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

Policy # 00320
Original Effective Date: 11/16/2011
Current Effective Date: 01/18/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider testing for BRAF V600 mutations in tumor tissue of patients with unresectable or metastatic melanoma to select patients for treatment with Food and Drug Administration (FDA)-approved BRAF inhibitors to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers testing for BRAF V600 mutations for all other patients with melanoma, including but not limited to use in patients with resectable melanoma to be investigational.*

Background/Overview
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 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 4 at diagnosis, prognosis is extremely poor; 5-year survival is about 15% to 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 (RAF-MEK-ERK [also called MAPK] pathway) that is associated with oncogenic proliferation. In general, 50% to 70% of melanoma tumors harbor a BRAF mutation; of these, 80% are positive for BRAF V600E and 16% are positive for BRAF V600K.

Thus, approximately 45% to 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 codeveloped under an agreement withARRY and DERMATION. The other two molecules, dabrafenib (trade name Tafinlar®) and vemurafenib (trade name Zelboraf®), have similar efficacy with the exception of a much greater ability to penetrate the central nervous system.
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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 mutated kinase and with 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 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, as the supportive clinical trials were enrichment trials, enrolling only patients with tumors positive for the BRAF V600E mutation.

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.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
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, 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, 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 on 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 FDA. Although the guidance allows for the development of competitor companion tests, those tests must be submitted to FDA for review and approval or clearance.
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In August 2011, vemurafenib and a class III companion diagnostic test, the cobas 4800 BRAF V600 Mutation Test, were coapproved by FDA through the premarket approval process as an aid in selecting melanoma patients whose tumors carry the BRAF V600 mutation for treatment with vemurafenib.15 Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. The vemurafenib full prescribing information states that confirmation of the BRAF V600 mutation using an FDA-approved test is required for selection of patients appropriate for therapy.

In May 2013, dabrafenib (GlaxoSmithKline) was approved by FDA through the new drug application process for the treatment of patients with unresectable or metastatic melanoma with 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.

In May 2013, trametinib (GlaxoSmithKline) was approved by FDA through the new drug application process for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or 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.

The companion diagnostic test coapproved 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, dabrafenib and trametinib (GlaxoSmithKline) were approved by FDA through the accelerated approval process 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 1/2 trial described next (see Rationale section). 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.

FDA product code: OWD.
Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
Rationale/Source
This policy was originally created in 2011 based on a Special Report by the Technology Evaluation Center. For the TEC Special Report, the MEDLINE® database was searched (via PubMed) for articles using the terms “PLX4032,” “vemurafenib,” “V600E,” and “BRAF inhibitor,” all coupled with the term “melanoma.” Reference lists of relevant study publications and review articles also were examined. Meeting abstracts for the 2011 annual meeting of the American Society of Clinical Oncology were searched using the MEDLINE search terms. If available, virtual presentations and slides were reviewed for key abstracts. The “grey literature” was consulted in the form of drug and laboratory test approval information released by the U.S. FDA, ongoing clinical trials from online site www.ClinicalTrials.gov, and online searches for status and ancillary information. The most recent searches using updated search terms included the period through November 10, 2015. Following is a summary of the key publications and regulatory documents to date.

Since the TEC Special Report, 2 additional phase 3 randomized controlled trials (RCTs) have been published. These trials, which evaluated dabrafenib and trametinib for advanced melanoma in BRAF-positive patients, are summarized next. Additionally, a phase 2 single-arm study of combination dabrafenib plus trametinib is reviewed briefly.

The components of the evidence evaluation are analytic validity, clinical validity, and clinical utility, as defined in the methods of the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group.

Analytic Validity
The analytic validity of a genetic test is its ability to accurately and reliably measure the genotype (or analyte) of interest in the clinical laboratory, and in specimens representative of the population of interest. Submission to the Office of In Vitro Diagnostics of FDA for marketing clearance or approval of a diagnostic test requires an extensive demonstration of the analytic validity of the test. Data for cleared or approved tests are summarized in the kit insert (prepared by the manufacturer) and in the Summary of Safety and Effectiveness of the test (prepared by FDA and publicly available). Analytic validity of FDA-approved BRAF mutation tests has been assessed in several studies where the results of the test have been correlated with Sanger sequencing.

Cobas 4800 BRAF V600 Mutation Test
The cobas 4800 BRAF V600 Mutation Test is a real-time polymerase chain reaction (PCR) test intended for the qualitative detection of the BRAF V600E mutation specifically in DNA that has been extracted from formalin-fixed, paraffin-embedded (FFPE) human melanoma tissue.

Correlation of cobas 4800 BRAF V600 Mutation Test results with Sanger sequencing was tested in the phase 3 trial of vemurafenib on 596 consecutive patients, 449 of whom were evaluable. The percent agreement of the BRAF V600 Mutation Test with Sanger sequencing is shown in the first line of Table 1 when only V600E results were counted as positive. The cobas 4800 BRAF V600 Mutation Test detected 27 V600 mutations (primarily V600K) that were not V600E by Sanger Sequencing. Limited evidence suggests that patients with V600K mutated tumors may also respond to vemurafenib.
Tumor specimens from patients enrolled in the phase 2 trial were also sequenced by Sanger sequencing; specimens that were invalid by Sanger, or that were identified as V600K mutated or as V600 wild-type by Sanger, were resequenced by the more sensitive 454 pyrosequencing method to resolve differences. Correlation to 454 pyrosequencing was 100% if V600K-positive samples were counted as true positives (see Table 1).

Tumor specimens from 55 patients enrolled in a phase 1 clinical trial of vemurafenib were subjected to cobas 4800 BRAF V600 Mutation Test and to Sanger sequencing. The limit of detection was 5% mutant allele for cobas 4800 BRAF V600 Mutation Test and 20% for Sanger sequencing. The cobas 4800 BRAF Mutation Test is highly predictive for V600E; however, it also detects other BRAF V600 mutations (V600K; 65.8% agreement with Sanger sequencing, V600D, V600E2, and V600R; not determined) with less sensitivity. Data presented on study 3 are presented in Table 1.

Halait et al (2012) assessed the analytical performance of cobas 4800 BRAF V600 Mutation Test and Sanger sequencing in 219 melanoma specimens. A greater than 96% correct call rate was obtained across all specimen types with 5% mutation sequences. The cobas 4800 BRAF V600 Mutation Test and Sanger sequencing correlation results for V600E in study 4 are presented in Table 1. After discrepant analysis with 454 pyrosequencing, the positive percent agreement increased to 100%, the negative percent agreement increased to 93%, and the overall percent agreement increased to 96%.

A similar study by Anderson et al (2012) used screening specimens from phase 2 and phase 3 trials of vemurafenib. Of 477 available specimens, 433 had both a valid cobas result and valid Sanger sequencing. Correlation results were similar to those obtained by Halait et al and are shown in Table 1. Of 42 discordant results (cobas mutation-positive/Sanger V600E-negative), 17 (40%) were V600E-positive and 24 (57%) were V600K-positive by 454 pyrosequencing; 1 sample with a V600D mutation on Sanger sequencing was wild-type by 454 pyrosequencing. Reproducibility was assessed across 3 sites. Correct interpretations were made for all wild-type specimens and for specimens with more than 5% mutant allele, the limit of detection of the cobas test.

According to the COSMIC database v54 (http://www.sanger.ac.uk/perl/genetics/CGP/cosmic), in tumors originating in the skin, V600E mutations accounted for 92.5%, V600K mutations for 5.6%, V600R mutations for 1%, "V600E2" for 0.7% and all other V600 mutations, 0.2%. Halait et al analyzed the cross-reactivity of 14 BRAF non-V600E mutant melanoma specimens with the Cobas test. The one V600R mutant specimen did not show cross reactivity. The remaining 13 mutant specimens showed cross reactivity with the test (V600D, 1/1; V600E2, 1/3; V600K, 6/9).

Regulatory documents contain additional data detailing the evaluation of analytic sensitivity and specificity, cross-reactivity, interference, reproducibility, repeatability, and additional studies of test robustness. In general, correlation with sequencing and extensive analytic validation data support that the test is a sensitive, specific, and robust assay for the detection of the V600E mutation in FFPE melanoma specimens. Patients with V600K mutations will also be identified as positive, although it is unclear whether all patients with V600K mutations will be positive. There is very limited evidence that patients with V600K mutations may respond to vemurafenib. Infrequently, patients with V600E2 and V600D mutations may also
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be detected. Additionally, the method is available as a kit and is partially automated, which should result in wide access and rapid turnaround time relative to the reference standard of sequencing.

Table 1. Correlation of Vemurafenib Companion Test Results with Sanger Sequencing

<table>
<thead>
<tr>
<th>Definition of Positive</th>
<th>Positive % Agreement</th>
<th>Negative % Agreement</th>
<th>Overall % Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3 trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only V600E</td>
<td>97.3</td>
<td>84.6</td>
<td>90.9</td>
</tr>
<tr>
<td>All V600</td>
<td>87.7</td>
<td>95.4</td>
<td>90.6</td>
</tr>
<tr>
<td>V600E + V600K</td>
<td>92.7</td>
<td>95.2</td>
<td>91.1</td>
</tr>
<tr>
<td>Phase 2 trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only V600E</td>
<td>92.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V600E + V600K</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 1 trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only V600E</td>
<td>97.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analytical performance trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only V600E</td>
<td>96</td>
<td>82</td>
<td>88</td>
</tr>
<tr>
<td>Only V600E</td>
<td>96.4</td>
<td>80</td>
<td>88.5</td>
</tr>
</tbody>
</table>

The THxID BRAF kit is a real-time PCR test intended for the qualitative detection of BRAF V600E and V600K mutations in DNA samples extracted from FFPE human melanoma tissue. Two oligonucleotide probes labeled with different fluorescent dyes (one for internal controls, the other for mutation sequence alleles) are measured at characteristic wavelengths and compared by an autoanalyzer. Results are reported as either “mutation(s) detected” or “mutation(s) not detected” (or “invalid,” which requires troubleshooting and a repeat of the test). The threshold of detection, defined as the smallest proportion of mutated alleles for which the assay yields a positive result in 95% of tests, is 5% for V600E and V600K mutations.

Correlation of the THxID BRAF assay with Sanger sequencing was tested in 898 consecutive clinical trial samples. Forty-three samples (5%) were invalid or quantity not sufficient. Excluding these samples, there were 35 discordant cases (4%). The THxID BRAF kit detected as V600E mutation-positive 2 samples determined by Sanger sequencing to be V600D mutation-positive. Additional results are shown in Table 2.

Table 2. Correlation of Dabrafenib and Trametinib Companion Test Results with Sanger Sequencing

<table>
<thead>
<tr>
<th>Overall Agreement</th>
<th>V600E and V600K</th>
<th>V600E</th>
<th>V600K</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPA</td>
<td>NPA</td>
<td>PPA</td>
<td>NPA</td>
</tr>
<tr>
<td>Including invalids and QNS</td>
<td>92.3</td>
<td>96.4</td>
<td>89.9</td>
</tr>
<tr>
<td>Excluding invalids and QNS</td>
<td>95.9</td>
<td>98.1</td>
<td>93.9</td>
</tr>
</tbody>
</table>

NPA: negative percent agreement; NR: not reported; PPA: positive percent agreement; QNS: quantity not sufficient.

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 decision making compared with current management without genetic testing.
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When a treatment is developed for a specific biological 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, which use the test to select patients, provide evidence of both clinical validity and clinical utility. We review the phase 3 clinical trials of treatments in which testing for the BRAF mutation was required for selection into the trial. In the absence of clinical trials in which both patients with and without BRAF mutations are entered into randomized clinical trials of novel therapies, it cannot be certain that the test has clinical utility, because it is unknown whether the treatment would be effective in patients without BRAF mutation. However, patients without BRAF mutations have not been enrolled in clinical trials of BRAF inhibitors.

Vemurafenib
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 in which patients who were positive for a V600 mutation were enrolled.

The BRIM-3 trial is summarized in Table 3. A total of 675 patients were randomly assigned to either vemurafenib (960 mg twice daily orally) or dacarbazine (1000 mg/m² body surface area by intravenous [IV] infusion every 3 weeks) to determine whether vemurafenib would prolong the rate of overall survival (OS) or progression-free survival (PFS), compared with dacarbazine. All enrolled patients had unresectable, previously untreated stage IIIIC or IV melanoma with no active central nervous system metastases. Melanoma specimens from all patients tested positive for the BRAF V600E mutation on the cobas 4800 BRAF V60 Mutation Test. Included were 19 patients with BRAF V600K mutations and 1 with a BRAF V600D mutation.

Tumor assessments including computed tomography were performed at baseline, at weeks 6 and 12, and every 9 weeks thereafter. Tumor responses were determined by investigators according to RECIST, version 1.1. Primary end points 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 end points 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 overall survival were strongly in favor of 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 coapproval of both drug and companion test.

Table 3. Phase 3 RCTs of BRAF Inhibitors for BRAF-Positive Advanced Melanoma

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Follow-Up, mo</th>
<th>Group</th>
<th>N</th>
<th>OS (95% CI)</th>
<th>PFS (95% CI), mo</th>
<th>ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapman (2011)</td>
<td>6</td>
<td>Vemurafenib</td>
<td>337</td>
<td>84%</td>
<td>5.3a</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(78% to 89%)</td>
<td>(42% to 55%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dacarbazine</td>
<td>338</td>
<td>65%</td>
<td>1.6a</td>
<td>5%</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard ratio</th>
<th>p value</th>
<th>Hazard ratio</th>
<th>p value</th>
<th>Hazard ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib</td>
<td>(0.37 to 0.55)</td>
<td>&lt;0.001</td>
<td>(0.26 to 0.33)</td>
<td>&lt;0.001</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dabrafenib (2012)</td>
<td>4.9</td>
<td>&lt;0.001</td>
<td>5.1</td>
<td>&lt;0.001</td>
<td>50%</td>
<td>NA</td>
</tr>
<tr>
<td>Dacarbazine (2012)</td>
<td>0.61</td>
<td>(0.25 to 1.48)</td>
<td>0.33</td>
<td>(0.20 to 0.54)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Trametinib</td>
<td>0.54</td>
<td>(0.32 to 0.92)</td>
<td>0.47</td>
<td>(0.34 to 0.65)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Trametinib (2012)</td>
<td>6</td>
<td>0.01</td>
<td>11.0</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy (2012)</td>
<td>0.71</td>
<td>(0.55 to 0.92)</td>
<td>0.67</td>
<td>(0.53 to 0.84)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Long (2015)</td>
<td>0.01</td>
<td>0.0004</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabrafenib plus trametinib</td>
<td>0.72</td>
<td>11.4</td>
<td>64%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib (2015)</td>
<td>0.69</td>
<td>0.56</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.005</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IV: intravenous; NA: not applicable; 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 dacarbazine 1000 mg/m² IV or paclitaxel 175 mg/m² IV every 3 weeks at investigator discretion.

**Dabrafenib**

One phase 3, open-label RCT of dabrafenib for advanced (stage IV or unresectable stage III) melanoma has been published; the results of this trial are summarized in Table 3. The main objective of this RCT was to study the efficacy of dabrafenib vs standard dacarbazine treatment in patients with BRAF V600E-mutated metastatic melanoma. Two hundred fifty patients were randomized 3:1 to receive oral dabrafenib 150 mg twice daily versus IV dacarbazine 1000 mg/m² every 3 weeks. The primary outcome was PFS, and secondary outcomes were OS, overall response rate, and adverse events.
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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 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 greater 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 adverse events grade 2 or higher occurred in 53% of patients who received dabrafenib and in 44% of patients who received dacarbazine. Grade 3-4 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).

Analytic validity of the THxID BRAF test kit was validated by comparing outcomes of patients identified by the test kit with outcomes of patients identified by an assay performed at a central lab. Of 250 patients enrolled in the trial, specimens from 237 patients (177 [95%] in the dabrafenib arm, 55 [87%] in the dacarbazine arm) were retested with the THxID BRAF kit. Reanalysis of the primary end point, PFS, in patients who were V600E-positive by the THxID BRAF kit showed a treatment effect that was nearly identical to that of patients identified by central assay.

Trametinib
Clinical efficacy and safety of trametinib were assessed in the phase 3, open-label METRIC trial. 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 1000 mg/m² IV every 3 weeks or paclitaxel 175 mg/m² IV every 3 weeks at investigator discretion. Most patients (67%) were previously untreated. The primary efficacy end point was PFS; secondary end points 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 (see Table 3). 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 of 108 patients (47%) in the chemotherapy group crossed over at disease progression to receive trametinib. In the trametinib and chemotherapy groups, adverse events 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; 2 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 adverse events 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.
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Analytic validity of the THxID BRAF kit was demonstrated by comparison of patient outcomes identified by the kit versus those identified by a central lab assay. 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 in patients identified by central assay. Additional analysis for discordant results assuming a worst case scenario as above yielded an HR of 0.48 (95% CI, 0.35 to 0.63).

**Combination BRAF (Dabrafenib) and MEK (Trametinib) Inhibition**

Efficacy of combination dabrafenib plus trametinib treatment has been established with 2 phase 3 clinical trials.

Combination dabrafenib plus trametinib was evaluated in the phase 3 open-label by Long et al. In this study, 4234 patients with unresectable stage IIC or stage IV melanoma with a BRAF V600E or V600K mutation were randomized to combination dabrafenib plus trametinib or to dabrafenib and placebo. The primary end point was PFS, reported in a first publication, followed by a second publication in which longer term OS was reported.

Median PFS was 9.3 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 difference that was statistically significant using standard statistical criteria, but which 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 versus 18.7 months in the dabrafenib-only group.

Another phase 3 RCT compared dabrafenib plus trametinib to vemurafenib. A total of 704 patients with metastatic melanoma with BRAF V600E or V600K mutations were randomized equally. The study 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). 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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 4. This table shows active phase 3 and phase 4 studies of BRAF inhibitor therapy in melanoma listed at ClinicalTrials.gov. Most studies evaluate combination therapy. All assess patients with unresectable stage III or stage IV melanoma, except for NCT01667419 under Single Agent and NCT01682083 under Combination Treatments, which evaluate patients with completely resected melanoma.
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Table 4. Summary of Key Trials

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<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing Single agent</td>
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<tr>
<td>NCT01667419⁸</td>
<td>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</td>
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<td>Mar 2022</td>
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<tr>
<td>NCT01898585⁸</td>
<td>An Open-Label, Single-Arm, Multicenter Study To Assess The Safety Of Vemurafenib In Patients With Braf V600 Mutation Positive Metastatic Melanoma In South Africa</td>
<td>60</td>
<td>Dec 2016</td>
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<tr>
<td>NCT02224781</td>
<td>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 BRAFV600 Mutant Melanoma</td>
<td>300</td>
<td>Apr 2016</td>
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<tr>
<td>NCT01689519⁹</td>
<td>A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus GDC-0973 (Cobimetinib) in Previously Untreated BRAFV600-Mutation Positive Patients With Unresectable Locally Advanced or Metastatic Melanoma</td>
<td>499</td>
<td>Dec 2017</td>
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<tr>
<td>NCT01909453³</td>
<td>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</td>
<td>900</td>
<td>Mar 2018</td>
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<tr>
<td>NCT01682083³</td>
<td>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 High-risk BRAF V600 Mutation-positive Melanoma After Surgical Resection</td>
<td>852</td>
<td>Jul 2018</td>
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<tr>
<td>Unpublished</td>
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<tr>
<td>NCT01683188⁸</td>
<td>A Multi-Center Study of High Dose Aldesleukin (Interleukin-2) + Vemurafenib Therapy in Patients With BRAFV600 Mutation Positive Metastatic Melanoma</td>
<td>53</td>
<td>Terminated</td>
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</table>

NCT: national clinical trial.
⁸ Denotes industry-sponsored or cosponsored trial.

Summary of Evidence

The evidence for BRAF gene mutation testing and treatment with FDA–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...
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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.

References

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Current Effective Date: 01/18/2017
11/03/2011 Medical Policy Committee review
11/01/2012 Medical Policy Committee review
12/12/2013 Medical Policy Committee review
12/18/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2015 Coding Update
01/08/2015 Medical Policy Committee review
01/21/2015 Medical Policy Implementation Committee approval. New policy.
01/07/2016 Medical Policy Committee review
01/22/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017 Medical Policy Committee review
01/18/2017 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 01/2018

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<th>Code Type</th>
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<td>HCPCS</td>
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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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