with stage IIC, IIIA, or IIIB disease, median disease-free survival was prolonged with vemurafenib, but this result was considered exploratory. Data showing treatment effects in patients without BRAF variants do not exist; therefore, *BRAF* variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have glioma who receive *BRAF* gene variant testing to select a treatment with BRAF or MEK inhibitors, the evidence includes small, prospective, uncontrolled studies and case reports. The relevant outcomes are OS, disease-specific survival, and test accuracy. Studies assessing the use of sorafenib in patients with newly diagnosed and recurrent gliomas combined with various other treatments have not shown benefit, although most did not report *BRAF* V600 variant status. Evaluation of the BRAF and MEK inhibitors vemurafenib, dabrafenib, and trametinib in patients with gliomas has been limited to a phase 2 "basket" study, including eight patients with glioma, as well as case reports and small case series. Early reports have suggested clinical benefit, but confirmatory randomized controlled trials are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Supplemental Information

### Practice Guidelines and Position Statements

The National Comprehensive Cancer Network Guidelines for melanoma (v.2.2018) recommends *BRAF* variant status should be tested "using an FDA-approved [Food and Drug Administration] test or by a facility approved by CLIA [Clinical Laboratory Improvement Amendments] facility."[60] Combination dabrafenib plus trametinib and combination vemurafenib plus cobimetinib therapies have a category 1 recommendation as a preferred regimen for advanced or metastatic melanoma. Vemurafenib and dabrafenib also have category 1 recommendations for advanced or metastatic melanoma. The National Comprehensive Cancer Network also recommends dabrafenib plus trametinib combination therapy as an option for patients with stage III melanoma who have a *BRAF* V600-activating variant and sentinel lymph node metastasis greater than 1 mm (category 1).

The National Comprehensive Cancer Network (2019) updated the melanoma guidelines to be specific to cutaneous melanoma (v.2.2019).[61] The guidelines state, "for patients with cutaneous melanoma who are without evidence of disease," a mutational analysis of the primary lesion for BRAF is not recommended, "unless required to guide adjuvant or other systemic therapy or consideration of clinical trials." However, for patients who are symptomatic and/or have quickly progressing melanoma, testing for BRAF V600 could be indicated; BRAF/MEK inhibitors have shorter response time compared with checkpoint immunotherapies and may be the preferred treatment.[62]

Network guidelines for central nervous system cancers (v.1.2018) indicate the following on the use of BRAF molecular markers to guide treatment decisions for primary brain cancers: "BRAF V600E tumors may respond to BRAF inhibitors such as vemurafenib, but comprehensive clinical trials are still ongoing."[63] The 2019 update (v.1.2019) includes no new recommendations regarding the use of BRAF gene variant testing.[36]

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 8.

**Table 8. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |
| ***Melanoma*** | | | |
| NCT01909453 | A 2-part Phase III Randomized, Open-Label, Multicenter Study of LGX818 Plus MEK162 Versus Vemurafenib and LGX818 Monotherapy in Patients With Unresectable or Metastatic *BRAF* V600 Mutant Melanoma (COLUMBUS) | 921 | Jan 2024 |
| NCT01667419[a] | A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients With Surgically Resected, Cutaneous *BRAF* Mutant Melanoma at High Risk for Recurrence | 475 | Oct 2020 |
| NCT02224781 | A Randomized Phase III Trial of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib at Progression in Patients With Advanced *BRAF*V600 Mutant Melanoma | 300 | Oct 2022 |
| NCT01682083[a] | COMBI-AD: A Phase III Randomized Double Blind Study of Dabrafenib (GSK2118436) in COMBInation With Trametinib (GSK1120212) Versus Two Placebos in the ADjuvant Treatment of | 852 | Mar 2023 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| | High-risk *BRAF* V600 Mutation-positive Melanoma After Surgical Resection | | |
| ***Glioma*** | | | |
| NCT01089101 | A Phase 1 and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma | 180 | Dec 2020 |
| NCT01748149[a] | PNOC-002: Safety, Phase 0, and Pilot Efficacy Study of Vemurafenib, an Oral Inhibitor of *BRAF*V600E, in Children and Young Adults With Recurrent/Refractory *BRAF*V600E- or *BRAF* Ins T Mutant Brain Tumors | 54 | Jun 2019 |
| NCT01677741[a] | Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects With Advanced *BRAF* V600-Mutation Positive Solid Tumors | 86 | Sep 2019 |
| NCT02285439 | Phase I Study of MEK162 for Children With Progressive or Recurrent Cancer and a Phase II Study for Children With Low-Grade Gliomas and Other Ras/Raf/MAP Pathway Activated Tumors | 80 | Jun 2020 |
| NCT02034110[a] | A Phase II, Open-label, Study in Subjects With *BRAF* V600E-Mutated Rare Cancers With Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib | 225 | Aug 2020 |
| NCT02465060 | Molecular Analysis for Therapy Choice (MATCH) | 6452 | Jun 2022 |
| NCT02684058 | Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With *BRAF* V600 Mutation PositiveLow Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG) | 142 | Sep 2024 |
| NCT02684058[a] | Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib Treatment in Children and Adolescent Patients With *BRAF* V600 Mutation Positive Relapsed or Refractory High Grade Glioma (HGG) | 142 | Sep 2024 |
| NCT03155620 | NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol | 1500 | Sep 2027 |

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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## Documentation for Clinical Review

**Please provide the following documentation (if/when requested):**

- History and physical and/or consultation notes including:
  - Differential diagnosis, prognosis, and cancer staging
  - Specific FDA-approved test requested (e.g., cobas 4800 BRAF V600 Mutation Test)
  - Clinical justification/reason for testing
  - Treatment plan
- Laboratory and pathology reports (including cancer staging and FDA-approved BRAF V600 mutation test results)

**Post Service**

- Results/reports of tests performed

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.*

***MN/IE***

**The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.**

| Type | Code | Description |
|---|---|---|
| **CPT®** | 81210 | BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s) |
| **HCPCS** | None | |
| **ICD-10 Procedure** | None | |

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action | Reason |
|---|---|---|
| 07/06/2012 | BCBSA Medical Policy adoption | Medical Policy Committee |
| 02/22/2013 | Coding Update | Administrative Review |
| 03/01/2013 | Policy Guideline update for clarification purposes | Medical Policy Committee |
| 04/04/2014 | Policy revision with position change | Medical Policy Committee |

| Effective Date | Action | Reason |
|---|---|---|
| 07/31/2015 | Coding update | Administrative Review |
| 02/01/2016 | Coding update | Administrative Review |
| 03/01/2016 | Policy revision without position change | Medical Policy Committee |
| 08/01/2017 | Policy title change from BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Targeted Therapy<br>Policy revision without position change | Medical Policy Committee |
| 08/01/2018 | Policy title change from BRAF Gene Mutation Testing to Select Melanoma or Glioma Patients for Targeted Therapy<br>Policy revision without position change | Medical Policy Committee |
| 09/01/2019 | Policy revision without position change | Medical Policy Committee |

## Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*