

BRAF Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Effective: October 1, 2021

Next Review: August 2022

Last Review: August 2021

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

BRAF and MEK inhibitors are drugs that were originally designed to target a variant in the *BRAF* gene found in some advanced melanoma tumors. This BRAF-variant kinase is believed to be actively involved in oncogenic proliferation, and specific inhibition of the kinase has been shown to slow tumor growth and may improve patient survival.

MEDICAL POLICY CRITERIA

- I. Testing for *BRAF* variants in tumor tissue to select melanoma patients for treatment with Food and Drug Administration (FDA)-approved BRAF or MEK inhibitors may be considered **medically necessary** for any of the following:
 - A. Metastatic (stage IV) melanoma, or
 - B. Unresectable melanoma, or
 - C. Resected stage III melanoma
- II. Testing for *BRAF* variants for all other patients with melanoma is considered **investigational**.
- III. Testing for *BRAF* variants in patients with glioma is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing?
6. Medical records related to this genetic test
 - o History and physical exam
 - o Conventional testing and outcomes
 - o Conservative treatment provided, if any

CROSS REFERENCES

1. [Genetic Testing for Lynch Syndrome and APC-associated and MUTYH-associated Polyposis Syndromes](#), Genetic Testing, Policy No. 06
2. [KRAS, NRAS, and BRAF Variant Analysis and MicroRNA Expression Testing for Colorectal Cancer](#), Genetic Testing, Policy No. 13
3. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
4. [Targeted Genetic Testing for Selection of Therapy for Non-Small Cell Lung Cancer \(NSCLC\)](#), Genetic Testing, Policy No. 56
5. [Expanded Molecular Testing of Cancers to Select Targeted Therapies](#), Genetic Testing, Policy No. 83

BACKGROUND

MELANOMA

Overall incidence rates for melanoma have been increasing for at least 30 years. 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, prognosis is poor, with a five-year survival of only 15-20%. For several decades since its approval in 1975, cytotoxic chemotherapy with dacarbazine was considered the standard systemic therapy but has low response rates of only 15-25% and median response durations of five to six months. Less than 5% of responses are complete.^[1] Temozolomide has similar efficacy with a greater ability to penetrate the central nervous system. Recently immunotherapy with ipilimumab or with checkpoint inhibitors such as pembrolizumab and nivolumab has demonstrated superior efficacy to chemotherapy^[2-6] regardless of *BRAF* status and is now recommended as one potential first-line treatment of metastatic or unresectable melanoma by the National Comprehensive Cancer Network (NCCN).^[7]

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 that is associated with oncogenic proliferation. In general, 50 to 70% of melanoma tumors harbor a *BRAF* variant and of these, 80% are positive for *BRAF* V600E and 16% are positive for *BRAF* V600K.^[8] Thus,

approximately 45% to 60% of advanced melanoma patients might respond to a BRAF inhibitor targeted to this variant kinase.

BRAF inhibitors (e.g., vemurafenib, dabrafenib) and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors (e.g., trametinib, cobimetinib) have been developed for use in patients with advanced melanoma. Vemurafenib (trade name Zelboraf®, also known as PLX4032 and RO5185426) was co-developed under an agreement between Roche (Genentech) and Plexxikon. Vemurafenib was developed using a fragment-based, structure-guided approach that allowed the synthesis of a compound with high potency to inhibit the BRAF V600E variant kinase and significantly lower potency to inhibit most of many other kinases tested.^[9] Preclinical studies demonstrated that vemurafenib selectively blocked the RAF/MEK/ERK pathway in *BRAF*-variant cells^[10-12] and caused regression of *BRAF*-variant human melanoma xenografts in murine models.^[9] Paradoxically, preclinical studies also showed that melanoma tumors with the *BRAF* wild-type gene sequence could respond to variant BRAF-specific inhibitors with accelerated growth,^[10-12] suggesting that it might 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 as the supportive clinical trials were enrichment trials, enrolling only those patients with tumors positive for the *BRAF* V600E variant.

Dabrafenib (trade name Tafinlar®, also known as GSK2118436 or SB-590885) is a BRAF inhibitor developed by GlaxoSmithKline, now Novartis.^[13, 14] Dabrafenib inhibits several kinases, including variant forms of BRAF, with greatest activity against the V600E BRAF variant. In vitro and in vivo studies demonstrated dabrafenib's ability to inhibit growth of *BRAF* V600 variant-positive melanoma cells.^[15]

Trametinib (trade name Mekinist™) is an inhibitor of MEK1 and MEK2 developed by GlaxoSmithKline. MEK kinases regulate extracellular signal-related kinase (ERK), which promotes cellular proliferation. *BRAF* V600E and V600K variants result in constitutive activation of MEK1 and MEK2.^[16] Trametinib inhibits growth of BRAF V600 variant-positive melanoma cells in vitro and in vivo.^[17]

Cobimetinib, formally GDC-0973/XL518 (trade name Cotellic®) was developed by Genentech^[18] and Exelixis^[19]. It is a MEK inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with vemurafenib. Cobimetinib is not indicated for treatment of patients with wild-type *BRAF* melanoma.

Nivolumab (OPDIVO®), developed by Bristol-Myers Squibb, is not a BRAF or MEK inhibitor, but instead inhibits the PD-1 protein on cells.^[20] PD-1 blocks the body's immune system from attacking melanoma tumors. Nivolumab is intended for patients who have been previously treated with ipilimumab and, for melanoma patients whose tumors express a *BRAF* V600 variant, for use after treatment with ipilimumab and a BRAF inhibitor.

GLIOMA

Gliomas encompass a heterogeneous group of tumors and classification of gliomas has changed over time. In 2016, World Health Organization (WHO) published an update of its classification of gliomas based on both histopathologic appearance and molecular parameters.^[21] 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.

Low-grade gliomas were historically those classified as WHO grade I or II and include pilocytic astrocytoma, diffuse astrocytoma, and oligodendroglioma. Surgical resection of the tumor is generally performed, along with additional radiation and chemotherapy following surgery except in the case of 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 one-year survival in U.S. patients with anaplastic astrocytoma is about 63% and with glioblastoma is about 38%.^[22]

There is a high frequency of *BRAF* V600E variants in several types of gliomas. For example, *BRAF* V600E variants have been found in approximately 5% to 10% of pediatric diffusely infiltrating gliomas, 10% to 15% of pilocytic astrocytoma, 20% of ganglioglioma, and more than 50% of pleomorphic xanthoastrocytoma.^[23-28] However, it may be rare in adult glioblastoma.^[29] There is considerable interest in targeted therapies that inhibit the MAPK pathway, particularly in patients with high-grade glioma 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 suggest some efficacy for brain tumor response with vemurafenib and dabrafenib,^[30, 31] indicating that these agents might be potential therapies for primary brain tumors.

REGULATORY STATUS

The FDA Centers for Devices and Radiological Health (CDRH), for Biologics Evaluation and Research (CBER), and for Drug Evaluation and Research (CDER) developed a draft guidance on in vitro companion diagnostic devices, released on July 14, 2011,^[32] to address the “emergence of new technologies that can distinguish subsets of populations that respond differently to treatment.” As stated, the FDA encourages the development of treatments that depend on the use of companion diagnostic devices “when an appropriate scientific rationale supports such an approach.” In such cases, the FDA intends to review the safety and effectiveness of the companion diagnostic test as used with the therapeutic treatment that depends on its use. The rationale for co-review and approval is the desire to avoid exposing patients to preventable treatment risk.

- **Vemurafenib**

Vemurafenib and a Class III companion diagnostic test, the cobas® 4800 *BRAF* V600 Mutation Test, were co-approved by the FDA in August 2011.^[33] The test is approved as an aid in selecting melanoma patients whose tumors carry the *BRAF* V600 variant for treatment with vemurafenib.^[34] Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 variant. The vemurafenib full prescribing information states that confirmation of a *BRAF* V600 variant using an FDA-approved test is required for selection of patients appropriate for therapy.^[35]

- **Dabrafenib**

Dabrafenib was originally FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E variant, as detected by an FDA-approved test.^[15] A 2018 updated approval indicates that it may be used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants. Dabrafenib is specifically not indicated for the treatment of patients with wild-type *BRAF* melanoma.

- **Trametinib**

Trametinib was originally FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants, as detected by an FDA-approved test.^[17] A 2018 update indicates that it may be used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants. Trametinib is specifically not indicated for the treatment of patients previously treated with BRAF inhibitor therapy.^[17]

- **Nivolumab**

Nivolumab was originally FDA-approved December 2014 for the treatment of unresectable or metastatic melanoma.^[36] Nivolumab is intended for patients who have been previously treated with ipilimumab and, for melanoma patients whose tumors express an activating BRAF V600 variant, for use after treatment with ipilimumab and a BRAF inhibitor. Nivolumab may also be used in combination with ipilimumab in patients without a *BRAF* V600 variant.

- **Cobimetinib**

Cobimetinib was FDA-approved November 2015 for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with vemurafenib, as detected by an FDA-approved test. Cobimetinib is not indicated for treatment of patients with wild-type *BRAF* melanoma.^[37]

- **Binimetinib**

Binimetinib was FDA-approved in 2018 for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with encorafenib.

- **Encorafenib**

Encorafenib was FDA-approved in 2018 for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K variant, in combination with binimetinib.

In 2014, the FDA granted accelerated approval of trametinib and dabrafenib as a combination therapy for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants, as detected by an FDA-approved test.^[38] Approval of the combination therapy was based on the demonstration of durable objective responses in a multicenter, open-label, randomized (1:1:1), active-controlled, dose-ranging trial enrolling 162 patients with histologically confirmed Stage IIIC or IV melanoma determined to be *BRAF* V600E or V600K. No more than one prior chemotherapy regimen and/or interleukin-2 were permitted. Patients with prior exposure to BRAF inhibitors or MEK inhibitors were ineligible.

In November 2015, cobimetinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variant, in combination with vemurafenib.^[37] Additionally, in 2011, ipilimumab (Yervoy®) was approved by the FDA for the treatment of patients with unresectable or metastatic melanoma. For the first time, a survival advantage was demonstrated in previously treated patients: median survival on ipilimumab of 10 months versus 6.4 months on control medication. However, side effects of ipilimumab can include severe and fatal immune-mediated adverse reactions, especially in patients who are already immune-compromised. Ipilimumab's clinical study did not test metastatic melanoma patients' tumors for *BRAF* status; therefore, it's not known what, if any, clinical relevance *BRAF* status has with respect to ipilimumab.

In 2018, the FDA approved encorafenib and binimetinib together for unresectable or metastatic melanoma with *BRAF* V600 variants.

NOTE: Currently only vemurafenib, dabrafenib, cobimetinib, nivolumab, trametinib, encorafenib, and binimetinib are FDA-approved specifically for the treatment of advanced *BRAF*-variant melanoma. There are no FDA-approved targeted therapies for *BRAF* V600 variant-positive glioma.

EVIDENCE SUMMARY

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, which refers to how the results of the diagnostic test will be used to change management of the patient, and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review is focused on the clinical validity and utility of testing.

UNRESECTABLE OR METASTATIC MELANOMA

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 and/or MEK inhibitors versus 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 although it was never demonstrated to improve survival. However, chemotherapy is now generally used only in second- or third-line settings or not at all. 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 randomized controlled trials (RCTs) directly comparing BRAF and MEK inhibitors with immunotherapy and no prospective data on optimal sequencing of BRAF and MEK inhibitors and immunotherapy for patients with a *BRAF* V600 pathogenic variant.

Clinical Validity and Utility

The clinical validity of a genetic test is its ability to accurately and reliably predict the clinically defined disorder or phenotype of interest; the clinical utility of a genetic test is the evidence of improved measurable clinical outcomes and its usefulness and added value to patient management and decision making compared with current management without genetic testing.^[39]

When a treatment is developed for a specific biological target that characterizes only some patients with a particular disease, and a test is co-developed to identify diseased patients with that target, clinical validity and clinical utility studies are no longer separate and sequential. Rather, the clinical studies of treatment benefit, which use the test to select patients, provide evidence of both clinical validity and clinical utility.

Nivolumab

Larkin (2015a) published results systematic review and meta-analysis to evaluate the efficacy and safety of nivolumab in patients with wild-type *BRAF* and variant *BRAF* metastatic melanoma.^[40] The analysis included four trials: three phase 1 studies and one phase 3 trial known as CheckMate 037. Four hundred and forty patients from these trials with unresectable state III or stage IV melanoma who had been tested for *BRAF* variants were included in this review. Of a total of 440 patients, 334 were *BRAF* wild-type and 106 were positive for *BRAF* V600 variant. With the exception of prior *BRAF* inhibitor therapy, the demographics were well balanced between the two cohorts. In patients evaluable for response, the objective response rates were 34.6% (95% confidence interval [CI] 28.3 to 41.3) for the 217 patients with wild-type *BRAF* status and 29.7% (95% CI 19.7 to 41.5) for the 74 with variant *BRAF* status. The objective response rates did not seem to be affected by prior *BRAF* inhibitor therapy, prior ipilimumab therapy, or PD-1 ligand 1 (PD-L1) status of the tumor. The median duration of objective response was 14.8 months (95% CI 11.1 to 24.0 months) for wild-type *BRAF* and 11.2 months (95% CI 7.3 to 22.9 months) for variant *BRAF*. Median time to objective response was 2.2 months in both patient groups. The incidence of treatment-related adverse events of any grade was 68.3% in the wild-type *BRAF* group and 58.5% in the variant *BRAF* group, with grade 3 or 4 adverse events (AEs) in 11.7% and 2.8% of patients, respectively. Treatment-related AEs of any grade that occurred in at least 5% of patients in either group were fatigue, pruritus, rash, and diarrhea.

The overall survival (OS) in the CheckMate 037 trial, which compared outcomes with nivolumab treatment to those with chemotherapy, was reported by Larkin (2017).^[41] The patients were stratified by *BRAF* status, PD-L1 expression, and prior cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) therapy response, and 272 patients were randomized to nivolumab and 133 were randomized to the investigator's choice of chemotherapy. Treatment continued until patients had disease progression or unacceptable toxicity, and there was approximately two years of follow-up. The nivolumab group had a higher frequency of brain metastasis (20% vs. 14% in the chemotherapy group) and increased lactate dehydrogenase levels (52% vs. 38% in the chemotherapy group) at baseline, and more patients in the chemotherapy group received anti-PD-1 agents after therapy assignment (41% vs. 11% in the nivolumab group). Although overall response rate and median duration of response were higher in the nivolumab group than in the chemotherapy group (27% vs. 10% and 32 months vs. 13 months, respectively), there were no significant differences in OS or progression-free survival (PFS) between groups.

Larkin (2015b) published results from a randomized, double-blind, phase 3 trial, called CheckMate067, that included 945 previously untreated patients with unresectable stage III or IV melanoma and compared nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone.^[42] PFS and OS were coprimary end points of the trial. The median PFS was 11.5 months (95% CI 8.9 to 16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI 2.8 to 3.4) with ipilimumab (hazard ratio [HR] for death or disease progression 0.42, 99.5% CI 0.31 to 0.57, $p < 0.001$), and 6.9 months (95% CI 4.3 to 9.5) with nivolumab (HR for the comparison with ipilimumab 0.57, 99.5% CI 0.43 to 0.76, $p < 0.001$). In patients with tumors positive for the PD-L1, the median PFS was 14.0 months in the nivolumab-plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1-negative tumors, PFS was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI 8.0 to not reached] vs. 5.3 months [95% CI 2.8 to 7.1]). Treatment-related AEs of grade 3 or 4 occurred in 16.3% of the patients in the nivolumab group, 55.0% of those in the nivolumab-plus-ipilimumab group, and 27.3% of those in the ipilimumab group. The health-related quality of life (HRQoL) results from this study were reported by Shadendorf (2017), which showed no significant differences between the groups.^[43]

Hazarika (2017) reported on a trial of nivolumab for patients with unresectable or metastatic melanoma following progression on ipilimumab, and, if *BRAF* V600 variant-positive, a *BRAF* inhibitor, which led to accelerated FDA approval of nivolumab for these indications.^[44] This open-label trial showed a clinically meaningful objective response rate in 120 patients treated with 3 mg/kg intravenously every two weeks, who had at least six months of follow-up. The response rate of 31.7% (95% CI 23.5 to 43.8) was determined by a blinded independent review committee using the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. There were 13 patients that had a response duration of six months or more.

An international, double-blinded trial reported by Beaver (2017) supported the FDA approval of nivolumab as a first-line treatment for patients with unresectable or metastatic melanoma with wild-type *BRAF* V600.^[45] The trial randomized 418 patients to either nivolumab (3 mg/kg intravenously every two weeks) or dacarbazine (1,000 mg/m² intravenously every three weeks). OS was significantly higher in the nivolumab group compared with the dacarbazine group (HR 0.42, 95% CI 0.30 to 0.60, $p < 0.0001$), as was PFS (HR 0.43, 95% CI 0.34 to 0.56, $p < 0.0001$). The most common AEs in the nivolumab group were fatigue, diarrhea, constipation, nausea, rash, pruritus, and musculoskeletal pain. The authors stated that although nivolumab had a more favorable risk-benefit profile than dacarbazine, it was not clear that treatment beyond disease progression with nivolumab led to overall clinical benefit.

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. This comparative trial, known as BRIM-3, randomly assigned 675 patients to either vemurafenib (960 mg twice daily orally) or dacarbazine (1,000 mg/m² body surface area by intravenously every three weeks) to compare the rates of overall or PFS for the two medications.^[39] All enrolled patients had unresectable, previously untreated Stage IIIc or IV melanoma with no active central nervous system (CNS) 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 the *BRAF* V600K variant and one with a *BRAF* V600D variant. Final OS results from BRIM-3 were reported by Chapman (2017).^[46] 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, $p=0.01$).

Tumor assessments including computed tomography (CT) were performed at baseline, at weeks 6 and 12, and every 9 weeks thereafter. Tumor responses were determined by the investigators according to RECIST v.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, reporting 118 deaths. The median survival had not been reached. AEs in the vemurafenib group included grade 2 or 3 photosensitivity skin reactions in 12% of patients and cutaneous squamous cell carcinoma in 18% of patients. The Data and Safety Monitoring Board determined that both co-primary endpoints had met prespecified criteria for statistical significance and recommended that patients in the dacarbazine group be allowed to cross over and receive vemurafenib. The results of this trial comprised the data supporting the efficacy and safety of vemurafenib for submission to the FDA and established the safety and effectiveness of the cobas 4800 BRAF V600 Mutation Test, resulting in co-approval of drug and companion test.

A phase 2 trial known as BRIM-2 enrolled patients at 13 centers who had failed at least one previous treatment for metastatic melanoma.^[47] All patients were selected with the cobas 4800 BRAF V600 Mutation Test; 122 cases had *BRAF* V600E–positive melanoma, and 10 cases were positive for *BRAF* V600K. The target overall response rate (primary outcome) was 30%, with a lower boundary of the 95% CI of at least 20%. At a median follow-up of 10 months, this target was met with an overall response rate of 53% by independent review committee (95% CI 44 to 62%). At 10 months, 27% of patients were still on treatment; the majority of discontinuations were due to disease progression. The most common AEs of any grade were arthralgias (58%), skin rash (52%), and photosensitivity (52%). The most common grade 3 AEs were squamous cell carcinomas; these were seen in about 25% of patients, tended to occur in the first two months of treatment, and were managed with local excision. There were very few grade 4 AEs.

Puzanov (2015) reported a long-term follow-up phase 1 clinical trial to assess disease progression and clinical management of vemurafenib monotherapy in *BRAF* V600E melanoma patients.^[48] Patients received vemurafenib 240-1120 mg (dose escalation cohort) or 960 mg (extension cohort) orally twice daily. Clinical response was evaluated every eight weeks by RECIST. Patients with progressive disease amenable to local therapy (surgery or radiotherapy) were allowed to continue vemurafenib after progression. Forty-eight patients (escalation cohort, $n=16$; extension cohort, $n=32$) received therapeutic doses of vemurafenib (≥ 240 mg twice daily). Forty-four patients had progressive disease by the time of this analysis and four remained progression free (follow-up time 1.2 to 56.1 months). Median OS was 14 months (range 1.2 to 56.1); three- and four-year melanoma-specific survival rate in the extension cohort was 26% and 19%, respectively. Median OS was 26.0 months (range 7.7 to 56.1) among 20 patients who continued vemurafenib after local therapy. Median treatment duration beyond initial disease progression was 3.8 months (range 1.1 to 26.6). In the extension cohort, six and five patients were alive after three and four years, respectively, on vemurafenib monotherapy.

The two-year results of a multicenter, open-label safety study of vemurafenib in 3,219 patients with *BRAF* V600 variant-positive metastatic melanoma were reported by Blank (2017).^[49] All

patients had previously treated or untreated metastatic melanoma and received 960 mg of vemurafenib twice a day. The median follow-up was 32.2 months, and 3079 (96%) of patients had discontinued treatment, mainly due to disease progression. The most common AEs related to treatment were arthralgia (37%), alopecia (25%), and hyperkeratosis (23%). Squamous cell carcinoma of the skin (8%) and keratoacanthoma (8%) were the most common grade 3/4 AEs.

Dabrafenib

One phase 3 randomized controlled trial on dabrafenib for melanoma has been published.^[50] The main objective of this RCT was to study the efficacy of dabrafenib vs. standard dacarbazine treatment in patients selected to have *BRAF* V600E variant-positive metastatic melanoma. Two-hundred-fifty patients were randomized 3:1 to receive oral dabrafenib 150 mg twice daily versus intravenous dacarbazine 1,000 mg/m² every three weeks. The primary outcome was PFS and secondary outcomes were overall survival, objective response rates, and adverse events.

Median PFS for the dabrafenib and dacarbazine groups was 5.1 months and 2.7 months, 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 patients (44%) 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%) compared with the dacarbazine group (6%, 95% CI 1.8 to 15.5%). Treatment-related AEs grade 2 or higher occurred in 53% of patients who received dabrafenib and in 44% of patients who received dacarbazine. Grade 3-4 AEs were uncommon in both groups. The most common serious AEs were cutaneous squamous cell carcinoma (7% vs. none in controls); serious non-infectious, febrile drug reactions (3% grade 3 pyrexia vs. none in controls); and severe hyperglycemia (>250-500 mg/dL), requiring medical management in non-diabetic or change in management of diabetic patients (6% vs. none in controls). The results demonstrate that targeting dabrafenib against *BRAF* V600E variant-positive melanoma results in a benefit in PFS. Patients were allowed to cross over at the time of progression, and the effect of dabrafenib on OS was favorable but not statistically significant.

Trametinib

The clinical efficacy and safety of trametinib was assessed in the phase 3, open-label METRIC trial.^[51] Patients with stage IV or unresectable stage IIIC cutaneous melanoma were randomized 2:1 to receive trametinib 2 mg orally once daily (n=214) or chemotherapy (n=108), either dacarbazine 1,000 mg/m² IV every three weeks or paclitaxel 175 mg/m² IV every three 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 at weeks 6, 12, 21, and 30, and then every 12 weeks.

Median PFS was 4.8 months (95% CI 4.3 to 4.9) in the trametinib arm and 1.5 months (95% CI 1.4 to 2.7) in the chemotherapy arm, a statistically significant difference. Although median overall survival had not been reached at the time of the report publication, six-month survival was statistically longer in the trametinib group than in the chemotherapy group (p=0.01); 51 of 108 patients (47%) in the chemotherapy group crossed over at disease progression to receive trametinib. In the trametinib and chemotherapy groups, AEs led to dose interruption in 35%

and 22% of patients, respectively, and to dose reduction in 27% and 10% of patients, respectively. Decreased ejection fraction or ventricular dysfunction was observed in 14 patients (7%) in the trametinib group; two patients had grade 3 cardiac events that led to permanent drug discontinuation. Twelve percent of the trametinib group and 3% of the chemotherapy group 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 AEs in the trametinib group were rash, diarrhea, peripheral edema, and fatigue; rash was grade 3 or 4 in 16 patients (8%). Cutaneous squamous cell carcinoma was not observed during treatment.

Tumor tissue was evaluated for *BRAF* variants at a central site using a clinical trial assay. Retrospective THxID *BRAF* analysis was conducted on tumor samples from 289 patients (196 [92%] in the trametinib arm and 93 [86%] in the chemotherapy arm). Reanalysis of PFS in patients who were V600E or V600K-positive by the THxID *BRAF* kit showed a treatment effect that was almost identical to the overall result by central assay. Additional analysis for discordant results assuming a worst case scenario as above yielded a hazard ratio of 0.48 (95% CI 0.35 to 0.63).^[52]

Combination BRAF and MEK Inhibition

Dabrafenib and Trametinib

Long (2016) reported the OS and clinical characteristics of *BRAF* inhibitor-naïve, long-term responders and survivors treated with dabrafenib plus trametinib in a phase 1 and 2 trial of 78 patients with *BRAF* V600 variant-positive (V600E or V600K) metastatic melanoma.^[53] In one group, 24 *BRAF* inhibitor-naïve patients received dabrafenib 150 mg twice daily plus trametinib 2 mg once daily (the 150/2 group). In group two, 54 patients were randomly assigned to each of three treatment groups: dabrafenib monotherapy, dabrafenib plus trametinib 1 mg once daily, and dabrafenib plus trametinib 2 mg once daily (the 150/2 group). For patients on the combination therapy (n=78), the PFS at 1, 2, and 3 years was 44%, 22%, and 18%, respectively, for group one (n=24) and 41%, 25%, and 21%, respectively, for group two (n=54). Median OS was 27.4 months in group one and 25 months in group two. OS at one, two, and three years was 72%, 60%, and 47%, respectively, for group one and 80%, 51%, and 38%, respectively, for group two. The median OS for *BRAF* inhibitor-naïve variant-positive patients who received dabrafenib plus trametinib (150/2) in the randomized phase 2 part of this study was more than two years, and the two- and three-year survival rates were 51% and 38%, respectively.

Menzies (2015) assessed the features associated with efficacy and long-term survival in *BRAF* variant-positive metastatic melanoma patients treated with *BRAF* inhibitor monotherapy (dabrafenib [n=70]; or vemurafenib [n=41]) or combined dabrafenib and trametinib (n=31).^[54] One hundred and nineteen patients (84%) had the V600E variant, whereas 23 patients (16%) had either V600K or V600R. The median follow-up was 15.7 months (range 0.6 to 60.5 months). Patients treated with monotherapy were grouped together for analysis. The two-, three-, and four-year OS rates were 43%, 24%, and 24%, respectively. Factors associated with longer PFS and OS were female sex and a normal pretreatment serum lactate dehydrogenase level. The *BRAF* V600E genotype was independently associated with longer PFS (HR 0.51, p=0.006) but not OS. One of the limitations of this study is the heterogeneous patient population in the monotherapy group; the type of monotherapy provided was not accounted for in the analysis.

A similar study by Schadendorf (2017) examined factors associated with clinical outcomes for dabrafenib and trametinib combination therapy in a pooled analysis of phase 3 trials.^[55] They found that baseline lactate dehydrogenase level and the number of organ sites were significantly associated with PFS and OS. Individuals with normal LDH, baseline sum of lesion diameters of less than 66 mm, and less than three organ sites (n=183 [33% of 563]) had the most favorable prognosis, with 42% demonstrating three-year PFS.

Johnson (2015) published results from an open-label phase 1/2 trial to assess the safety and efficacy of dabrafenib and trametinib in patients who had received prior BRAF inhibitor treatment.^[56] Seventy-one patients were enrolled in the study and treated with combination therapy after disease progression with BRAF inhibitor treatment administered before study enrollment (part B; n=26) or after cross-over at progression with dabrafenib monotherapy (part C, n=45). In parts B and C, confirmed objective response rates (ORR) were 15% (95% CI 4% to 35%) and 13% (95% CI 5% to 27%), respectively; an additional 50% and 44% experienced stable disease \geq 8 weeks, respectively. The median PFS was 3.6 months (95% CI 2 to 4), and median overall survival was 11.8 months (95% CI 8 to 25) from cross-over. Patients who previously received dabrafenib for at least six months had superior outcomes with the combination compared with those treated for fewer than six months; median PFS was 3.9 (95% CI 3 to 7) versus 1.8 months (95% CI 2 to 4, HR 0.49, p=0.02), and ORR was 26% (95% CI 10% to 48%) versus 0% (95% CI 0% to 15%).

A study by Schreuer (2017) also evaluated dabrafenib plus trametinib in a small, single-arm, open-label study with 25 pretreated patients. In this case, patients had previously experienced disease progression on BRAF inhibitors with or without MEK inhibitor use.^[57] After patients were off treatment for 12 weeks or more, they began dabrafenib and trametinib therapy. The primary endpoint was overall response rate, as determined using RECIST v.1.1., on two occasions, at least 28 days after the first recorded response. Eight patients had a partial response, and 10 patients appeared to have stable disease during this period. Grade 3 AEs occurred in two patients (pyrexia and panniculitis), and there were no grade 4 or 5 AEs.

Robert (2015) published results from an open-label phase 3 clinical trial to examine overall survival in patients with metastatic melanoma.^[58] There were 704 patients with a *BRAF* V600 variant that received either a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or vemurafenib (960 mg twice daily) orally as first-line therapy. At the preplanned interim overall survival analysis, which was performed after 77% of the total number of expected events occurred, the OS rate at 12 months was 72% (95% CI 67 to 77) in the combination-therapy group and 65% (95% CI 59 to 70) in the vemurafenib group. The study was stopped in July 2014 because the prespecified interim stopping boundary had been crossed. Median PFS was 11.4 months in the combination-therapy group and 7.3 months in the vemurafenib group (HR 0.56, 95% CI 0.46 to 0.69, p<0.001). The objective response rate was 64% in the combination-therapy group and 51% in the vemurafenib group (p<0.001). Rates of severe AEs and study-drug discontinuations were similar in the two groups. Cutaneous squamous-cell carcinoma and keratoacanthoma occurred in 1% of patients in the combination-therapy group and 18% of those in the vemurafenib group.

Schadendorf (2015) reported results from a double-blind randomized phase 3 COMBI-d and COMBI-v trials that investigated the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with *BRAF* V600E/K-variant metastatic melanoma.^[59] These trials showed significantly prolonged PFS for the combination. Health-related quality of life was evaluated by questionnaire at baseline, during study treatment, at progression, and

post progression to assess various dimensions (global health/quality of life, functional status, and symptom impact). Questionnaire completion rates were >95% at baseline, >85% to week 40 and >70% at disease progression. Baseline scores across both arms were comparable for all dimensions. Global health dimension scores were significantly better at weeks 8, 16 and 24 for patients receiving the combination during treatment and at progression. The majority of functional dimension scores (physical, social, role, emotional and cognitive functioning) trended in favor of the combination. Pain scores were significantly improved and clinically meaningful (6- to 13-point difference) for patients receiving the combination for all follow-up assessments compared to those receiving dabrafenib monotherapy. For other symptom dimensions (nausea and vomiting, diarrhea, dyspnea, and constipation), scores trended in favor of dabrafenib monotherapy. A three-year survival and safety analysis from this study was reported by Long (2017). The PFS at three years was higher in the combination group (22%) than in the monotherapy group (12%), as was OS (44% vs. 32%, respectively).^[60] The five-year outcomes from these trials were reported by Robert (2019).^[61] Among those receiving the drug combination (n=563), the PFS at four years was 21% (95% CI 17 to 24), and at five years was 19% (95% CI 15 to 22). Overall survival at five years was 34% (95% CI 30 to 38), and 19% of the patients had a complete response.

Long (2015) published results from a double-blind phase 3 industry sponsored study at 113 sites in 14 countries.^[62] The 423 enrolled participants were previously untreated patients with BRAF V600E or V600K variant-positive unresectable tumors and were randomly assigned to receive either dabrafenib and trametinib (n=211) or dabrafenib only (n=212). Overall survival was 74% at one year and 51% at two years in the dabrafenib and trametinib group versus 68% and 42%, respectively, in the dabrafenib only group. Based on 301 events, median PFS was 11.0 months (95% CI 8.0 to 13.9) in the dabrafenib and trametinib group and 8.8 months (5.9 to 9.3) in the dabrafenib only group (HR 0.67, 95% CI 0.53 to 0.84, p=0.0004, unadjusted for multiple testing). Treatment-related AEs occurred in 181 (87%) of 209 patients in the dabrafenib and trametinib group and 189 (90%) of 211 patients in the dabrafenib only group; the most common were pyrexia (108 patients, 52%) in the dabrafenib and trametinib group, and hyperkeratosis (70 patients, 33%) in the dabrafenib only group. Grade 3 or 4 AEs occurred in 67 (32%) patients in the dabrafenib and trametinib group and 66 (31%) patients in the dabrafenib only group.

An open-label Phase 1/2 trial examined the pharmacokinetics, safety, and efficacy of dabrafenib plus trametinib combination therapy in 247 patients with metastatic (stage IV) melanoma and BRAF V600E or V600K variants.^[63] Maximum tolerated combination dosing was not reached. One dose-limiting toxic effect, recurrent neutrophilic panniculitis, occurred in 24 patients who received the highest dose level (dabrafenib 150 mg twice daily plus trametinib 2 mg daily), and this was the recommended dose for efficacy testing. Median PFS, the primary efficacy endpoint, was 9.4 months in the combination therapy group (n=54) and 5.8 months in the dabrafenib (150 mg twice daily) monotherapy group (n=54, HR 0.39, 95% CI 0.25 to 0.62, p<0.001). Complete or partial response occurred in 76% of patients in the combination therapy group and 54% of the monotherapy group (p=0.03). Median duration of response was 10.5 (95% CI 7.4 to 14.9) months and 5.6 months (95% CI 4.5 to 7.4), respectively. Cutaneous squamous cell carcinoma occurred in 7% of the combination therapy group and 19% of the monotherapy group (p=0.09). Fever was more common in the combination therapy group (71% vs. 26% monotherapy, p<0.001).

Vemurafenib and Cobimetinib

A multicenter, double-blinded, phase 3 RCT, known as coBRIM, evaluated the combination of the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetinib in 495 patients with previously untreated, *BRAF* V600 variant-positive, unresectable or metastatic melanoma.^[64] All patients received vemurafenib 960 mg orally twice daily on days 1 to 28 and were randomized in a 1:1 ratio to also receive cobimetinib 60 mg once daily on days 1 to 21 or cobimetinib placebo. The primary outcome was PFS. Analyses were done on the intention-to-treat population. Median follow-up was 14 months. PFS was significantly increased with vemurafenib and cobimetinib compared to vemurafenib and 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 and cobimetinib versus 17 months for vemurafenib and placebo (HR 0.70, 95% CI 0.55 to 0.90, $p = 0.005$). Serious AEs were reported in 92 (37%) patients in the vemurafenib and cobimetinib group and 69 (28%) patients in the vemurafenib and placebo group. The most common serious AEs in the vemurafenib and cobimetinib group were pyrexia and dehydration. The most common grade 3 to 4 AEs occurring more frequently in the vemurafenib and cobimetinib group were γ -glutamyl transferase increase, blood creatine phosphokinase increase, and alanine transaminase.

Dréno (2017) published a report on toxicities in the coBRIM study, after a median follow-up of 18.5 months.^[65] Nearly all of the 493 patients that received treatment experienced an AE. The majority of AEs occurred during the first treatment cycle. The frequency of serious AEs (grade 3 and above) was higher in the combination therapy group than the monotherapy group (75% and 61%, respectively). Common AEs, including rash, diarrhea, photosensitivity, pyrexia, and serous retinopathy decreased in incidence over time. A study by de la Cruz-Merino (2017) focused on patients in this trial who had serous retinopathy.^[66] There was a total of 86 serous retinopathy events in 70 patients, with the vast majority reported in the combination therapy group (79 vs. 7 events in the monotherapy group). Most retinopathy events were managed by observation and did not require discontinuation or dose modification of cobimetinib.

Larkin (2015) published results from a phase 3 trial that evaluated the combination of vemurafenib and cobimetinib in 495 patients with previously untreated, unresectable, locally advanced or metastatic, *BRAF* V600 variant-positive melanoma.^[67] Patients were randomly assigned to received vemurafenib and cobimetinib (combination group) or vemurafenib and placebo (control group). The median PFS was 9.9 months in the combination group and 6.2 months in the control group (HR for death or disease progression 0.51, 95% CI 0.39 to 0.68, $p < 0.001$). The rate of complete or partial response in the combination group was 68%, as compared with 45% in the control group ($p < 0.001$), including rates of complete response of 10% in the combination group and 4% in the control group. PFS, as assessed by independent review, was similar to investigator-assessed PFS. Interim analyses of OS showed nine-month survival rates of 81% (95% CI 75 to 87) in the combination group and 73% (95% CI 65 to 80) in the control group. Vemurafenib and cobimetinib was associated with a nonsignificantly higher incidence of AEs of grade 3 or higher, as compared with vemurafenib and placebo (65% vs. 59%), and there was no significant difference in the rate of study-drug discontinuation. The number of secondary cutaneous cancers decreased with the combination therapy.

Ribas (2014) published results from a phase 1b clinical trial to assess the safety and efficacy of combined BRAF inhibition with vemurafenib and MEK inhibition with cobimetinib in patients with advanced *BRAF* V600 variant-positive melanoma.^[68] The primary endpoint was safety of the drug combination and to identify dose-limiting toxic effects and the maximum tolerated

dose. One hundred and twenty-nine patients were included who had either recently progressed on vemurafenib or never received a BRAF inhibitor. Patients received vemurafenib twice a day continuously and cobimetinib once a day for either 14 days on and 14 days off (14/14), 21 days on and 7 days off (21/7), or continuously (28/0).

Across all dosing regimens, the most common AEs were diarrhea (83 patients, 64%), non-acneiform rash (77 patients, 60%), liver enzyme abnormalities (64 patients, 50%), fatigue (62 patients, 48%), nausea (58 patients, 45%), and photosensitivity (52 patients, 40%). Most AEs were mild-to-moderate in severity. The most common grade 3 or 4 AEs were cutaneous squamous-cell carcinoma (12 patients, 9%; all grade 3), raised amounts of alkaline phosphatase (11 patients, 9%), and anaemia (nine patients, 7%). Confirmed objective responses were recorded in 10 (15%) of 66 patients who had recently progressed on vemurafenib, with a median PFS of 2.8 months (95% CI 2.6 to 3.4). Confirmed objective responses were noted in 55 (87%) of 63 patients who had never received a BRAF inhibitor, including six (10%) who had a complete response; median PFS was 13.7 months (95% CI 10.1 to 17.5).

Encorafenib and Binimetinib

Dummer (2018) reported on results of a phase 3 COLUMBUS 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.^[69] 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 versus 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 was 14.9 months vs. 7.3 months in the vemurafenib group; HR 0.54, 95% CI 0.41 to 0.71, p<0.001). The OS was not reported. The most common grade 3 or 4 AEs 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.

Ascierto (2020) published long-term outcomes from the COLUMBUS trial.^[70] The median follow-up for overall survival was 48.8 months. Compared with vemurafenib, the combination of encorafenib plus binimetinib significantly reduced the risk of death by 39% (HR 0.61, 95% CI 0.48 to 0.79) and increased the duration of PFS (HR 0.51, 95% CI 0.39 to 0.67). The overall survival rates at three years were 47%, 41%, and 31% for encorafenib plus binimetinib, encorafenib, and vemurafenib groups, respectively. All subgroup analyses favored combination treatment with encorafenib plus binimetinib versus treatment with vemurafenib alone.

Combination BRAF and MEK inhibition with Immunotherapy

Vemurafenib and Cobimetinib with Atezolizumab

Gutzmer (2020) reported primary results from IMspire150, a phase 3, double-blind RCT of atezolizumab, vemurafenib, and cobimetinib (n=256) compared to placebo, vemurafenib, and cobimetinib (n=258) as first-line treatment for unresectable advanced *BRAF* V600-positive

melanoma.^[71] The primary endpoint was investigator-assessed PFS. The median follow-up in the overall study population was 18.9 months. At data cut-off, 327 patients had progressive disease by investigator assessment or had died, including 148 (58%) of patients in the atezolizumab group and 179 (69%) in the control group. The atezolizumab with vemurafenib and cobimetinib group experienced a median PFS per investigator assessment of 15.1 months (95% CI 0.63 to 0.97) compared to 10.6 months (95% CI 9.3 to 12.7) in the control group. A 77% concordance rate for progressive disease assessment by study investigators versus independent review committee was reported. The primary reason for discordant results (n=109) was assessment of progressive disease per study investigators but not independent review committee. The prevalence of treatment-related adverse events was comparable between the two groups. PD-L1 expression status was not significantly associated with treatment effect.

BRAF and MEK inhibition vs. Immunotherapy

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

Amdahl (2016) reported a network meta-analysis of RCTs to compare dabrafenib plus trametinib in previously untreated patients versus other first-line treatments that were approved by Health Canada as of February 2015 (dabrafenib, vemurafenib, trametinib, ipilimumab, dacarbazine) for submission to Canadian reimbursement authorities.^[72] Seven studies (total n=2,834 patients) were included. Bayesian network meta-analyses were performed to estimate hazard ratios for PFS and OS. The combination of dabrafenib and trametinib was associated with prolonged PFS and OS compared to all other first-line therapies included in analysis. For PFS, the HRs favoring dabrafenib and trametinib were: 0.23 (95% credible interval [CrI] 0.18 to 0.29) versus dacarbazine; 0.32 (95% CI 0.24 to 0.42) versus ipilimumab plus dacarbazine; 0.52 (95% CrI 0.32 to 0.83) versus trametinib; 0.57 (95% CrI 0.48 to 0.69) versus vemurafenib; and 0.59 (95% CrI 0.50 to 0.71) versus dabrafenib. For OS, the hazard ratios were: 0.41 (0.29 to 0.56) versus dacarbazine; 0.52 (95% CrI 0.38 to 0.71) versus ipilimumab plus dacarbazine; 0.68 (0.47 to 0.95) versus trametinib; 0.69 (95% CrI 0.57 to 0.84) versus vemurafenib; and 0.72 (95% CrI 0.60 to 0.85) versus dabrafenib. Nivolumab, pembrolizumab, and cobimetinib were not approved in Canada at the time the analysis was conducted.

Devji (2017) performed a network meta-analysis comparing first-line treatments and including RCTs in treatment-naïve patients in which at least one intervention was a BRAF and MEK inhibitor or an immune checkpoint inhibitor.^[73] Fifteen RCTs (total n=6,662 patients) were included. Treatments were combined into drug class: targeted therapy (BRAF and/or MEK inhibitor), immunotherapy (CTLA-4, PD-1, and/or granulocyte macrophage colony-stimulating factor [GM-CSF]), chemotherapy, and combinations of these treatments. Bayesian network meta-analyses were performed to calculate hazard ratios for OS and PFS and ORs for overall response rate. 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/GM-CSF; there was no significant difference in OS between BRAF plus MEK inhibition and PD-1 (HR 1.02; 95% CrI 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 overall response rate. Chemotherapy and PD-1 therapy had the lowest risk of serious AEs.

Pasquali (2017) also compared immune checkpoint inhibitors and BRAF-targeted therapies in a network meta-analysis including 12 RCTs (total n=6,207 patients) reporting on anti-PD-1 antibodies, antiCTLA-4 antibodies, BRAF inhibitors, and MEK inhibitors.^[74] BRAF plus MEK inhibition was associated with longer PFS compared to 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 were associated with the most toxicity.

Section Summary: Clinical Validity and Clinical Utility

RCTs of BRAF and MET inhibitor therapy in patients selected on the basis of *BRAF* V600 variant testing have shown improvements in OS and PFS. Single-agent BRAF inhibitor treatment with vemurafenib and dabrafenib compared with chemotherapy shows superior outcomes for response and PFS. Combination BRAF and MEK inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib shows superior OS when compared with either vemurafenib or dabrafenib alone. There are no RCTs directly comparing BRAF and MEK inhibitor therapy with immunotherapy as first-line treatment for patients with *BRAF* pathogenic variants. Network meta-analyses including indirect comparisons suggest that BRAF and MEK combination therapy might prolong PFS but with higher toxicity compared to immunotherapy.

RESECTED STAGE III MELANOMA

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.

Long (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.^[75] 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 three-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). The OS rates at three years were 86% and 77%, respectively (HR 0.57, 95% CI 0.42 to 0.79, p<0.001). Patient-reported outcomes for this study were reported by Schadendorf (2019).^[76] During treatment and after follow-up (range 15 to 48 months) there were no significant differences between treatment groups for European Quality of Life 5-Dimensions 3-Levels (EQ-5D-3L) visual analogue scale (EQ-VAS) or utility scores. VAS and utility scores significantly decreased in both groups at recurrence.

Maio (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.^[77] 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 to 42 months) in cohort 2 and 31 months (interquartile range, 26 to 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.

Section Summary: Clinical Validity and Clinical Utility

RCTs of BRAF and MET inhibitor therapy in stage III melanoma patients selected by *BRAF* 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 IIC 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

The purpose of testing for *BRAF* pathogenic variants in individuals with glioma is to inform a decision whether to treat with BRAF and/or MEK inhibitors versus other standard treatments for glioma. Standard treatment for patients with glioma includes surgical resection followed by radiotherapy and/or chemotherapy with temozolomide.

Analytical Validity

Currently there is no standard method for testing *BRAF* status in neuropathology. DNA-based tests for melanomas and immunohistochemistry are used. The analytic validity of these methods is described in the previous section.

Clinical Validity and Clinical Utility

Sorafenib

Sorafenib is a multikinase inhibitor with potent in vitro activity against both wild-type *BRAF* and the V600E variant, as well as vascular endothelial growth factor receptors (VEGFR), 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, low- and high-grade gliomas in various combinations with other treatments, but results have not shown sorafenib to be effective. Most studies did not report *BRAF* V600 variant status. Table 4 describes prospective studies of sorafenib in glioma.

Table 4. Prospective Studies of Sorafenib in Patients with Glioma

Author (Year)	Populations	N	Treatment(s)	Results (95% CI), mo	
				Median PFS	Median OS
Karajannis (2014) ^[78]	Children with recurrent or progressive low-grade astrocytomas	11 overall; 5 positive for constitutive <i>BRAF</i> activation (<i>KIAA-BRAF</i> fusion or <i>BRAF</i> -activating variant including <i>BRAF</i> V600E)	Sorafenib bid at 200 mg/m ² per dose in continuous 28-d cycles	2.8 (2.1 to 31.0) ^a	
Hottinger (2014) ^[79]	Adults with newly diagnosed high-grade glioma	17; <i>BRAF</i> 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 (2013) ^[80]	Adults with recurrent GBM	54; <i>BRAF</i> status not reported	Bevacizumab 5 mg/kg per 2 wk plus sorafenib 200 mg qd or bid	Six-month 20.4%	5.6 (4.7 to 8.2)
Zustovich (2013) ^[81]	Adults with recurrent GBM	53; <i>BRAF</i> status not reported	TMZ 40 mg/m ² per day plus sorafenib 400 mg bid	3.2 (1.8 to 4.8)	7.4 (5.6 to 9)
Den (2013) ^[82]	High-grade glioma (primary or recurrent) with at least 2 wk RT	18; <i>BRAF</i> status not reported	Sorafenib 200-400 mg bid plus: <ul style="list-style-type: none"> • Primary disease, TMZ 75 mg/m² per day and 60-Gy RT • Recurrent disease, 35 Gy in 10 fractions 		18 (6 to undefined)
Peereboom (2013) ^[83]	Adults with recurrent or progressive GBM	56; <i>BRAF</i> 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 (2012) ^[84]	Adults with recurrent GBM or gliosarcoma	18; <i>BRAF</i> status not reported	Sorafenib 800 mg qd plus temsirolimus 25 mg/wk	8 wk (5 to 9) ^a	

bid: twice daily; 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, Trametinib, and Binimetinib

Several case reports and small case series have suggested clinical benefit with vemurafenib, dabrafenib, trametinib, and binimetinib in patients with glioma and *BRAF* V600 pathogenic variants.

Hyman (2015) published results of a multicenter phase 2 “basket” study of vemurafenib in *BRAF* V600 variant-positive nonmelanoma cancers.^[85] A total of 122 patients with *BRAF* V600 pathogenic variants were enrolled, including eight patients with gliomas. Response was

assessed by site investigators using RECIST criteria. Of the eight glioma patients, two died before the one-month evaluation; four had stable disease at 12, 6, 4, and 3 months and two had progressive disease at two and seven months, all respectively.

Kaley (2018) published results of an open-label, nonrandomized, basket study for *BRAF* V600-mutant non-melanoma cancers, including 24 patients (median age, 32 years; 18 female and 6 male) with glioma.^[86] Patients received vemurafenib 960 mg twice per day. Confirmed objective response rate was 25% (95% CI 10 to 47) and median PFS was 5.5 months (95% CI 3.7 to 9.6).

Selumetinib

Selumetinib is an oral kinase inhibitor of MEK1/2 that is FDA-approved for the treatment of pediatric patients two years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas. Case series and phase 1 studies have been conducted in pediatric, low-grade glioma and have demonstrated tolerable toxicities.

Fangusaro (2019) published a phase 2 study of selumetinib in 50 pediatric patients with low-grade glioma with a Lansky or Karnofsky performance score greater than 60 who had failed at least one standard therapy.^[87] There were 25 patients each two strata: one that included patients with WHO grade I pilocytic astrocytoma with a *BRAF* fusion or V600E variant, and one that included patients with NF1-associated, WHO grade I or II glioma. Selumetinib was given in 28-day courses for a total of up to 26 courses. The median PFS at two years was 70% (95% CI 47% to 85%) for the *BRAF* variant group and 96% (95% CI 74% to 99%) for the NF1 group. OS was not reported.

Section Summary: Clinical Validity and Clinical Utility

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 has been limited to a “basket” study (including less than 40 patients with glioma), case reports, and small case series. Several early phase studies are ongoing and a phase 3 RCT of selumetinib compared to carboplatin/vincristine in previously untreated low-grade glioma not associated with *BRAF* V600E variants or systemic NF1 is underway. 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.^[88]

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)

NCCN guidelines for cutaneous melanoma, version 2.2021, recommend *BRAF* variant testing for patients with stage IV disease and for patients with stage III disease for whom future *BRAF*-directed therapy may be an option.^[7] Combination dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib therapies are recommended as preferred regimens for metastatic or unresectable melanoma with *BRAF* V600-activating variants, and dabrafenib/trametinib is also recommended for local and nodal recurrence.

National Comprehensive Cancer Network guidelines for central nervous system cancers, version 1.2021 recommend *BRAF* testing in the appropriate clinical context for glioma, stating

that: “Some studies have shown that tumors with a *BRAF* V600E mutation may respond to BRAF inhibitors such as vemurafenib, but ongoing trials with further clarify targeted treatment options in the presence of a *BRAF* fusion or V600E mutation.”^[89]

SUMMARY

There is enough research to show that *BRAF* variant testing can improve health outcomes for some melanoma patients by helping them to select targeted treatment. In addition, clinical guidelines based on research recommend treatment with these BRAF inhibitors in patients with a V600 *BRAF* variant. Therefore, *BRAF* variant testing may be considered medically necessary to select melanoma patients for treatment with FDA-approved BRAF inhibitors, when policy criteria are met. Testing for *BRAF* variants for all other patients with melanoma is considered investigational.

There is not enough research to show that genetic testing for targeted treatment with BRAF or MEK inhibitors can improve survival and other health outcomes for patients with glioma. In addition, there are no clinical guidelines based on research that recommend such testing. Therefore, testing for *BRAF* variants for patients with glioma is considered investigational.

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CODES

Codes	Number	Description
CPT	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
HCPCS	None	

Date of Origin: January 2012