Kansas City

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

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Next Review: 12/2014

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for BRAF gene mutation testing to select melanoma patients for BRAF inhibitor targeted therapy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Testing for the $BRAF^{V600}$ 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. (see Considerations)

When Policy Topic is not covered

Testing for the $BRAF^{V600}$ mutation for all other patients with melanoma, including but not limited to, use in patients with lesser stage melanoma, is considered **investigational**.

Considerations

Currently only vemurafenib has FDA approval for treatment of advanced melanoma.

There is an FDA-approved BRAF testing kit that is intended to be used to select patients for vemurafenib treatment. There are also commercial labs that perform BRAF testing using non-FDA approved testing. The vemurafenib 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 this testing kit is to minimize the potential for inappropriate treatment based on an inaccurate test.

The Phase III clinical trial 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 the $BRAF^{V600K}$, is less certain.

Effective for 2012, there is a specific CPT code:
81210: *BRAF (v-raf murine sarcoma viral oncogene homolog B1)* (e.g., colon cancer), gene analysis, V600E variant

Prior to 2012, the test would have been reported with a combination of the molecular pathology codes 83890-83913.

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.

Background

Overall incidence rates for melanoma have been increasing for at least 30 years; in 2011, more than 70,000 new cases will have been diagnosed. (1) 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. (2) Temozolomide has similar efficacy with the exception of a much greater ability to penetrate the central nervous system. Combination regimens increase response rates, but not overall survival. Very recently, ipilimumab was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma. For the first time, a survival advantage was demonstrated in previously treated patients: median survival on ipilimumab of 10 months versus 6.4 months on control medication. However, side effects of ipilimumab can include severe and fatal immune-mediated adverse reactions, especially in patients who are already immune-compromised.

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 that is associated with oncogenic proliferation. In general, 50-70% of melanoma tumors harbor a BRAF mutation and of these, 80% are positive for $BRAF^{V600E}$. (3) Thus, 40-60% of advanced melanoma patients might respond to a BRAF inhibitor targeted to this mutated kinase.

Two companies developed targeted BRAF inhibitors that have proceeded to Phase III clinical trials in melanoma patients. 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 significantly lower potency to inhibit most of many other kinases tested. (4). Preclinical studies demonstrated that vemurafenib selectively blocked the RAF/MEK/ERK pathway in BRAF mutant cells (5-7) and caused regression of BRAF mutant human melanoma xenografts in murine models. (4) 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, (5-7) suggesting that it might be harmful to administer BRAF inhibitors to patients with BRAF wild type melanoma tumors. Potentiated growth in BRAF wild type tumors has not yet been confirmed in melanoma patients, as the supportive clinical trials were enrichment trials, enrolling only those patients with tumors positive for the $BRAF^{V600E}$ mutation.

Dabrafenib (also known as GSK2118436 or SB-590885) is a BRAF inhibitor developed by GlaxoSmithKline (GSK). (8, 9) The results of a Phase III clinical trial of dabrafenib have recently been published. On August 3, 2012, GSK submitted a new drug application to the U.S. Food and Drug Administration for dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation, as detected by an FDA-approved test. BioMérieux has filed for FDA premarket approval of the molecular theranostic test to detect BRAF V600 (V600E and V600K) gene mutations found in several cancers, including melanoma.

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, (10) 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.

While the guidance is not yet finalized, it represents the FDA's current thinking on the topic and likely the direction given to sponsors of applicable treatments and companion diagnostics in development at the same 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.

Rationale

Literature Review

This policy was originally created in 2011 based on a Special Report by the Technology Evaluation Center. (11) For the TEC Special Pharmacy 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." The reference lists of relevant study publications and review articles were also examined. The 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 FDA, ongoing clinical trials from online site www.clinicaltrials.gov, and online searches for status and ancillary information. The most recent searches included the period through August 2012. Following is a summary of the key publications and regulatory documents to date.

Since the TEC Specialty Report, one additional Phase III randomized controlled trial (RCT) has been published. This trial, which evaluates dabrafenib for advance melanoma in BRAF-positive patients, will be summarized. No other publications were identified for dabrafenib.

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. (12)

Analytic Validity

Vemurafenib. 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. (12) 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).

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 to Sanger sequencing was tested in the Phase III trial of vemurafenib (13) 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 the patients enrolled in the Phase II trial (14) were also sequenced by Sanger sequencing; specimens that were invalid by Sanger, or that were identified as V600K mutation or as V600 wild type by Sanger, were re-sequenced 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 is in Table 1. (15)

Halait et al. 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 are presented in study 4 in Table 1. After discrepant analysis with 454 sequencing, the positive percent agreement increased to 100%, the negative percent agreement increased to 93% and the overall percent agreement increased to 96%. (16)

According to the COSMIC database v54 (available online 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 trial companion test results with Sanger sequencing.

Definition of Positive	**Positive % Agreement**	**Negative % Agreement**	**Overall % Agreement**
Phase III trial(13)			
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(14)			
Only V600E	92.4		
V600E + V600K	100		
Phase I trial(15)			
Only V600E	97.3		
Analytical Performance trial(16)			
Only V600E	96	82	88

Dabrafenib. Because the FDA submission is in progress, no information on analytic validity of the companion test for dabrafenib is available.

Clinical Validity and Utility

Vemurafenib. 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. (12)

When a treatment is developed for a specific biological target that characterizes only some patients with a particular disease, and a test is co-developed to identify diseased patients with that target, clinical validity and clinical utility studies are no longer separate and sequential. Rather, the clinical studies of treatment benefit, which use the test to select patients, provide evidence of both clinical validity and clinical utility. The 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 comparative trial, also known as BRIM-3, is summarized in Table 2. A total of 675 patients were randomly assigned to either vemurafenib (960 mg twice daily orally) or dacarbazine (1,000 mg/m2 body surface area by intravenous [IV infusion] every 3 weeks) to determine whether vemurafenib would prolong the rate of overall or progression-free survival, compared to dacarbazine. (13) All enrolled patients had unresectable, previously untreated Stage IIIC or IV melanoma with no active central nervous system (CNS) metastases. Melanoma specimens from all patients tested positive for the $BRAF^{V600E}$ 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 the investigators according to the RECIST, version 1.1. Primary endpoints were the rate of overall survival and progression-free survival. An interim analysis was planned at 98 deaths and a final analysis at 196 deaths; the published report is the interim analysis, reporting 118 deaths. The median survival had not been reached; results are summarized in Table 2. 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% of patients. The Data and Safety Monitoring Board determined that both co-primary endpoints had met prespecified criteria for statistical significance and recommended that patients in the dacarbazine group be allowed to cross over and receive vemurafenib. The results of this trial comprised the data supporting the efficacy and safety of vemurafenib for submission to the FDA and established the safety

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

Table 2. RCTs of BRAF inhibitors for BRAF-positive advanced melanoma

Study/year	F/U	Group	N	OS[1] (95% CI)	PFS[2] mths (95% CI)	ORR[3] (95% CI)
Vemurafenib						
Chapman 2011	6 mth.	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)	NR[4]
		p value		<0.001	<0.001	NR
Dabrafenib						
Hauschild 2012	4.9 mth (median)	Dabrafenib	187	89%	5.1 (median)	50% (42.4-57.1)
		Dacarbazine	63	86%	2.7 (median)	6% (1.8-15.5)
	Range (0-9.9 mth)	Hazard ratio		0.61 (0.25-1.48)	0.30 (0.18-0.51)	NR
		p value		NR	<0.0001	NR

[1] Overall survival
[2] Progression-free survival
[3] Objective response rate, including complete and partial responses
[4] NR – not reported

Phase II Clinical Trial. A Phase II trial, also known as BRIM-2, is currently ongoing at 13 centers. All patients were selected with the cobas 4800 BRAF V600 Mutation Test; 122 cases had $BRAF^{V600E}$-positive melanoma, and 10 cases were positive for $BRAF^{V600K}$. The early results of this trial have been published only as a meeting abstract and a meeting slide presentation. (14) The target overall response rate (primary outcome) was 30%, with a lower boundary of the 95% confidence interval (CI) of at least 20%. At a median follow-up of 10 months, this target was met with an overall response rate of 53% by independent review committee (IRC) (95% CI: 44-62%). 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 trial were to first determine the maximum dose in a dose-escalation phase, then determine the objective response rate and monitor toxicity. (17) This trial 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 trial, 26 of 32 patients with the $BRAF^{V600E}$ mutation responded (81%; 24 partial, 2 complete responses).

Dabrafenib. One Phase III randomized controlled trial on dabrafenib for melanoma has been published; the results of this trial are summarized in Table 2. 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.(18) Two-hundred-fifty patients were randomized 3:1 to receive oral dabrafenib 150 mg twice daily versus intravenous dacarbazine 1,000 mg/m2 every 3 weeks. The primary outcome was progression-free survival and secondary outcomes were overall survival, objective response rates, and adverse events.

Median progression-free survival 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 [HR]: 0.61,·30; 95% CI: 0.25-1.48). The objective response rate, defined as complete plus partial responses was higher 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 results demonstrate that targeting dabrafenib against BRAF V600E mutated melanoma results in a benefit in progression-free survival. 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.

Ongoing Clinical Trials

Despite impressive response rates in the Phase I trial, the duration of response to vemurafenib was limited to between 2 and 18 months 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. (19, 20) 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 MAP kinase signal-transduction pathway; like BRAF inhibitors, MEK inhibitors have been designed to interfere with this pathway and could be used in combination. Trametinib (GlaxoSmithKline), an MEK inhibitor, has recently been submitted to the FDA.

As noted, the BRAF inhibitor, dabrafenib is currently in Phase II and III clinical trials (NCT01227889; NCT01266967), and has been submitted to the FDA, along with a companion diagnostic test.

Resistance to BRAF inhibitors

Vemurafenib has demonstrated impressive ability to shrink tumors in patients with BRAF mutant melanomas; however, responses are typically short-lived (PFS, 5-7months) with resistance occurring in nearly every case. (13, 17, 18) Clinical trials are already underway combining treatment with vemurafenib and a MEK inhibitor in patients who have already been treated with vemurafenib (NCT01271803) and with dabrafenib and trametinib (NCT01584648) in hopes of overcoming resistance.

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 in advanced melanoma patients who are positive for the $BRAF^{V600E}$ mutation. One RCT evaluated vemurafenib and the second RCT evaluated dabrafenib. Both reported a benefit in progression-free survival for treatment with a BRAF inhibitor. In addition, the vemurafenib trial reported a significant improvement in overall mortality, while the dabrafenib trial did not demonstrate a difference in overall survival. These results, which are corroborated by earlier non-randomized studies, support the clinical validity and clinical utility of the cobas 4800 BRAF V600 Mutation Test, the companion diagnostic test for selection of patients for treatment with a BRAF inhibitor.

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. Vemurafenib currently has FDA-approval for treatment of BRAF-positive patients with advanced melanoma, but dabrafenib has not yet received FDA-approval.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN) Guidelines version 1.2013 Melanoma recommends vemurafenib for patients with V600E mutation of the BRAF gene, as documented by an FDA-approved or CLIA-approved facility.(21)

Medicare National Coverage
There is no national coverage determination.

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Billing Coding/Physician Documentation Information

81210 BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant

Additional Policy Key Words

Genetic testing

Policy Implementation/Update Information

4/1/03 New policy; may be medically necessary.
12/1/13 Policy Guidelines corrected to eliminate the sentence that states that there is no specific CPT code. No other policy statement changes.
