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Clinical Cancer Research

CCR Perspectives in Drug Approval

FDA Approval Summary: Vemurafenib for Treatment of Unresectable or Metastatic Melanoma with the BRAF^{V600E} Mutation

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Abstract

On August 17, 2011, the U.S. Food and Drug Administration (FDA) approved vemurafenib tablets (Zelboraf, Hoffmann-LaRoche Inc.) for the treatment of patients with unresectable or metastatic melanoma with the BRAF^{V600E} mutation as detected by an FDA-approved test. The cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems, Inc.) was approved concurrently. An international, multicenter, randomized, open-label trial in 675 previously untreated patients with BRAF^{V600E} mutation–positive unresectable or metastatic melanoma allocated 337 patients to receive vemurafenib, 960 mg orally twice daily, and 338 patients to receive dacarbazine, 1,000 mg/m^2 intravenously every 3 weeks. Overall survival was significantly improved in patients receiving vemurafenib [HR, 0.44; 95% confidence interval (CI), 0.33–0.59; $P < 0.0001$]. Progression-free survival was also significantly improved in patients receiving vemurafenib (HR, 0.26; 95% CI, 0.20–0.33; $P < 0.0001$). Overall response rates were 48.4% and 5.5% in the vemurafenib and dacarbazine arms, respectively. The most common adverse reactions (≥30%) in patients treated with vemurafenib were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, and nausea. Cutaneous squamous cell carcinomas or keratoacanthomas were detected in approximately 24% of patients treated with vemurafenib. Other adverse reactions included hypersensitivity, Stevens–Johnson syndrome, toxic epidermal necrolysis, uveitis, QT prolongation, and liver enzyme laboratory abnormalities. *Clin Cancer Res; 20(19); 4994–5000. ©2014 AACR.*

Introduction

Melanoma is the fifth leading cancer type in men and the seventh leading cancer type in women, with an estimated total of 76,100 new cases and 9,700 deaths due to melanoma in 2014 (1). The prognosis of metastatic melanoma is grim, with a median survival of approximately 6 months (2). Most somatic mutations in *BRAF* result in increased activity of BRAF kinase, leading to ERK activation and aberrant and uncontrolled cell proliferation and survival (3). In a prospective series of 308 patients with metastatic melanoma, 46% had a *BRAF* mutation—73% were V600E, 19% were V600K, and 6% were other (4).

At the time of approval of vemurafenib, three drugs were approved by the FDA for the treatment of advanced melanoma. Dacarbazine was approved over 30 years ago but no survival benefit has been demonstrated. In randomized trials, the response rates with single-agent dacarbazine ranged from 7% to 32% and the median overall survival (OS) ranged from 5.6 to 11 months (5). The aldesleukin approval in 1998 was based on 8 single-arm trials involving 270 patients with metastatic melanoma (6). The overall response rate (ORR; complete and overall responses) was 16% with a complete response rate of 6% and a median duration of complete response greater than 5 years. A meta-analysis of chemoimmunotherapy versus chemotherapy found increased response rates and toxicity with chemoimmunotherapy but no improvement in survival (7). Ipilimumab, a monoclonal antibody targeting CTLA-4, was approved in 2011 on the basis of a double-blind, randomized trial comparing ipilimumab to ipilimumab in combination with the peptide gp100 to gp100 alone (8). On FDA

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review, the HRs for death were 0.66 [95% confidence interval (CI), 0.51–0.87] for the comparison of ipilimumab to gp100 and 0.68 (95% CI, 0.55–0.85) for the comparison of ipilimumab plus gp100 to gp100. Median OS was 10 months in the ipilimumab and ipilimumab plus gp100 arms and 6 months in the gp100 alone arm. In another trial, ipilimumab in combination with darcabazine was compared with dacarbazine alone (9). Median OS in the ipilimumab–dacarbazine group was reported to be 11.2 months compared with 9.1 months in the dacarbazine group (HR, 0.72; 95% CI, 0.59–0.87).

Chemistry

The chemical name of vemurafenib is propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4difluoro-phenyl}-amide. Vemurafenib is supplied as 240 mg tablets for oral administration.

Nonclinical Pharmacology and Toxicology

Vemurafenib is a kinase inhibitor with activity against some BRAF kinases with activating mutations, particularly BRAF^{V600E}, wild-type BRAF, and other kinases. Antitumor activity was demonstrated in cellular and xenograft melanoma models with the BRAF^{V600E} mutation. Paradoxically, a dose-dependent acceleration of implanted human cutaneous squamous cell carcinomas (cuSCC) cell growth occurred in vemurafenib-treated mice.

The liver was the major target organ for toxicity in both rats and dogs with increases in cholesterol and liver enzymes observed. QTc prolongation occurred in cardiovascular safety pharmacology studies and long-term dog studies. Dogs also showed significant elevations in eosinophils, neutrophils, and monocytes. Although vemurafenib was negative for embryo-fetal toxicity in rat and rabbit reproductive toxicity studies, alterations in the BRAF signaling cascade have been associated with serious embryo-fetal toxicity, including embryolethality, severe growth retardation, and postnatal death. Also, congenital mutations of *BRAF* in humans have been associated with serious genetic disorders. Therefore, vemurafenib was designated Pregnancy Category D.

Clinical Pharmacology

In a population pharmacokinetic analysis, plasma concentration-time profile of vemurafenib was described by a one-compartment pharmacokinetic model with first-order absorption and first-order elimination. The pharmacokinetics at steady state was linear between 240 and 960 mg.

Bioavailability of vemurafenib had not been determined. Following oral administration of 960 mg twice daily for 15 days, the median t_{max} was approximately 3 hours, the mean (±SD) C_{max} was 62 μg/mL ± 17, and the AUC_{0-12} was 601 ± 170 μg*h/mL. A food effect study had not been conducted and vemurafenib was administered without regard to food in the clinical trial.

Vemurafenib is highly bound (>99%) to human albumin and alpha-1 acid glycoprotein, and the volume of distribution (V_{ss}) was estimated to be 106 L. Vemurafenib is mainly excreted in feces (94%), plasma clearance was 31 L/day, and the median elimination half-life was 57 hours. Vemurafenib clearance was similar in patients with normal, mild, and moderate hepatic impairment, but the effect of severe hepatic impairment on vemurafenib exposure was unknown. *In vitro*, vemurafenib is a substrate of CYP3A4 and both a substrate and inhibitor of P-glycoprotein. *In vivo*, vemurafenib is an inducer of human CYP3A4, a moderate inhibitor of CYP1A2 and a weak inhibitor of CYP2D6.

There was a statistically significant exposure–response relationship between progression-free survival (PFS) and vemurafenib exposure (C_{min}) but a conclusive relationship between exposure and OS could not be demonstrated. There was also a significant exposure–response relationship between the risk of cuSCC development and vemurafenib exposure (C_{min}). An exposure–QTc response analysis using data from the phase II trial showed that following treatment with vemurafenib 960 mg twice daily, the QTc interval was prolonged in a concentration-dependent manner but no large changes (i.e., >20 ms) in the mean QTc interval were detected.

Clinical Trials

The approval of vemurafenib was primarily based on a randomized, controlled, open-label, international, multicenter trial (BRIM-3) comparing vemurafenib with dacarbazine in 675 previously untreated patients with BRAF^{V600E} mutation–positive unresectable or metastatic melanoma as detected by the cobas 4800 BRAF V600 Mutation Test (10). Patients were randomly allocated to receive vemurafenib, 960 mg orally twice daily ($N = 337$), or dacarbazine, 1,000 mg/m^2 intravenously every 3 weeks ($N = 338$). Treatment was continued until disease progression, unacceptable toxicity, and/or consent withdrawal. Randomization was stratified according to disease stage, lactate dehydrogenase, ECOG performance status, and geographic region. The final co-primary endpoints were OS and investigator-assessed PFS. Key secondary endpoints included confirmed investigator-assessed best ORRs, time to response, duration of response, and safety.

The trial was originally designed with OS as the primary endpoint and a planned accrual of 680 patients to detect a difference in median OS of 10.7 versus 8 months and a HR of 0.75 with 80% power and two-sided 2.5% level of significance. However, in August 2010, the FDA became aware of the unprecedented activity of vemurafenib via publication of the phase I trial results reporting an unconfirmed ORR of 81% (26/32) in the extension phase (11). In addition, preliminary results of the phase II trial provided by the sponsor suggested a confirmed ORR of approximately 50%; final results were reported in 2012 (12). In addition to other recommendations, the sponsor was encouraged to modify the statistical analysis plan (SAP) of the ongoing BRIM-3 trial to increase overall study alpha level to two-sided 5%, set up an alpha spending rule with higher probability to cross at the interim analysis, use a less conservative

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target HR of 0.65, and add PFS as a co-primary endpoint (13, 14). The sponsor agreed and revised the SAP to conduct a final PFS analysis at the time of an interim OS analysis. The unstratified log-rank test was to be used in the analyses of both endpoints. Patients on dacarbazine were also allowed to crossover to vemurafenib after disclosure of positive study results.

Baseline characteristics were balanced between treatment groups. Fifty-six percent of patients were male, 99% were Caucasian, median age was 54 years, all patients had an ECOG performance status of 0 or 1, and 95% had metastatic disease. The median time from diagnosis of metastatic disease to enrollment on trial was 3 months.

Efficacy results

Efficacy results are summarized in Table 1. At the interim analysis of OS, the HR was 0.37 (95% CI, 0.26–0.55; $P < 0.001$) in favor of the vemurafenib arm. In an updated OS analysis before approval, the HR was 0.44 (95% CI, 0.33–0.59; $P < 0.0001$). The median OS had not been reached (NR) in the vemurafenib arm (95% CI, 9.6–NR) but was 7.9 months in the dacarbazine arm (95% CI, 7.3–9.6). The Kaplan–Meier curves for OS and PFS are shown in Figs. 1 and 2, respectively. In the final analysis of investigator-assessed PFS, the HR was 0.26 (95% CI, 0.20–0.33; $P < 0.0001$). The confirmed, investigator-assessed best ORR rate was 48.4% (95% CI, 41.6%–55.2%) in the vemurafenib arm compared with 5.5% (95% CI, 2.8%–9.3%) in the dacarbazine arm. There were 2 complete responses (0.9%) and 104 partial responses (47.4%) in the vemurafenib arm and 12 responses (5.5%), all partial, in the dacarbazine arm.

Updated results from the BRIM-3 trial were recently published (15). At 478 deaths and with a median follow-up on the vemurafenib arm of 13.4 months, the median OS without censoring at crossover from dacarbazine to vemurafenib was 13.6 months (95% CI, 12.0–15.3) on the vemurafenib arm and 10.3 months (95% CI, 9.1–12.8) on the dacarbazine arm.

Safety results

The primary safety population included 336 patients in the BRIM-3 trial who received at least one dose of vemurafenib and 287 patients who received at least one dose of dacarbazine. Dose reductions were reported in 33% and 15% of patients receiving vemurafenib and dacarbazine, respectively. Dose delays were reported in 44% of patients receiving vemurafenib and 2% of patients receiving dacarbazine. Treatment discontinuations due to adverse drug reactions occurred in 7% of patients receiving vemurafenib and 4% of patients receiving dacarbazine. The most common adverse reactions leading to treatment discontinuation on the vemurafenib arm were arthralgia, dysphagia, and pneumonia.

As shown in Table 2, the most common (≥10%) grade 1–4 adverse reactions in patients receiving vemurafenib were nausea, diarrhea, vomiting, constipation, fatigue, pyrexia, peripheral edema, asthenia, increased lactate dehydrogenase (LDH), increased alkaline phosphatase, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased γ-glutamyl transpeptidase (GGT), increased bilirubin, increased creatinine, decreased appetite, arthralgia, pain in extremities, myalgia, skin papilloma, cuSCC, headache, dysgeusia, rash, alopecia, pruritus, erythema, photosensitivity reaction, hyperkeratosis, and dry skin. The most common (≥5%) grade 3–4 adverse reactions in patients receiving vemurafenib were cuSCC, increased GGT, and rash. Other notable toxicities included uveitis, blurred vision, iritis, and photophobia.

Deaths not directly attributed to disease progression and occurring within 28 days of the last dose of study drug were reported in four (1%) patients receiving vemurafenib and in two (<1%) patients receiving dacarbazine. Fatal adverse reactions in patients receiving vemurafenib were cerebrovascular accident, pneumonia, cardiopulmonary failure, and aortic aneurysm rupture. None were attributed to vemurafenib.

Table 1. Efficacy of vemurafenib in previously untreated patients with *BRAF*^{V600E} mutation–positive melanoma[a]

	Vemurafenib ($N = 337$)	Dacarbazine ($N = 338$)	P[d]
OS			
Number of deaths	78 (23%)	121 (36%)	
HR (95% CI)[b]	0.44 (0.33–0.59)		<0.0001
Median survival, mo (95% CI)[c]	Not reached (9.6–not reached)	7.9 (7.3–9.6)	—
Median follow-up, mo (range)	6.2 (0.4–13.9)	4.5 (<0.1–11.7)	
PFS			
HR (95% CI)[b]	0.26 (0.20–0.33)		<0.0001
Median PFS, mo (95% CI)[c]	5.3 (4.9–6.6)	1.6 (1.6–1.7)	—

[a]As detected by the cobas 4800 BRAF V600 Mutation Test.
[b]HR estimated using Cox model; a HR of <1 favors Zelboraf.
[c]Kaplan–Meier estimate.
[d]Unstratified log-rank test.

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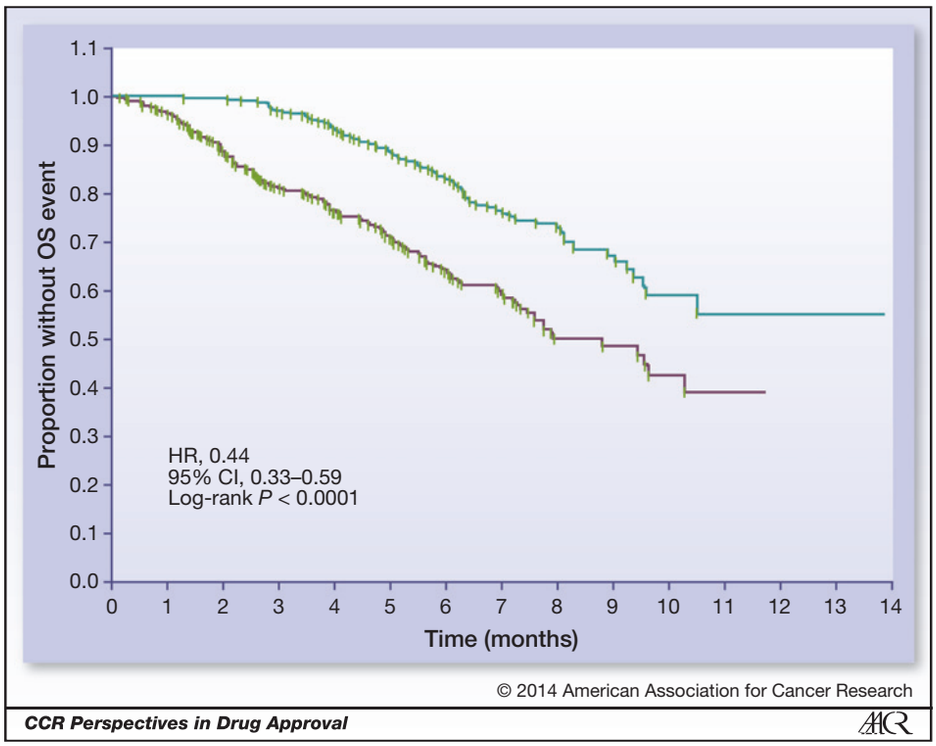

Figure 1. Kaplan–Meier curves of overall survival.

Keratoacanthomas or cuSCCs occurred in approximately 24% of patients receiving vemurafenib. There were also 8 new primary melanoma lesions in 7 patients in the vemurafenib group. The cuSCCs and melanomas were excised, and patients continued vemurafenib without dose interruption or reduction.

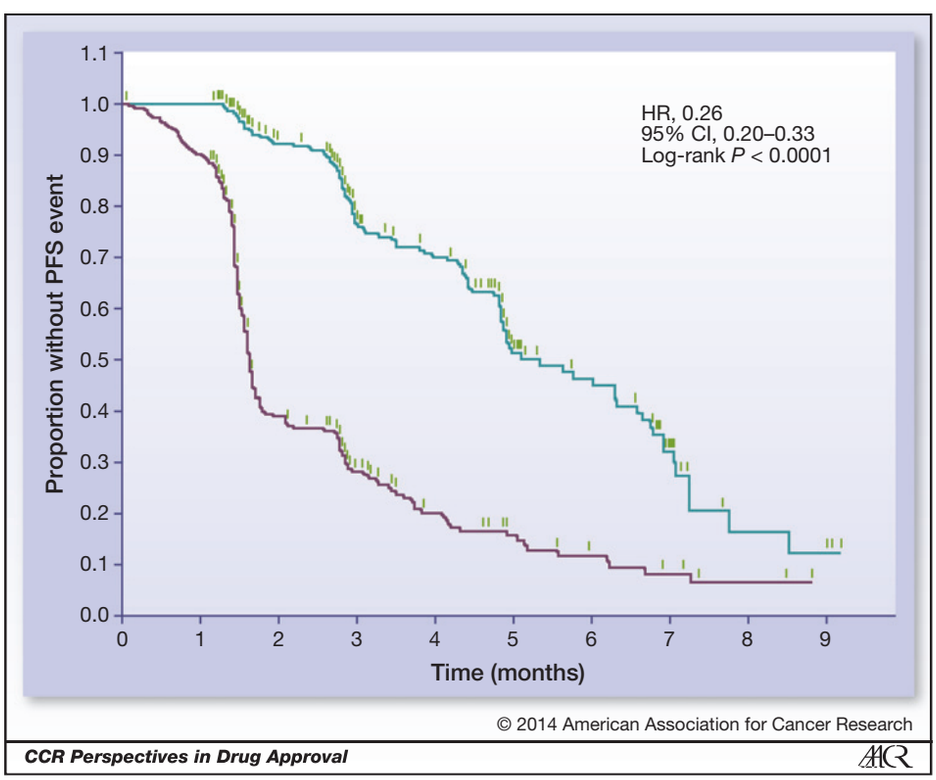

Figure 2. Kaplan–Meier curves of PFS.

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Table 2. Adverse reactions reported in ≥10% of patients treated with vemurafenib

	Vemurafenib ($N = 336$)		Dacarbazine ($N = 287$)	
	Grade 1–4 (%)	Grade 3–4 (%)	Grade 1–4 (%)	Grade 3–4 (%)
Any adverse event	331 (98.5)	197 (58.6)	261 (90.9)	96 (33.4)
Gastrointestinal disorders				
Nausea	116 (34.5)	7 (2.1)	124 (43.2)	5 (1.7)
Diarrhea	95 (28.3)	3 (<1)	37 (12.9)	1 (<1)
Vomiting	60 (17.9)	4 (1.2)	76 (26.4)	3 (1)
Constipation	40 (11.9)	1 (<1)	68 (23.6)	0
General disorders and admin site conditions				
Fatigue	127 (37.8)	7 (2.1)	96 (33.4)	6 (2.1)
Pyrexia	64 (19)	2 (<1)	25 (8.7)	3 (1)
Peripheral edema	56 (16.7)	3 (<1)	13 (4.5)	0
Asthenia	36 (10.7)	2 (<1)	25 (8.7)	2 (<1)
Investigations				
Increased LDH	219 (65.2)	9 (2.7)	159 (56.4)	12 (4.3)
Hyperglycemia	184 (54.8)	7 (2.1)	155 (55)	6 (2.1)
Increased alkaline phosphatase	168 (50)	10 (3)	74 (26.2)	2 (<1)
Increased ALT	145 (43.2)	9 (2.7)	104 (36.9)	5 (1.8)
Increased GGT	136 (40.5)	38 (11.3)	107 (37.9)	24 (8.5)
Increased AST	129 (38.4)	3 (<1)	76 (27)	1 (<1)
Increased bilirubin	119 (35.4)	6 (1.8)	34 (12.1)	0
Increased creatinine	100 (29.8)	5 (1.5)	32 (11.3)	5 (1.8)
Metabolism and nutrition disorders				
Decreased appetite	60 (17.9)	0	24 (8.3)	1 (<1)
Musculoskeletal and connective tissue disorders				
Arthralgia	180 (53.6)	15 (4.5)	9 (3.1)	2 (<1)
Pain in extremity	60 (17.9)	2 (<1)	17 (5.9)	5 (1.7)
Myalgia	42 (12.5)	1 (<1)	4 (1.4)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Skin papilloma	72 (21.4)	1 (<1)	0	0
cuSCC[a]	81 (24)	74 (22)	1 (<1)	1 (<1)
Nervous system disorders				
Headache	78 (23.2)	3 (<1)	30 (10.4)	0
Dysgeusia	48 (14.3)	0	9 (3.1)	0
Skin and subcutaneous tissue disorders				
Rash	124 (36.9)	28 (8.3)	7 (2.4)	0
Alopecia	150 (44.6)	2 (<1)	6 (2.1)	0
Photosensitivity reaction	110 (32.7)	9 (2.7)	10 (3.5)	0
Pruritus	77 (22.9)	5 (1.5)	4 (1.4)	0
Hyperkeratosis	82 (24.4)	4 (1.2)	2 (<1)	0
Dry skin	63 (18.8)	0	3 (1)	0
Erythema	48 (14.3)	0	7 (2.4)	0

[a]Includes both squamous cell carcinoma of the skin and keratoacanthoma.

In vitro diagnostic

The cobas 4800 BRAF V600 Mutation Test is real-time PCR-based *in vitro* diagnostic using DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue. It is intended for the selection of patients with $BRAF^{V600E}$-mutated melanoma for treatment with vemurafenib. The cobas and bidirectional Sanger sequencing results were compared in 449 evaluable cases (16). By the cobas test, there were 216 "mutation detected" cases. However, 35 of these were not V600E mutations by sequencing: 8 were wild-type, 25 were V600K, 1 was V600E2, and 1 was V600D. Six specimens were identified as "mutation not detected" by cobas but were V600E by sequencing. The positive percent agreement was 97.3%, the negative percent agreement was 84.6%, and the overall percent agreement was 90.9%.

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Seven of 16 (44%) patients with tumors positive for the V600E mutation by the cobas test but V600K by sequencing received vemurafenib and had a confirmed response, a response rate similar to that seen in the V600E population. The applicant agreed to a postmarketing commitment to develop an Investigational Use Only Companion Diagnostic (IUO CoDx) that reliably detects the *BRAF*^{V600K} mutation in tumors of patients with unresectable or metastatic melanoma and to conduct an open-label, single-arm trial in a population identified by this test with ORR and duration of response as the primary endpoints.

Discussion

Until 2011, there were no approved agents that had demonstrated a survival benefit in advanced malignant melanoma. Vemurafenib represents an important new treatment option for patients with BRAF^{V600E} mutation–positive unresectable or metastatic melanoma and is the first personalized therapy for melanoma in which patients are selected using an analytically and clinically validated test. The new drug application was approved less than 4 months after submission.

Except for 5 patients in the dose-escalation portion of the phase I trial, vemurafenib had not been studied in patients whose melanomas were negative by the cobas test for the BRAF^{V600E} mutation. No responses were seen and vemurafenib was not recommended for use in patients with wild-type (*wt*)*BRAF* or other *BRAF* mutations. In addition, there are data from xenograft models that RAF inhibitors can activate the RAF–MEK–ERK pathway in *wtBRAF* tumors and enhance growth (17).

This application provides an example of the need for sponsors and the FDA to communicate and respond rapidly to important new information. With publication of the unprecedented results from the phase I trial, followed shortly thereafter by preliminary confirmation of activity of vemurafenib in the phase II trial, it became clear that the assumptions used to design the BRIM-3 trial were overly conservative. The FDA and the sponsor worked together quickly to amend the rapidly accruing BRIM-3 trial and to open an expanded access program.

The risk of developing cuSCCs was identified early in clinical trials, and dermatologic monitoring plans were implemented in all subsequent trials. cuSCCs have also been seen in patients receiving sorafenib, and the mechanism may be related to activating *RAS* mutations (18). New primary malignant melanomas were identified as a risk in the BRIM-3 trial. Although the risk:benefit ratio for vemurafenib was clearly favorable for the indicated population, secondary malignancies in the adjuvant setting or in other patient populations are more of a concern. This led to two postmarketing requirements for annual reporting to FDA of secondary malignancies occurring in ongoing phase III adjuvant melanoma and phase II papillary thyroid cancer trials.

Potential mechanisms of drug resistance reported include promotion of RAF dimerization by elevation of wtRAF expression or RAS activity, a variant form of BRAF^{V600E} (p61BRAF V600E) with enhanced dimerization in cells with low levels of RAF activation, BRAF^{V600E} splicing variants lacking the RAS-binding domain, receptor tyrosine kinase-mediated activation of alternative survival pathways, activated RAS-mediated reactivation of the MAPK pathway, PDGFRβ upregulation, NRAS mutations, or COT activation of ERK (19–22).

Other postmarketing requirements included an *in vitro* screen to determine whether vemurafenib inhibits CYP2C8 or CYPB9, drug interaction trials to evaluate the effects of strong CYP3A inducers and inhibitors on the pharmacokinetics of vemurafenib, a trial to assess the effects of severe hepatic impairment on the pharmacokinetics of vemurafenib, and a final analysis of safety in BRIM-3. Other postmarketing commitments included submission of updated survival results from the BRIM-3 trial and an assessment of changes from baseline in *NRAS* mutation status at disease progression in patients with advanced melanoma positive for the V600E mutation who have been treated with vemurafenib.

After approval, information about non-cuSCCs of the head and neck and the potential for promotion of *wtBRAF* melanomas and malignancies associated with activation of *RAS* was added to the labeling as Warnings and Precautions. Other new warnings and precautions included increases in transaminases and bilirubin in patients receiving concomitant ipilimumab and vemurafenib and drug reaction with eosinophilic systemic symptoms syndrome (23).

Disclosure of Potential Conflicts of Interest

Q.C. Xu was an employee of the FDA at the time of article submission; she is now an employee of Celgene. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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