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Medical Policy Manual

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

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IMPORTANT REMINDER

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

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

DESCRIPTION

Serine-threonine protein kinase B-RAF (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 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 2013, more than 75000 new cases will be 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 with 5-year survival at 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 $BRAF^{V600E}$ and 16% are positive for $BRAF^{V600K}$.[3] Thus, approximately 45-60% of advanced melanoma patients might 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 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 (trade name Tafinlar®, also known as GSK2118436 or SB-590885) is a BRAF inhibitor developed by GlaxoSmithKline (GSK).[8,9] 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.[10]

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.[11] Trametinib inhibits growth of BRAF V600 mutation-positive melanoma cells in vitro and in vivo.[12]

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,[13] 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.

<u>Vemurafenib</u>

Currently only vemurafenib has FDA approval for treatment of advanced melanoma. 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.[14] 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.[15]

Dabrafenib

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.[10] Dabrafenib is specifically not indicated for the treatment of patients with wild-type BRAF melanoma.

Trametinib

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.[12] Trametinib is specifically not indicated for the treatment of patients previously treated with BRAF inhibitor therapy.[12]

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."[14]

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

MEDICAL POLICY CRITERIA

I. Testing for $BRAF^{V600}$ mutations 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.

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

SCIENTIFIC EVIDENCE

This policy was originally created in 2011 based on a Special Report by the BlueCross BlueShield Association Technology Evaluation Center (TEC).[16] 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.[17] Following is a summary of the key publications and regulatory documents included in the report.

Since the TEC Special Report, two additional Phase III randomized controlled trials (RCT) 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.

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.[17] 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.

Vemurafenib

Correlation of cobas 4800 BRAF V600 Mutation Test results to Sanger sequencing was tested in the Phase III trial of vemurafenib[18] on 596 consecutive patients, 449 of which 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[19] 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 BRAFV600 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.[20]

Halait et al. analyzed the analytical performance of cobas 4800 BRAF V600 Mutation Test and Sanger sequencing in 219 melanoma specimens.[21] 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%.

A similar study by Anderson et al. (2012) used screening specimens from Phase II and Phase III trials of vemurafenib.[22] 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.[21] 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 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[18]			
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[23]			
Only V600E	92.4		
V600E + V600K	100		
Phase I trial[20]			
Only V600E	97.3		
Analytical Performance Trial[21,22]			
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 formalin-fixed paraffin-embedded (FFPE) human melanoma tissue.[24] Two oligonucleotide probes labeled with different fluorescent dyes (one for internal controls and the other for mutation sequence alleles) were measured at characteristic wavelengths and compared by an autoanalyzer. Results were 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 was 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.

Clinical Validity and Utility

The clinical validity of a genetic test is its ability to accurately and reliably predict the clinically defined disorder or phenotype of interest; the clinical utility of a genetic test is the evidence of improved measurable clinical outcomes and its usefulness and added value to patient management and decision making compared with current management without genetic testing.[19]

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.

Vemurafenib

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, randomly assigned 675 patients 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.[19] 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 $BRAF^{V600D}$ 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. 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.

Phase II Clinical Trial

A Phase II trial, also known as BRIM-2, enrolled patients at 13 centers who had failed at least one previous treatment for metastatic melanoma.[23] All patients were selected with the cobas 4800 BRAF V600 Mutation Test; 122 cases had $BRAF^{V600E}$–positive melanoma, and 10 cases were positive for $BRAF^{V600K}$. The target overall response rate (primary outcome) was 30%, with a lower boundary of the 95% 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.[25] 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.[26] 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 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 with 14% in the dacarbazine group (hazard ratio [HR]: 0.61,·30; 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 higher

in the dabrafenib group (50%, 95% CI: 42.4-57.1%) compared with 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 non-infectious, febrile drug reactions (3% grade 3 pyrexia vs. none in controls); and severe hyperglycemia (>250-500 mg/dL), requiring medical management in non-diabetic or change in management of diabetic patients (6% vs. none in controls). The results demonstrate that targeting dabrafenib against BRAF V600E 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.

All tissue specimens from patients screened for enrollment in the clinical trial were analyzed centrally by a clinical trial assay.[24] 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. 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).

Trametinib

The clinical efficacy and safety of trametinib was assessed in the Phase III, open-label METRIC trial.[27] 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. 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. 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).[24]

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[18,23,25]; 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.[28,29] 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, such as trametinib, have been designed to interfere with this pathway and could 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.[30] 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.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN) Guidelines for melanoma, version 2.2014, recommend vemurafenib, dabrafenib, and trametinib "only for patients with V600 mutation of the BRAF gene, as documented by an FDA-approved or CLIA-approved facility."[31] Vemurafenib and dabrafenib both have category 1 recommendations as preferred regimens for advanced or metastatic melanoma. Trametinib (monotherapy) has a category 1 recommendation as an "other active regimen." There is no recommendation for combination therapy with these agents but NCCN acknowledge that "the clinical efficacy of combination therapy remains under investigation."

Summary

A large proportion of patients with advanced melanoma have a mutation in the serine-threonine protein kinase B-RAF (*BRAF)* gene. There are 2 Phase III randomized controlled trials (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 progression-free survival 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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32. BlueCross BlueShield Association Medical Policy Reference "BRAF Gene Mutation Testing To Select Melanoma Patients for BRAF Inhibitor Targeted Therapy." Policy No. 2.04.77

CROSS REFERENCES

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KRAS and BRAF Mutation Analysis in Colorectal Cancer, Genetic Testing, Policy No. 13

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

CODES	NUMBER	DESCRIPTION
CPT	81210	BRAF (*v-raf murine sarcoma viral oncogene homolog B1*) (e.g., colon cancer), gene analysis, V600E variant
HCPCS	None	