BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Therapy

**Description of Procedure or Service**

BRAF inhibitors are drugs designed to target a somatic mutation in the *BRAF* gene of patients with advanced melanoma. BRAF codes for a kinase component in the RAF-MEK-ERK signal transduction phosphorylation cascade. The mutated version of the BRAF kinase results in constitutive activity, which is believed to be actively involved in oncogenic proliferation. Direct and specific inhibition of the mutated kinase has been shown to significantly retard tumor growth and may improve patient survival.

Overall incidence rates for melanoma have been increasing for at least 30 years; in 2013, there were more than 76,000 new cases. In advanced (Stage 4) melanoma, the disease has spread beyond the original area of skin and nearby lymph nodes. Although only a small proportion of cases are Stage 4 at diagnosis, prognosis is extremely poor; 5-year survival is about 15-20%.

Dacarbazine has long been considered the treatment standard for systemic therapy, but has disappointingly low response rates of only 15 to 25% and median response durations of 5 to 6 months; less than 5% of responses are complete. Temozolomide has similar efficacy with the exception of a much greater ability to penetrate the central nervous system.

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

Three BRAF inhibitors 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<sup>V600E</sup> mutated kinase, and significantly lower potency to inhibit most of many other kinases tested. Preclinical studies demonstrated that vemurafenib selectively blocked the RAF/MEK/ERK pathway in BRAF mutant cells and caused regression of BRAF mutant human melanoma xenografts in murine models. 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, 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<sup>V600E</sup> mutation.
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Dabrafenib (trade name Tafinlar®, also known as GSK2118436 or SB-590885) is a BRAF inhibitor developed by GlaxoSmithKline (GSK). Dabrafenib inhibits several kinases, including mutated forms of BRAF kinase, with greatest activity against V600E-mutated BRAF. In vitro and in vivo studies demonstrated dabrafenib’s ability to inhibit growth of BRAF V600-mutated melanoma cells.

Trametinib (trade name Mekinist™) is an inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 developed by GSK. MEK kinases regulate extracellular signal-related kinase (ERK), which promotes cellular proliferation. BRAF V600E and V600K mutations result in constitutive activation of MEK1 and MEK2. Trametinib inhibits growth of BRAF V600 mutation-positive melanoma cells in vitro and in vivo.

Nivolumab (Opdivo®, also known as BMS-936558, MDX-1106, or ONO-4538) is a genetically engineered, fully human immunoglobulin G4 monoclonal anti-programmed death-1 protein antibody developed by Ono Pharmaceutical and Medarex and manufactured by Bristol-Myers Squibb.

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, which was released on July 14, 2011, 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. FDA issued the finalized version of this document August 6, 2014.

Important points from the guidance include that a new therapeutic product and its corresponding companion diagnostic test should be developed together, and that both diagnostic test and therapeutic product should be approved or cleared at the same time by the FDA. While the guidance allows for the development of competitor companion tests, those tests must be submitted to the FDA for review and approval or clearance.

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

Dabrafenib was FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with \( \text{BRAF}^{V600E} \) mutation, as detected by an FDA-approved test. Dabrafenib is specifically not indicated for the treatment of patients with wild-type BRAF melanoma.

Trametinib was FDA-approved in May 2013 for the treatment of patients with unresectable or metastatic melanoma with \( \text{BRAF}^{V600E} \) or \( \text{V600K} \) mutations, as detected by an FDA-approved test. Trametinib is specifically not indicated for the treatment of patients previously treated with BRAF inhibitor therapy.
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The companion diagnostic test co-approved for both dabrafenib and trametinib is the THxID™ BRAF Kit manufactured by bioMérieux. The kit is intended “as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with dabrafenib and as an aid in selecting melanoma patients whose tumors carry the BRAF V600E or V600K mutation for treatment with trametinib.”

In January 2014, FDA granted accelerated approval to dabrafenib and trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. Approval was based on response rather than survival outcomes observed in the phase ½ trial. Continued approval is contingent on results from a phase 3 trial comparing combination therapy with dabrafenib monotherapy in patients with metastatic or unresectable melanoma.

On December 22, 2014, nivolumab (Opdivo® Injection; Bristol-Myers Squibb) was granted accelerated approval through the biologics license application (BLA) process for the treatment of patients with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab and if BRAF V600 mutation positive. On September 30, 2015, FDA granted accelerated approval for use of nivolumab in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma and, on January 23, 2016, FDA approved a supplemental BLA, expanding the approved indications for nivolumab. For single-agent use, FDA removed the restriction on patients who have disease progression following treatment with ipilimumab and a BRAF inhibitor; and for combination with ipilimumab, FDA removed the restriction on BRAF V600 wild-type.

Related Policy
Genetic Testing for Colon Cancer

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
BCBSNC will provide coverage for BRAF Gene Mutation Testing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When BRAF Gene Mutation Testing is covered
Testing for the BRAF^{V600E} mutations in tumor tissue of patients with unresectable or metastatic melanoma may be considered medically necessary to select patients for treatment with FDA-approved BRAF inhibitors (see Policy Guidelines).

When BRAF Gene Mutation Testing is not covered
Testing for the BRAF^{V600} mutations for all other patients with melanoma, including but not limited to, use in patients with resectable melanoma, is considered investigational.
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**Policy Guidelines**

Currently only vemurafenib, dabrafenib, and trametinib are FDA approved specifically for the treatment of advanced BRAF mutated melanoma.

FDA-approved BRAF testing kits intended to be used to select patients for treatment with vemurafenib and with dabrafenib and trametinib. There are also commercial labs that perform BRAF testing using non-FDA approved testing. The full prescribing information states that confirmation of the BRAF_{V600E} mutation using an FDA-approved test is required for selection of patients appropriate for therapy. The intent of the FDA-approval of these testing kits is to minimize the potential for inappropriate treatment based on an inaccurate test.

The Phase III clinical trial of vemurafenib selected all patients with a BRAF_{V600} mutation using the FDA-approved test. The majority of these mutations were BRAF_{V600E} mutations, and a small number (19/675, 2.8%) were BRAF_{V600K} mutations. The authors stated that patients with the BRAF_{V600K} also appeared to respond to vemurafenib, but no formal subgroup analysis was performed. Therefore, the results of the trial refer primarily to patients with the BRAF_{V600E} mutation. The efficacy of vemurafenib for patients with other mutations, including BRAF_{V600K}, is less certain.

Pivotal trials for vemurafenib, dabrafenib, and trametinib enrolled patients in the following stages of advanced melanoma:

- Vemurafenib- stage IIIC or stage IV
- Dabrafenib- unresectable stage III or stage IV
- Trametinib- unresectable stage IIIC or stage IV

A Phase II, single-arm study of dabrafenib enrolled 172 patients with either BRAF_{V600E} or BRAF_{V600K}-mutated melanoma with brain metastasis. Overall intracranial response was limited to patients with the BRAF_{V600E} mutation and was negligible in patients with the BRAF_{V600K} mutation.

The evidence for BRAF gene mutation testing and treatment with Food and Drug Administration–approved BRAF inhibitors when results are positive in select patients who have unresectable or metastatic melanoma includes studies of analytic validity and randomized trials. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. Studies of analytic validity show that BRAF mutation testing kits have high concordance with the reference standard of Sanger sequencing.

Randomized phase 3 trials of BRAF inhibitor therapy in patients selected on the basis of BRAF mutation testing have shown improvements in overall survival and progression-free survival. Single-agent BRAF inhibitor treatment compared with nontargeted treatments shows superior outcomes for most end points. Combination BRAF inhibitor treatment with dabrafenib plus trametinib shows superior overall survival when compared with either vemurafenib or dabrafenib alone. Data showing treatment effects in patients without BRAF mutations do not exist; therefore BRAF mutation testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.
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Applicable service codes: 81210, 81406

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Vermurafenib (Zelboraf™). TEC Specialty Pharmacy Reports 2011; #11-2011.


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Policy Implementation/Update Information

2/7/12 New policy developed. Testing for the BRAFV600E mutation in tumor tissue of patients with stage IIIC or IV melanoma may be considered medically necessary to select patients for treatment with vemurafenib. Testing for the BRAFV600E mutation for all other indications, including but not limited to, use in patients with lesser stage melanoma, or with non-melanoma tumors, is considered investigational. Medical Director review 1/2012. (mco)

12/11/12 Description section updated. “When Covered” section revised to state: “Testing for the BRAF V600E mutation in tumor tissue of patients with stage IIIC or IV melanoma may be considered medically necessary to select patients for treatment with FDA-approved BRAF inhibitors.” Policy Guidelines updated. New statement added to Policy Guidelines: “Currently only vemurafenib has FDA approval for treatment of advanced melanoma.” Added CPT code 81406 to Billing/Coding section. References updated. Medical Director review 11/2012. (mco)

4/16/13 Specialty Matched Consultant Advisory Panel review 3/20/2013. Regulatory Status added to Description section. No change to policy intent. (btw)

8/27/13 Statement in the When Not Covered section changed from “Testing for the BRAFV600E mutation for all other indications, including but not limited to, use in patients with lesser stage melanoma, or with non-melanoma tumors, is considered investigational.” to “Testing for the BRAFV600 mutation for all other patients with melanoma, including but not limited to, use in patients with lesser stage melanoma, is considered investigational.” (btw)

1/28/14 Description and Policy Guidelines sections updated. No change to policy intent. Medical Director review 1/10/2014. Reference added. (btw)


11/25/14 Description section and policy guidelines updated. Statements in When Covered section revised to align with current FDA approved indication “unresectable or metastatic” rather than “stage IIIC or IV.” No change to policy statements. Reference added. (lpr)

4/28/15 Specialty Matched consultant advisory panel review 3/25/2015. No change to policy intent. (lpr)

4/29/16 Updated Description and Policy Guidelines sections. Reference added. Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)

4/28/17 Updated Description section. Reference added. Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment
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and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.