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

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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 stage IIIC or IV melanoma to select patients for treatment with U.S. 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 indications, including but not limited to, use in patients with lesser stage melanoma, or with non-melanoma tumors to be **investigational.***

Background/Overview

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 BRAF kinase results in constitutive activity, which is believed to promote 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, more than 75,000 new cases will have been diagnosed. 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 (CNS). Combination regimens increase response rates, but not overall survival. Very recently, ipilimumab 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 with ipilimumab of 10 months versus 6.4 months with control medication. However, side effects of

ipilimumab can include severe and fatal immune-mediated adverse reactions, especially in patients who are already immune-compromised.

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 $BRAF^{V600E}$ and 16% are positive for $BRAF^{V600K}$. 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 $BRAF^{V600E}$ 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration
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.

Although the guidance is not yet finalized, it represents FDA's current thinking on the topic and likely the direction given to sponsors of applicable treatments and companion diagnostics in development at the time this guidance was being prepared. 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 *BRAF^{V600}mutation* for treatment with vemurafenib. 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.

Dabrafenib was FDA-approved in May 2013 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.

Trametinib was FDA-approved in May 2013 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 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."

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

There are 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,

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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.

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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination.

Rationale/Source

This policy was originally created in 2011 based on a Special Report by the Technology Evaluation Center (TEC). Following is a summary of the key publications and regulatory documents to date.

Since the TEC Special Report, two additional Phase III randomized controlled trials (RCTs) have been published. These trials, which evaluated dabrafenib and trametinib for advanced melanoma in *BRAF*-positive patients, are summarized below. Additionally, a Phase II 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 the 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 the FDA and publicly available).

Vemurafenib
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 deoxyribonucleic acid (DNA) that has been extracted from formalin-fixed, paraffin-embedded (FFPE) human melanoma tissue.

Correlation of cobas 4800 BRAF V600 Mutation Test results to Sanger sequencing was tested in the Phase III 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 II 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 I 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) analyzed 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 II and Phase III 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; one 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 (available at 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; and *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 not clear that 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 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

Definition of Positive	Positive % Agreement	Negative % Agreement	Overall % Agreement
Phase III trial			
Only V600E	97.3	84.6	90.9
All V600	87.7	95.4	90.6
V600E + V600K	92.7	95.2	91.1
Phase II trial			
Only V600E	92.4		
V600E + V600K	100		
Phase I trial			
Only V600E	97.3		
Analytical performance trials			
Only V600E	96	82	88
Only V600E	96.4	80	88.5

Dabrafenib

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 and 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

	Overall Agreement	V600E and V600K		V600E		V600K	
		PPA	NPA	PPA	NPA	PPA	NPA
Including invalids	92.3	96.4	89.9	96.3	99.2	92.2	99.5

and QNS							
Excluding invalids and QNS	95.9	98.1	93.9	NR	NR	NR	NR

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.

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, clinical studies of treatment benefit, which use the test to select patients, provide evidence of both clinical validity and clinical utility.

Vemurafenib
Primary evidence of clinical validity and utility for the cobas 4800 BRAF V600 Mutation Test is provided by the Phase III clinical trial of vemurafenib. In addition, evidence from Phase I and Phase II trials is supportive. All trials were enrichment trial designs, in which all patients were positive for a *V600* mutation (with a few exceptions in the Phase I trial). The justification for this was both efficiency and possibly potential for harm to patients with *BRAF* wild-type tumors.

Phase III Clinical Trial
This open-label, comparative trial, also known as BRIM-3, is summarized in Table 3. A total of 675 patients were randomly assigned to either vemurafenib (960 mg twice daily orally) or dacarbazine (1,000 mg/m^2 body surface area by intravenous [IV] infusion every 3 weeks) to determine whether vemurafenib would prolong the rate of overall or progression-free survival (PFS), compared to dacarbazine. All enrolled patients had unresectable, previously untreated stage IIIC or IV melanoma with no active CNS metastases. Melanoma specimens from all patients tested positive for the *BRAF*^{V600E} mutation on the cobas 4800 BRAF V600 Mutation Test. Included were 19 patients with *BRAF*^{V600K} mutations and one with a *BRAFV*^{600D} mutation.

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 investigators according to RECIST, version 1.1. Primary endpoints were the rate of overall survival 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 co-primary endpoints had met prespecified stopping criteria and recommended that patients in the dacarbazine group be allowed to cross over to receive vemurafenib. At the time the trial was halted, 118 patients had died; median survival had not been reached. Trial results are summarized in Table 3. 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 the FDA and established

safety and effectiveness of the cobas 4800 BRAF V600 Mutation Test, resulting in co-approval of both drug and companion test.

Table 3. Phase III RCTs of BRAF inhibitors for BRAF-positive advanced melanoma

Study/year	Follow-up	Group	N	OS[1] (95% CI)	PFS[2] mo (95% CI)	ORR[3] (95% CI)
Vemurafenib						
Chapman 2011	6 mo	Vemurafenib	337	84% (78-89%)	5.3 (median)	48% (42-55%)
		Dacarbazine	338	65% (56-73%)	1.6 (median)	5% (3-9%)
		Hazard ratio		0.37 (0.26-0.55)	0.26 (0.20-0.33)	NA[4]
		p value		< 0.001	< 0.001	NA
Dabrafenib						
Hauschild 2012	4.9 mo (median) Range (0-9.9 mo)	Dabrafenib	187	89%	5.1 (median)	50% (42.4-57.1)
		Dacarbazine	63	86%	2.7 (median)	6% (1.8-15.5)
		Hazard ratio		0.61 (0.25-1.48)	0.33 (0.20-0.54)	NA
		p value		NR	< 0.001	NA

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Trametinib						
Flaherty 2012	6 mo	Trametinib	214	81%	4.8 (median)	22% (17-28%)
		Chemotherapy[5]	108	67%	1.5 (median)	8% (4-15%)
		Hazard ratio		0.54 (0.32-0.92)	0.47 (0.34-0.65)	NA
		p value		0.01	<0.001	NA

[1] Overall survival.
[2] Progression free survival.
[3] Objective response rate, including complete and partial responses.
[4] NA, not applicable.
[5] Either dacarbazine 1,000 mg/m^2 IV or paclitaxel 175 mg/m^2 IV every 3 weeks at investigator discretion.

Phase II Clinical Trial
A Phase II single-arm study, known as BRIM-2, enrolled patients from 13 centers who had failed at least one previous treatment for metastatic melanoma. All patients were selected with the cobas 4800 BRAF V600 Mutation Test; 122 cases were *BRAF*^{V600E}-positive, and 10 cases were *BRAF*^{V600K}-positive. The target overall response rate (primary outcome) was 30%, with a lower boundary of the 95% confidence interval (CI) of 20%. At a median follow-up of 7 months, this target was met with an overall response rate of 52% by independent review committee (IRC) (95% CI: 43-61). At 10 months, 27% of patients were still on treatment; the majority of discontinuations were due to disease progression. The most common adverse events of any grade were arthralgias (58%), skin rash (52%), and photosensitivity (52%). The most common grade 3 adverse event was squamous cell carcinoma; these were seen in about 25% of patients, tended to occur in the first 2 months of treatment, and were managed with local excision. There were very few grade 4 adverse events.

Phase I Clinical Trial
The major goals of this study were first to determine the maximum dose in a dose-escalation phase, then determine the objective response rate and monitor toxicity. This study used a PCR assay that was likely a prototype of the final test; only a brief description of the assay was provided in the publication. In the dose-escalation phase, 5 patients with metastatic melanoma tumors who did *not* have the *BRAF*^{V600E} mutation received 240 mg or more vemurafenib twice daily (final recommended dose is 960 mg twice daily); of these, none responded. In the extension phase of the study, 26 of 32 patients with the *BRAF*^{V600E} mutation responded (81%; 24 partial, 2 complete responses).

Dabrafenib

One Phase III randomized, controlled, open-label trial 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 selected to have *BRAF V600E* mutated metastatic melanoma. Two-hundred-fifty patients were randomized 3:1 to receive oral dabrafenib 150 mg twice daily versus IV dacarbazine 1,000 mg/m^2 every 3 weeks. The primary outcome was PFS, and secondary outcomes were overall survival, objective response rate, and adverse events.

Median PFS for the dabrafenib and dacarbazine groups was 5.1 months and 2.7 months, respectively. Overall survival did not differ significantly between groups; 11% of patients in the dabrafenib group died compared to 14% in the dacarbazine group (hazard ratio: 0.61, 95% CI: 0.25-1.48). 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: 42.4-57.1%) compared to the dacarbazine group (6%, 95% CI: 1.8-15.5%). 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). Results demonstrated that targeting dabrafenib against *BRAF V600E* mutated melanoma results in a benefit in PFS. Patients were allowed to cross over at the time of progression, and the effect of dabrafenib on overall survival was favorable but not statistically significant.

All tissue specimens from patients screened for enrollment in the clinical trial were analyzed centrally by a clinical trial assay. Outcomes were linked retrospectively to BRAF testing by the THxID BRAF kit. Of 250 patients enrolled in the trial, specimens from 237 patients (177 [95%] in the dabrafenib arm and 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 the overall result by central assay. (Table 4) Additional analysis for discordant results assumed a worst case scenario, i.e., a hazard ratio of 1 for patients *V600E-mutation*-positive by the THxID BRAF test but mutation negative by central assay. The hazard ratio was 0.34 (95% CI: 0.23-0.50).

Table 4. PFS in patients testing V600E-mutation positive by central assay and by THxID BRAF kit

	Central assay		**THxID–BRAF kit**	
	N	**Median PFS (95% CI), months**	**N**	**Median PFS (95% CI), months**
Dabrafenib	187	5.1 (4.9-6.9)	177	5.0 (4.9-6.8)
Dacarbazine	63	2.7 (1.5-3.2)	55	2.7 (1.5-3.2)
Hazard ratio (95% CI)		0.33 (0.20-0.54)		0.34 (0.20-0.57)
p value		< 0.001		< 0.001

Trametinib

The clinical efficacy and safety of trametinib was assessed in the Phase III, 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 1,000 mg/m^2 IV every 3 weeks or paclitaxel 175 mg/m^2 IV every 3 weeks at investigator discretion. Most patients (67%) were previously untreated. The primary efficacy endpoint was PFS; secondary endpoints included overall survival, 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: 4.3-4.9) in the trametinib arm and 1.5 months (95% CI: 1.4-2.7) in the chemotherapy arm, a statistically significant difference. (Table 3) Although median overall survival 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 grouped experienced grade 3 hypertension. Nine percent of patients in the trametinib group experienced ocular events (mostly grade 1 or 2), most commonly blurred vision (4%). The most common adverse events in the trametinib group were rash, diarrhea, peripheral edema, and fatigue; rash was grade 3 or 4 in 16 patients (8%). Cutaneous squamous cell carcinoma was not observed during treatment.

Tumor tissue was evaluated for *BRAF* mutations 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 (Table 5). Additional analysis for discordant results assuming a worst case scenario as above yielded a hazard ratio of 0.48 (95% CI: 0.35–0.63).

Table 5. PFS in patients testing *V600E*- or *V600K*-mutation positive by central assay and by THxID BRAF kit

	Central assay		**THxID–BRAF kit**	
	N	**Median PFS (95% CI), months**	**N**	**Median PFS (95% CI), months**
Trametinib	214	4.8 (4.3-4.9)	196	4.8 (4.2-4.9)
Chemotherapy	108	1.5 (1.4-2.7)	93	1.5 (1.4-2.7)
Hazard ratio (95% CI)		0.47 (0.34-0.65)		0.48 (0.34-0.68)
p value		< 0.001		< 0.001

Resistance to BRAF Inhibitors

Median duration of response in the Phase I (extension), II, and III studies of vemurafenib was approximately 6 months, 6.7 months, and 5.5 months, respectively, suggesting the development of resistance; in some

patients with $BRAF^{V600E}$-positive tumors, there was no response at all, which was interpreted as primary resistance. Investigations of the mechanisms of resistance have reported evidence of different molecular mechanisms potentially responsible for resistance in different patients. It is likely that combined inhibition of BRAF and other key molecular targets, and the use of different combinations in different patients, will be needed in the future. For example, MEK proteins are also components of the mitogen-activated protein (MAP) kinase signal-transduction pathway; like BRAF inhibitors, MEK inhibitors, such as trametinib, have been designed to interfere with this pathway and may be used in combination.

An open-label Phase I/II 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* mutations. 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; hazard ratio 0.39, 95% CI: 0.25–0.62; 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: 7.4–14.9) months and 5.6 months (95% CI: 4.5–7.4), 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). Other trials of vemurafenib, dabrafenib, and trametinib in combination with each other and with other treatments (e.g., high-dose interleukin-2) are currently in progress, as listed below.

Ongoing Clinical Trials

Table 6 shows active Phase III trials of BRAF inhibitor therapy in melanoma currently listed at online site ClinicalTrials.gov. Most trials study combination therapy. All trials are in patients with unresectable stage III or stage IV melanoma, except for NCT01667419 under "Single agents" and NCT01682083 under "Combination treatments," which are in patients with completely resected melanoma. (See table notes for details.)

Table 6. Currently active Phase III trials of BRAF inhibitor therapy for melanoma

• **NCT Number** • **Sponsor**	**Title**	• **Study Design** • **N** • **Completion Date**
Single agents		
NCT01898585[1] Hoffmann LaRoche	An Open-Label Study of Zelboraf (Vemurafenib) in Patients With Braf V600-Mutation Positive Metastatic Melanoma	Single-arm study 60 June 2015
NCT01667419 Hoffmann LaRoche	BRIM8: A Study of Vemurafenib Adjuvant Therapy in Patients With	Double-blind RCT 725 June 2016

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	Resected Cutaneous BRAF Mutant Melanoma[2]	
Combination treatments		
NCT01683188[1] Prometheus	High-Dose Interleukin-2 + Vemurafenib in Patients With BRAF Mutation Positive Metastatic Melanoma (PROCLIVITY 01)	Single-arm study 185 April 2016
NCT01584648 GlaxoSmithKline	A Study Comparing Trametinib and Dabrafenib Combination Therapy to Dabrafenib Monotherapy in Subjects With BRAF-mutant Melanoma	Double-blind RCT 340 September 2013
NCT01597908 GlaxoSmithKline	Dabrafenib Plus Trametinib vs. Vemurafenib Alone in Unresectable or Metastatic BRAF V600E/K Cutaneous Melanoma (COMBI-V)	Open-label RCT 694 March 2014
NCT01682083 GlaxoSmithKline	The BRAF Inhibitor Dabrafenib in Combination With the MEK Inhibitor Trametinib in the Adjuvant Treatment of High-risk[3] BRAF V600 Mutation-positive Melanoma After Surgical Resection (COMBI-AD)	Double-blind RCT 852 July 2015
NCT01689519 Hoffmann LaRoche	coBRIM: A Phase 3 Study Comparing GDC-0973 (Cobimetinib), a MEK Inhibitor, in Combination With Vemurafenib vs. Vemurafenib Alone in Patients With Metastatic Melanoma	Double-blind RCT 500 August 2016
NCT01909453 Novartis	Study Comparing Combination of the RAF Kinase Inhibitor LGX818 Plus the MEK Inhibitor MEK162 and LGX818 Monotherapy Versus Vemurafenib in Unresectable or Metastatic BRAF V600 Mutant Melanoma (COLUMBUS)	Open-label RCT 900 June 2017

[1] Phase IV trial.
[2] Stage IIc (tumor > 4 mm with ulceration) or stage III melanoma with lymph node metastasis > 1 mm.
[3] Stage III melanoma with lymph node metastasis >1 mm.

Summary
A large proportion of patients with advanced melanoma have a mutation in the *BRAF* gene. There are 2 Phase III RCTs of BRAF inhibitors (vemurafenib and dabrafenib) in advanced melanoma patients who are positive for the *BRAFV600E* mutation and 1 Phase III trial of a MEK inhibitor (trametinib) in advanced melanoma patients who are positive for *BRAF V600E* or *V600K* mutations. All of the trials reported a benefit in PFS for treatment with a BRAF inhibitor. In addition, the vemurafenib and trametinib trials reported a

significant improvement in overall mortality; the dabrafenib trial did not demonstrate a difference in overall survival. These results support the clinical validity and clinical utility of the cobas 4800 BRAF V600 Mutation Test to select patients for treatment with vemurafenib, and the THxID BRAF kit to select patients for treatment with dabrafenib and trametinib.

Based on the results of Phase III trials, BRAF testing that uses a test approved by the FDA may be considered medically necessary to select advanced melanoma patients for treatment with FDA-approved BRAF inhibitors.

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11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. New policy.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. "Targeted" added to the title. Eligible for coverage statement modified to read "FDA-approved BRAF inhibitors" in place of "vemurafenib" .
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 12/2014

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