CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	8/10/2011
From	Yangmin Max Ning, MD, PhD John Jonson, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 202-429
Applicant	Hoffmann-La Roche Inc.
Date of Complete Submission	4/28/2011
PDUFA Goal Date	10/28/2011
Proprietary Name / Established (USAN) Name	ZELBORAF (vemurafenib)
Dosage forms / Strength	Film-coated tablet of 240mg vemurafenib
Proposed Indication(s)	For the treatment of $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma
Recommended:	Full Approval

1. Introduction

Hoffmann-La Roche Inc. submitted an NDA (202-429) for Zelboraf (vemurafenib tablet) on a rolling basis from February 14 to April 28, 2011. The NDA requested marketing approval of Zelboraf for "the treatment of unresectable or metastatic BRAF mutation-positive melanoma by the cobas® 4800 BRAF V600 Mutation Test".

The application is supported primarily by a randomized, open-label, dacarbazine-controlled phase 3 trial (NO25026) and a single-arm Phase 2 trial (NO22657) in patients with advanced melanoma positive for BRAF V600E mutation. The two studies were conducted and analyzed as preplanned in their protocol. The Phase 3 trial revealed compelling efficacy results from the interim analysis conducted in January 2011 and patients receiving dacarbazine in the trial were allowed to crossover to receive vemurafenib after the analysis.

Vemurafenib is a new molecular entity that acts as a serine-threonine kinase inhibitor of the oncogenic BRAF protein. The BRAF V600E mutation consists of a single substitution of glutamic acid for valine at codon 600 of the BRAF protein and is the most common activating mutation identified in BRAF. This mutation is found

in approximately 50% of patients with metastatic melanoma. Vemurafenib inhibits the gained function of BRAF from the V600E mutation.

This application is recommended for regular approval based on the review findings described in each review discipline involved. This CDTL review summaries key findings from all the disciplines and assesses the approvability of the NDA.

The recommended indication will be "ZELBORAF is indicated for the treatment of patients with unresectable or metastatic melanoma with the $BRAF^{V600E}$ mutation as detected by an FDA-approved test". This reflects the patient population in the clinical trials. At present, the FDA-approved test for detecting the $BRAF^{V600E}$ mutation will be the Roche's cobas® 4800 $BRAF^{V600}$ Mutation Test.

Confirmation of $BRAF^{V600E}$ mutation using an FDA-approved test is required before treatment with vemurafenib, since the safety and efficacy of vemurafenib have not been studied in patients with wild-type $BRAF^{V600}$ melanoma.

The approval also contains a Medication Guide proposed primarily to address the increased risk for cutaneous squamous cell carcinomas during use of vemurafenib. This Medication Gide also helps patients understand other risks associated with vemurafenib.

2. Background

Metastatic melanoma is the leading cause of deaths from skin cancers. In 2010, approximately 8,700 patients in the US died of the disease. The median survival of patients with metastatic melanoma is about 6-9 months based on retrospective analyses. However, the prognosis of those patients may be affected by a number of factors such as overall performance status, primary tumor pathologic feature, locations of metastasis, or serum lactate dehydrogenase level. [1,2] Recent evidence[3] suggests that patients whose metastatic melanoma has mutations in the BRAF oncogene may have a poorer survival compared to those with metastatic melanoma bearing wild-type BRAF. Approximately 50% of metastatic melanomas contain BRAF mutations. Patients with mutated BRAF in their tumors likely represent a unique subgroup of metastatic melanoma.

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[1] *Balch CM et al. Final Version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol (2009) 27:6199-6206.*
[2] *Korn EL et al. Meta-Analysis of Phase II Cooperative Group Trials in Metastatic Stage IV Melanoma to Determine Progression-Free and Overall Survival Benchmarks for Future Phase II Trials. J Clin Oncol (2008) 26:527-534.*
[3] *Long GL et al: Prognostic and Clinicopathologic Associations of Oncogenic BRAF in Metastatic Melanoma J Clin Oncol (2011) 29:1239-1246.*

To date, three products have received FDA approval for the treatment of metastatic melanoma, including ipilimumab (Yervoy, approved in 2011), interleukin-2 (Proleukin, approved in 1998) and dacarbazine (approved in 1975). Of the three products, ipilimumab is the only product whose approval was based on an improvement in overall survival (OS), the gold standard endpoint for assessing the clinical benefit of an active antitumor product.

Ipilimumab (Yervoy) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody that prolonged the OS of patients with advanced melanoma when used as a single agent[4] or in combination with dacarbazine[5] in metastatic melanoma. In patients with unresectable or metastatic melanoma who had received prior systemic therapy, ipilimumab alone was associated with a median survival of 10 months (95% CI 8.0, 13.8) compared with a median survival of 6 months (95% CI 5.5, 8.7) in the control [HR 0.66 (95% CI 0.51, 0.87)]. When administered in combination with dacarbazine in patients with previously untreated metastatic melanoma, ipilimumab was associated with a longer overall survival than dacarbazine plus placebo (HR 0.72; P<0.001). The median overall survival in the ipilimumab–dacarbazine arm was 11.2 months (95% CI, 9.4, 13.6) as compared with 9.1 months (95% CI, 7.8, 10.5) in the placebo-dacarbazine arm. Despite the improvement in OS, both trials showed no significant improvements in PFS or overall response rate when compared to the control in each trial, highlighting the previous notion that no relationship has been established between PFS or response rate and OS in metastatic melanoma[6].

Interleukin-2 (IL-2) and dacarbazine are also indicated for the treatment of advanced melanoma, but none of them were associated with an improvement in OS in clinical trials supporting their approval. The response rate to either product has been approximately 10-20% in patients with metastatic melanoma. Nevertheless, it is important to realize that IL-2 can induce long-lasting, complete response in approximately 5% of patients treated with the product. However, no reliable markers have been identified for selecting patients who would most likely benefit from IL-2 treatment.

Identification of activating BRAF mutations in cancers was reported initially in 2002. The most common mutation was a single substitution (V599E) of glutamic acid for valine.[7] This mutation, corrected later as V600E mutation instead[8], was found in

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[4] *Hodi FS et al: Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med (2010) 363;711-723*
[5] *Robert C et al. Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. N Engl J Med (2011); 364:2517-26.*
[6] *Korn EL, et al. Meta-Analysis of Phase II Cooperative Group Trials in Metastatic Stage IV Melanoma to Determine Progression-Free and Overall Survival Benchmarks for Future Phase II Trials. J Clin Oncol (2008) 26:527-534.*
[7] *Davies H et al. Mutations of the BRAF gene in human cancer. Nature (2002) 417: 949-954*

56% of melanoma cell lines screened. Since then, mounting evidence has revealed a similar prevalence of the BRAF V600E mutation in melanoma samples from patients and that suppression of its expression or its function caused tumor growth arrest or promoted apoptosis, making this mutation an attractive target for treatment of melanoma.

In 2006, an IND of PLX4032 (b) (4) also named RO5185426 or vemurafenib now, was submitted to the FDA for investigation in patients with tumors containing BRAF V600E mutation, including melanoma. The preclinical studies suggested that the product acts as a selective inhibitor of the BRAF V600E mutant.

The Phase 1 study[9] of PLX4032 demonstrated that 11 of 16 patients (68%) with metastatic melanoma positive for the BRAF V600E mutation responded to the product at dosing schedules of 240 mg –1200 mg BID in the dose-escalation phase. This unprecedented, high response rate in metastatic melanoma was further verified in the extension cohort of the study that showed 26 of 32 patients with BRAF V600E positive metastatic melanoma responded to PLX4032 at the determined MTD schedule of 960 mg BID.

In May of 2009, the current applicant and the original sponsor Plexxikon discussed the proposed development plan with the Agency based on the above dose-escalation phase results from the 16 patients (one year before the above extension cohort results became available). The Agency recommended the sponsors conduct a randomized Phase 3 trial with overall survival as the primary endpoint given that no evidence showed that response rate or PFS is an adequate surrogate endpoint in metastatic melanoma. In addition, the Agency expressed its willingness to discuss use of a single-arm study to support accelerated approval “once the sponsor has more data suggesting impressive activity”. To effectively identify study patients eligible for the product, the Agency also discussed issues on the development of a companion diagnostic to detect the BRAF V600E mutation with clinical trials.

In September of 2009, the applicant initiated an open-label, single-arm Phase 2 study in patients with previously treated metastatic melanoma positive for the BRAF V600E mutation. The efficacy endpoints were best overall response rate and response duration. The trial enrolled 132 patients and the preliminary results suggesting a response rate of about 50% were shared with the Agency in August 2010.

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[8] *Wellbrock C. et al: The RAF Proteins Take Center Stage. Nature Review (2004) 5: 875-885*
[9] *Flaherty KT et al. Inhibition of Mutated, Activated BRAF in Metastatic Melanoma N Engl J Med (2010) 363:809-19.*

In January of 2010, the applicant initiated a randomized, open-label Phase 3 trial in previously untreated patients with advanced melanoma positive for the BRAF mutation comparing the product with dacarbazine. This trial design adopted the Agency's recommendations to the applicant for revising its original protocol that intended to conduct a double-blind, double-placebo controlled, randomized Phase 3 trial with overall survival as the primary endpoint. In September and October of 2010, the Agency recommended that the sponsor amend the statistical plan for this Phase 3 trial after more data from the Phase 1 extension cohort and the Phase 2 emerged that suggested consistent, high responses to the product (response rates of 50%-80% with an estimated median progression-free time of 7 months) in the target patient population. The projected overall survival hazard ratio was adjusted from the original 0.75 to 0.65 in the amended statistical plan when an estimated median survival of 8 months remained the same for the dacarbazine arm. The change resulted in a reduction in the number of deaths required for final overall survival analysis from the originally planned 468 to approximately 196 after the adjustment. At the same time, PFS was added as a co-primary endpoint with the Agency's recommendation and the final analysis of PFS was to be performed at the time of the interim analysis of OS.

Other relevant regulatory actions were that Fast Track designation was granted to the product in June of 2010 and that an expanded access protocol for the product was approved in November of 2010. The product also received Orphan Drug Designation.

In January of 2011, the applicant informed the Agency that the pre-planned interim analysis results from the Phase 3 trial showed a statistically significant improvement in overall survival in patients receiving RO5185426 (vemurafenib) compared to patients receiving dacarbazine, with a hazard ratio of 0.376 ($p<0.001$). The Agency agreed to the recommended crossover of patients receiving dacarbazine in the trial to receive R05185426.

This NDA for vemurafenib (Zelboraf™) was submitted on a rolling basis with the last part (clinical datasets and study reports) received on April 28, 2011. The key clinical study supporting the proposed indication was the above Phase 3 trial. Results from the Phase 2 trial provided supportive evidence for the application.

3. CMC

All CMC-related deficiencies identified during the review have been resolved for this NDA. The CMC review recommended for approval with inclusion of the following expiration dating information on the intended commercial product batches in action letter.

"The drug product is granted a twelve (12) month expiry when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF). As agreed, validation batches M0020, M0021 and M0022 only are granted a twenty-four (24) month expiry at USP controlled room temperature provided you submit quarterly (every three months) stability updates for these three batches, as general correspondences to the NDA, through the 24-month expiry."

Vemurafenib (RO5185426) is a new molecular entity with the molecular formula $C_{23}H_{18}ClF_2N_3O_3S$ and a molecular weight of 489.9. It is provided as film-coated tablets containing 240 mg of vemurafenib in each tablet for oral administration. The product is supplied in bottles of 120 tablets. The inactive ingredients of vemurafenib tablets are as follows: Tablet Core: hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and hydroxypropyl cellulose. Coating: pinkish white: poly(vinyl alcohol), titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red.

The drug substance is relatively stable, but has poor aqueous solubility and low bioavailability (BCS Class IV drug). To improve the apparent solubility and bioavailability, (b) (4) The applicant initially provided CMC information on three commercial batches of drug product intended to supply launch materials (b) (4) and proposed a (b) (4) expiry for this product when stored in the commercial packaging at 25ºC. However, the applicant specified in July 2011 that the above supply launch materials were not going to be marketed. Instead, the applicant submitted information on three new marketing launch materials (validation batches M0020, M0021 and M0022, manufactured in April 2011 or after the initial NDA submission).

The CMC review of the new CMC data found that "these three validation batches would be subject to the 12 month drug product expiry and therefore patient supply for launch and beyond was not assured". As such, additional information for the new launch batches were requested in order to assess the feasibility of exercising regulatory discretion on their expiry to extend shelf life in the interests of avoiding a drug shortage. The final CMC review concluded that "sufficient information was provided to support the extension of the shelf life of the validation batches M0020, M0021 and M0022 to 24 months, provided additional stability monitoring is performed". As a result, the applicant is required to submit stability data on these

validation batches every three months through the 24-month expiration dating period. (See the CMC reviews for details).

4. Device

The CDRH review of the applicant's companion diagnostic named "cobas® 4800 BRAF V600 Mutation Test", submitted in parallel with this NDA, found adequate evidence to support use of the test for selecting patients whose melanoma has the BRAF V600E mutation.

This companion diagnostic is an automated PCR-based test, designed specifically to determine whether the BRAF V600E mutation is present in melanoma samples from a patient. The test was employed in the Phase 3 and Phase 2 clinical trial described in the clinical review and its accuracy was examined against the results from the Sanger's bidirectional sequencing (reference method) of the same melanoma sample.

The primary objective of the diagnostic study was to evaluate the performance of the cobas® 4800 BRAF V600 Mutation Test in detection of BRAF V600E mutation in melanoma samples. Its accuracy was assessed using 449 evaluable specimens from the Phase 3 trial for which Sanger sequencing data were also collected. The agreement analysis of the cobas test results with Sanger sequencing results for the detection of the V600E mutation demonstrated a positive agreement of 97.3%, a negative percent agreement of 84.6%, and an overall agreement of 90.9%. A total of 35 mutations detected by the cobas test were identified not representing V600E mutations per the Sanger's sequencing results: 25 were the V600K mutation, 8 were wild-type BRAF and 2 were other V600 mutation, suggestive of the cobas test's cross-reactivities in detecting non-V600E mutations or wild-type BRAF. The limited number of samples suggested that for the V600K mutation, the cobas test has a cross-reactivity rate of 65.8% (25 of 38 samples). On the other hand, 2.7 % of specimens harboring the V600E mutation as determined by Sanger sequencing were not identified by the cobas test, suggesting that the cobas test may miss a few of patients whose melanoma actually has the V600E mutation. The distribution of discrepant results within the evaluable sample population was comparable to that observed with the evaluable samples from the Phase 2 trial.

Overall, the analytical sensitivity and specificity results provided adequate evidence for use of the cobas® 4800 BRAF V600 Mutation Test to reliably detect the presence of the BRAF V600E mutation in melanoma samples. [See the CDRH Summary of Safety and Effectiveness Data (SSED) and product labeling for more complete information on cobas® 4800 BRAF V600 Mutation Test].

5. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology findings from the review of the submitted studies were supportive of approval for the proposed clinical indication.

Vemurafenib is an inhibitor of the BRAF serine-threonine kinase. In cultured cell assays vemurafenib inhibited the growth of cells expressing the V600E mutation at sub-micromolar concentrations. It also showed *in vivo* activity in xenograft studies in mice bearing various tumors containing the V600E mutation. Despite the observations, vemurafenib inhibited numerous other kinases at sub-micromolar concentrations in vitro, such as wild-type or other mutants of BRAF, CRAF, ARAF, SRMS, ACK1, MAP4K5 and FGR.

Vemurafenib caused QT prolongations in dogs. Studies with isolated canine cardiac Purkinje fibers showed a decrease in V_{max} of about 50%, suggesting the possibility of cardiac conduction inhibition.

Vemurafenib will be labeled a Pregnancy Category D product. The reproductive toxicity studies showed vemurafenib did not cause fetal damage during organogenesis at doses that caused only minimal or no toxicity to the dams. Nevertheless, in BRAF knockout mice the placenta fails to form properly. In addition, mutations in BRAF have been associated with congenital disorders in humans.

Studies of acute and chronic toxicity in animals showed gastrointestinal disturbances, hypoactivity, increases in enzymes or proteins from the liver and pancreas, a dose-dependent neutrophilia with profound eosinophilia, and weight changes in numerous organs including the liver, adrenal glands, and thymus. Most of these toxicities showed signs of resolution after a drug-free recovery period. Vemurafenib absorbs UV-A and UV-B light. It was phototoxic to mouse fibroblasts in vitro.

Studies submitted also showed that vemurafenib was not mutagenic in the Ames assay nor genotoxic in an in vitro test using fresh human peripheral blood lymphocytes and in the rat bone marrow erythrocytes micronucleus test.

Nonclinical carcinogenicity were not required or submitted for approval in a patient population with advanced cancer. However, vemurafenib increased the incidence of cutaneous squamous cell carcinomas in clinical trials. An increased detection of new primary melanomas was also noted in the clinical trials. (See primary clinical review)

6. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology and Pharmacometrics review concluded that this NDA is considered acceptable from a clinical pharmacology perspective.

The recommended dose of vemurafenib is 960 mg (four 240 mg tablets) twice daily. The first dose should be taken in the morning and the second dose should be taken in the evening approximately 12 hours later. Each dose can be taken with or without a meal. However, potential effects of food on vemurafenib absorption are currently unknown and a dedicated food effect trial is ongoing.

The absolute or relative bioavailability of vemurafenib is unknown. The median T_{max} was approximately 3 hours. Vemurafenib is highly bound (> 99%) to human albumin and alpha-1 acid glycoprotein plasma proteins. The median of the individual elimination half-life estimates for vemurafenib was 57 hours.

In the human mass balance trial, 94% of the oral vemurafenib dose was recovered in feces and 1% was recovered in urine. These results along with the population PK analysis suggest that renal clearance does not appear to be an important elimination pathway for vemurafenib. Vemurafenib clearance was similar in patients with normal hepatic function and patients with mild and moderate hepatic impairment. Therefore, dose adjustments are not needed for patients with mild and moderate hepatic impairment. The effect of severe hepatic impairment on vemurafenib exposure is unknown at present and needs to be studied.

In vivo, vemurafenib is a moderate inhibitor of human CYP1A2, a mild inhibitor of CYP2D6 and an inducer of CYP3A4. In vitro, vemurafenib is a CYP3A4 substrate. The in vivo effect of strong CYP3A4 inhibitors and inducers on vemurafenib pharmacokinetics was not assessed.

Vemurafenib prolonged the QTc interval in a concentration dependent manner based on the exposure-QTc response analysis using data from132 patients with BRAF V600E mutation-positive metastatic melanoma who were enrolled in the Phase 2 clinical trial of vemurafenib. On Day 15 of Cycle 1, the largest mean change from baseline was 12.8 ms (upper boundary of the 2-sided 90% confidence interval of 14.9 ms), detected at 2 hours post-dose. In the first 6 months of treatment, the largest observed mean change from baseline was 15.1 ms at a pre-dose time point (upper boundary of the 2-sided 90% confidence interval of 17.7 ms). No large changes (i.e., > 20 ms) in the mean QTc interval were detected.

Exploratory analyses showed that there was a statistically significant exposure-response relationship between PFS prolongation and vemurafenib exposure (C_{min}) ($p < 0.0001$), as well as between the incidence of squamous cell carcinomas and

vemurafenib exposure (C_{min}) (p <0.0001). (Also see the clinical review for more information)

7. Clinical Microbiology

There were no microbiology issues.

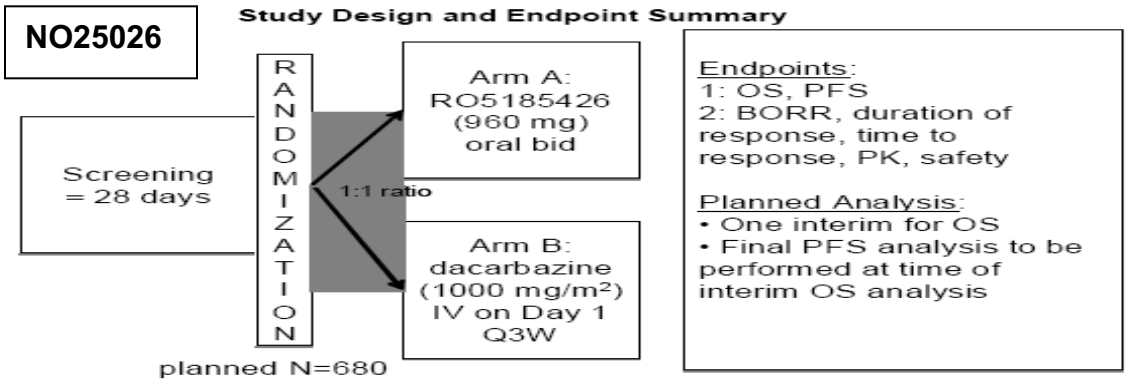
8. Clinical/Statistical- Efficacy

Both clinical and statistical reviews found substantial evidence to support the proposed indication.

This application is primarily based on a randomized, open-label, dacarbazine-controlled Phase 3 trial (NO25026 or BRIM 3) with a single-arm Phase 2 trial (NO22657) as supportive evidence. Both trials were conducted in patients with advanced melanoma positive for BRAF V600E mutation as detected by the cobas® 4800 BRAF V600 Mutation Test, but differed in whether patients received prior systemic therapy as well as in primary efficacy assessments. The Phase 3 trial enrolled patients who had no prior therapy with overall survival as the primary endpoint (PFS added as a co-primary endpoint during the trial), while the Phase 2 trial targeted patients who had received at least one prior systemic therapy with the best overall response rate as the primary endpoint. The two trials used the same dosing regimen of vemurafenib, 960 mg administered orally twice daily. In both trials, treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. The efficacy results from the two trials are summarized separately as follows.

Phase 3 Trial Design and Results:

NO25026 (BRIM 3) was a randomized, controlled, open-label, multicenter phase 3 trial comparing vemurafenib to dacarbazine in patients with BRAF V600E mutation-positive unresectable or metastatic melanoma. Its design is shown below:



Stratification factors at randomization included: metastatic disease stage classification, ECOG performance status, LDH level, and geographic region.
BORR = best overall response rate; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics.

The key eligibility criteria included:

1. Histologically confirmed metastatic melanoma (surgically incurable and unresectable Stage IIIC or Stage IV (American Joint Committee on Cancer [AJCC]). Unresectable Stage IIIC disease needed confirmation from a surgical oncologist.
2. Treatment-naïve, i.e., no prior systemic anti-cancer therapy for advanced disease (Stage IIIC and IV). Only prior adjuvant immunotherapy was allowed.
3. Must have had a *BRAF* V600-positive mutation (by Roche cobas test) prior to administration of study treatment
4. ECOG performance status of 0 or 1
5. Life expectancy > 3 months
6. Measurable disease by RECIST criteria (version 1.1) prior to the administration of study treatment
7. Adequate hematologic, renal, and liver function as defined by laboratory values performed within 28 days prior to initiation of dosing
8. Cutaneous SCC lesions identified at baseline had been excised
9. Mean QTc interval < 450 msec at screening

The major protocol amendment was on the original statistical analysis plan:

- Changed the estimated treatment effect of RO5185426 as measured by the hazard ratio for death from 0.75 to 0.65 (based on a change in the estimated median OS for the RO5185426 arm from 10.67 to 12.3 months) due to emerging results from Phase 1 and 2 studies that suggested the median survival among RO5185426 patients would be longer than originally considered. This resulted in a reduction in the number of deaths required for final overall analysis from 468 to approximately 196.
- Added PFS as a co-primary endpoint and specified that the final analysis of PFS was to occur at the time of the interim analysis of OS. A total of 187 PFS events were required to provide 90% power to detect an improvement of 2 months in median PFS (2.5 vs. 4.5 months; HR=0.55).
- Changed the alpha level from 0.025 (two-sided) to 0.05 (two-sided): 0.045 (two-sided) for OS and 0.005 (two-sided) for PFS.
- Added allowance for crossover from the dacarbazine arm to the RO5185426 arm if the p-value of the interim OS analysis was less than 0.05.

The trial began in January 2010 and enrolled a total of 675 patients (after screening of 2107 patients): 337 patients were assigned to the RO5185426 arm and 338 patients to the dacarbazine arm.

Patients' baseline characteristics were balanced between the arms. The majority of patients (99%) were White and 60% were enrolled from Western Europe. All patients

had an ECOG performance status of <2: 68% had a score of 0 and 32% had a score of 1. The majority of patients (95%) had metastatic disease and 42% of patients had an elevated level of serum LDH. The key disease characteristics are summarized below:

Key Disease Characteristics of Randomized Patients (ITT)

	Vemurafenib (n=337)		Dacarbazine (n=338)	
Melanoma Stage at Randomization:				
Unresectable IIIC	15	(4.5)	14	(4.1)
M1a	37	(11.0)	38	(11.2)
M1b	63	(18.7)	60	(17.8)
M1c	222	(65.9)	226	(66.9)
Melanoma Stage at Diagnosis:				
Stage 0	9	(2.7)	9	(2.7)
Stage I	68	(20.2)	79	(23.4)
Stage II	76	(22.6)	88	(26.0)
Stage III	76	(22.6)	65	(19.2)
Stage IV	99	(29.4)	87	(25.7)
Unknown	9	(2.7)	10	(3.0)
Adjuvant therapy:				
Yes	68	(20.2)	59	(17.5)
No	269	(79.8)	279	(82.5)
Time from Diagnosis of Metastatic Disease to Enrollment on				
Mean	11.1		10.1	
SD	21.1		21.1	
Median	3.5		3.1	
SEM	1.2		1.1	
Min-Max	0-160.3		0-186.6	

Adapted from the primary clinical review

The preplanned interim analysis was conducted in January 2011 with the data cutoff date of Dec 30, 2010. Patient's disposition at the analysis was summarized in the following table:

Patients' Disposition at the Preplanned Interim Analysis (ITT)

	Vemurafenib	*Dacarbazine*
Randomized	337	338
Evaluable for OS	336	336
Evaluable for PFS	275	274
Evaluable for BORR	219	220
Treated	336[1]	289
Refused Treatment/Withdrew Consent	0	37
Other Reasons	2[2]	11[3]
Still on Treatment	223	83
Discontinued Randomized Treatment	113	206
Disease Progression	89	170
Death	6	11
Lost to Follow Up/Patient Decision	6	12
Adverse Event	12	10
Other	0	3[4]

[1] 1 patient was randomized to Dacarbazine but was mistakenly given Vemurafenib

Derived from the primary statistical review

The interim OS analysis demonstrated a statistically significant difference in survival favoring the vemurafenib arm ($p < 0.0001$, the actual alpha allocation for this interim analysis was 0.032 by the Pocock alpha spending boundary). The unstratified hazard ratio for vemurafenib relative to dacarbazine was 0.37 (95% CI: 0.26, 0.55). The Kaplan-Meier estimate of median OS for the vemurafenib arm was 9.2 months (95% CI: 8.1, not reached) and 6 patients were at risk at the time of the estimated median. For the dacarbazine arm, the Kaplan-Meier estimate of median OS was 7.8 months (95% CI: 6.3, 10.3) and 10 patients were at risk at the time of the estimated median. These results were compelling since the p value from the log-rank test for OS ($p<0.0001$) crossed the efficacy boundary in favor of vemurafenib treatment. Patients on the dacarbazine arm were allowed to cross over to receive vemurafenib thereafter.

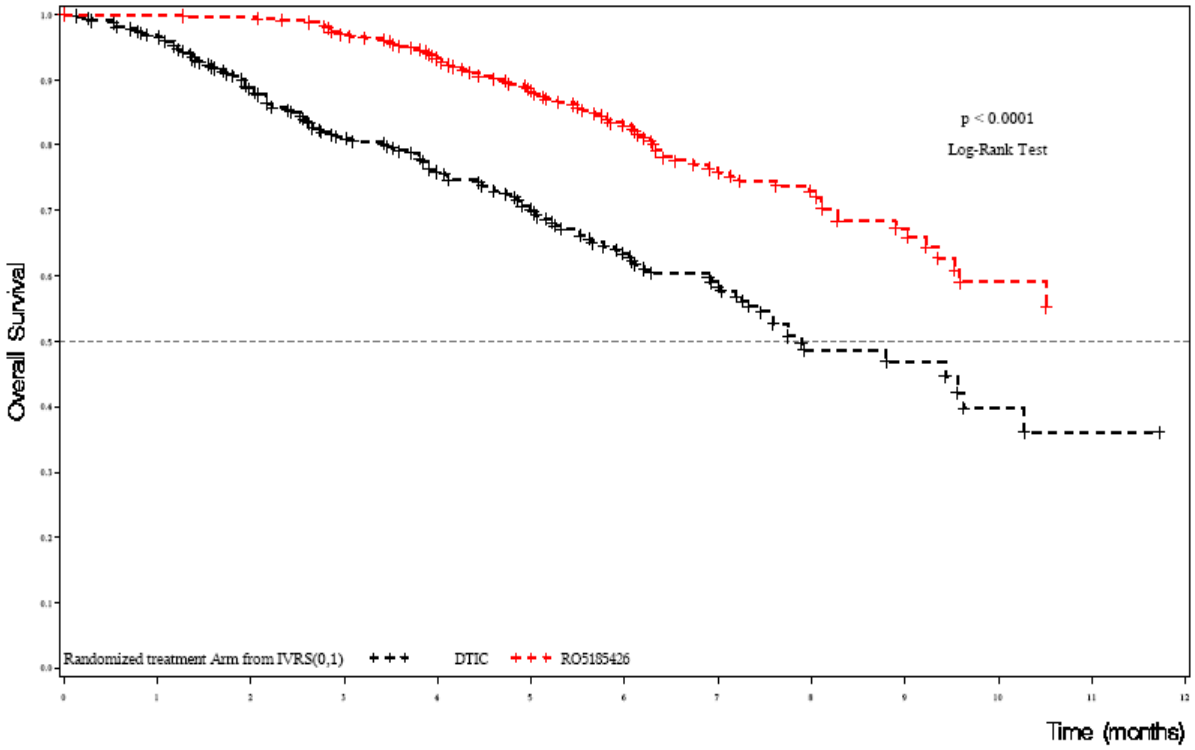
The updated OS analysis was conducted with the data cutoff of March 31, 2011 that had a total of 199 deaths (78 in the vemurafenib arm and 121 in the dacarbazine arm). The median follow-up at the time of this analysis was 6.2 and 4.5 months for the vemurafenib and dacarbazine arms, respectively. The results along with the co-primary endpoint PFS results are summarized in the following table and figure.

Updated Efficacy Results in Treatment-Naive Patients with BRAF^{V600E} Mutation Positive Melanoma (ITT)

	Vemurafenib (N=337)	**Dacarbazine (N=338)**	p-value[c]
Overall Survival			
Number of Deaths	78 (23%)	121 (36%)	
Hazard Ratio (95% CI)[a]	0.44 (0.33, 0.59)		<0.0001
Median Survival (months) (95 % CI)[b]	Not Reached (9.6, Not Reached)	7.9 (7.3, 9.6)	-
Median Follow-up (months) (range)	6.2 (0.4, 13.9)	4.5 (<0.1, 11.7)	
Progression-Free Survival[d] Hazard Ratio (95% CI)[a]	0.26 (0.20, 0.33)		<0.0001
Median PFS (months) (95% CI)[b]	5.3 (4.9, 6.6)	1.6 (1.6, 1.7)	-

[a] *Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors vemurafenib*
[b] *Kaplan-Meier estimate*
[c] *Unstratified log-rank test*
[d] *Based on investigator-assessed progression or death*

Kaplan-Meier Curves of Overall Survival – Treatment-Naive Patients (ITT)



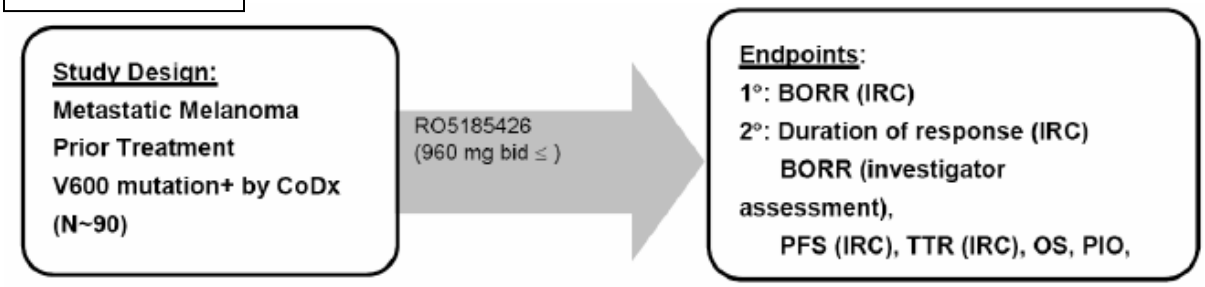
Although the updated OS analysis represented the final statistical plan for OS according to the protocol, survival estimates for patients receiving vemurafenib do not seem to be clinically mature because of the short median follow-up time of 6 months and 77% of the patients still living. Longer follow up for overall survival would provide more clinically relevant information for patients on the vemurafenib arm.

With the data cutoff of December 31, 2010, the confirmed, investigator-assessed best overall response rate (CR + PR) was 48.4% (95% CI: 41.6%, 55.2%) in the vemurafenib arm compared to 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, while all 12 responses in the dacarbazine arm were partial responses (5.5%).

Phase 2 Trial Design and Results:

NO22657 was a single-arm, multicenter Phase 2 trial in patients with $BRAF^{V600}$ mutation-positive metastatic melanoma who had received at least one prior systemic therapy. Its design is shown below:

Trial NO22657 **Study Design and Endpoint Summary**



This trial began in September of 2009 and enrolled a total of 132 patients. The median age was 52 years with 19% of patients being older than 65 years. The majority of patients were male (61%) and Caucasian (99%). Forty-nine percent of patients received ≥ 2 prior therapies and 51% of the patients had 1 prior therapy regimen. The median duration of follow-up was 6.9 months (range, 0.6 to 11.3) with the data cutoff date of September of 2010.

The confirmed best overall response rate (CR + PR) as assessed by an independent review committee (IRC) was 52% (95% CI: 43%, 61%). There were 3 complete responses (2.3%) and 66 partial responses (50.0%). The median time to response was 1.4 months with 75% of responses occurring after 1.6 months treatment with vemurafenib. The median duration of response by IRC assessment was 6.5 months (95% CI: 5.6, not reached).

The updated response analysis with a data cutoff of January 2011 showed a similar response rate of 53% with a median response-duration of 6.7 months.

Efficacy Summary:

Taken together, vemurafenib demonstrated consistent antitumor activity in the two trials, as evidenced by a response rate of approximately 50% in patients with metastatic melanoma positive for the BRAF V600E mutation regardless of prior systemic therapy. More importantly, this antitumor activity has been translated into an improvement in overall survival in those treatment-naïve patients as demonstrated in the randomized, Phase 3 trial comparing vemurafenib to dacarbazine. The magnitude of the survival improvement could not be reliably assessed because of the short median follow-up time when the updated survival analysis was conducted with the data cutoff date of March 31, 2011. Therefore, determination of the survival improvement magnitude would require longer follow-up of patients on the vemurafenib arm. A postmarketing commitment has requested an analysis of overall survival with a minimum follow-up of 24 months after the last patient was enrolled into the Phase 3 trial.

9. Safety

The safety of vermurafenib was found acceptable based on a population of 500 patients treated with the drug at 960 mg twice daily. The safety profile was further examined with the 3-month safety updates but had no remarkable changes. The clinical review findings also support implementation of a Medication Guide, proposed initially by the applicant to inform healthcare providers the increased incidence of cutaneous squamous cell carcinomas (cuSCC) associated with vemurafenib. This Medication Guide will also help address other potential risks (e.g. severe dermatologic and ophthalmologic reactions or new primary malignant melanomas) before and during treatment with vemurafenib.

The clinical evaluation of vermurafenib's safety was based on the three trials listed below. Adverse event grading was performed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Summary of Vemurafenib Trials in Safety Analysis

Study	Population	Design	Dose (mg B.I.D.)	# Any Vemurafenib	# Vemurafenib 960 mg B.I.D.
PLX06-02	Metastatic Melanoma and Colorectal Carcinoma	Dose Escalation	160-1120	56	32
NP22657/ BRIM2	BRAF-V600 Mutation-Positive Metastatic Melanoma	Activity	960	132	132
NO25026/ BRIM3	Unresectable Stage IIIc or Stage IV BRAF-V600 Mutation-Positive Melanoma	Phase 3 Vemurafenib vs. Dacarbazine	960	336	336
Total Exposed				**524**	**500**
ISS Total					**500**

Adopted from the clinical review
ISS: integrated safety database

The above safety database was considered sufficient to characterize toxicity in support of marketing approval. Since the majority of the patients in the safety database were from the randomized Phase 3 trial, the safety analyses in the clinical review focused primarily on data from this trial. Indeed, incidences of the most common, vemurafenib treatment-emergent adverse events in the Phase 3 trial were found similar to those in the integrated safety database, which are shown in the table below:

Similarity in Incidence of Most Common Treatment-Emergent Adverse Events (>15%) between the ISS Database and the Phase 3 Trial

	Phase 3 Trial (NO25026) N = 336		**ISS Database N = 500**	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Arthralgia	180 (53.6)	15 (4.5)	299 (59.8)	27 (5.4)
Alopecia	150 (44.6)	2 (<1)	182 (36.4)	1 (<1)
Fatigue	127 (37.8)	7 (2.1)	232 (46.4)	15 (3)
Rash	124 (36.9)	28 (8.3)	207 (41.4)	39 (7.8)
Nausea	116 (34.5)	7 (2.1)	166 (33.2)	8 (1.6)
Photosensitivity Reaction	110 (32.7)	9 (2.7)	191 (38.2)	15 (3)
Diarrhea	95 (28.3)	3 (<1)	132 (26.4)	4 (<1)
Hyperkeratosis	82 (24.4)	4 (1.2)	114 (22.8)	4 (<1)
Headache	78 (23.2)	3 (<1)	119 (23.8)	3 (<1)
Pruritus	77 (22.9)	5 (1.5)	123 (24.6)	8 (1.6)
Skin Papilloma	72 (21.4)	1 (<1)	108 (21.6)	1 (<1)
Pyrexia	64 (19)	2 (<1)	93 (18.6)	6 (1.2)
Dry Skin	63 (18.8)	0	83 (16.6)	0
Decreased Appetite	60 (17.9)	0	98 (19.6)	0
Vomiting	60 (17.9)	4 (1.2)	96 (19.2)	6 (1.2)
Squamous cell carcinoma of Skin*	58 (17.3)	55 (16.4)	98 (19.6)	95 (19)
Edema Peripheral	56 (16.7)	3 (<1)	88 (17.6)	1 (<1)
Myalgia	42 (12.5)	1 (<1)	79 (15.8)	1 (<1)
*not including keratoacanthoma				

Adopted from the clinical review

Deaths

In the randomized Phase 3 trial comparing vemurafenib with dacarbazine, approximately 1% of deaths on each arm were reported as treatment-emergent. There were no deaths that occurred within 30 days of the start of treatment in the vemurafenib arm but 9 deaths in the dacarbazine arm. Deaths within 28 days of last drug dose, excluding those secondary to disease progression, were 5 on the vemurafenib arm and 3 on the dacarbazine arm. The clinical review concluded that none of these deaths were considered to be related to study drug but rather to other medical conditions and interventions or possibly to disease progression.

Serious Adverse Events

Nonfatal serious adverse events were reported in 43% of patients on the vemurafenib arm and 18% of patients on the dacarbazine arm. The difference in the incidence rates is mostly related to the increased incidence of cuSCC with vemurafenib treatment: 26% in the vemurafenib arm versus <1% in the dacarbazine arm.

The cuSCCs tabulation included both squamous cell carcinomas (SCC) of the skin and keratoacanthomas. The median time to onset of vemurafenib treatment was 7.1 weeks. No cases were reported after 28 days off treatment. All cuSCCs were managed with surgical removal (e.g. punch biopsy/removal). No dose interruptions or reductions were undertaken in response to these cuSCCs.

Adverse Events

The following results of adverse events were based on a median treatment exposure of 4.2 months to vemurafenib as compared to a median exposure of 0.8 months to dacarbazine. Nevertheless, the relative dose intensity of treatment was close to 100% as planned on both arms.

- **Adverse Events Leading to Treatment Discontinuation or Dose Modification**

The rate of discontinuation due to adverse event was low: 7.1 % of patients on the vemurafenib arm compared to 4.2% on the dacarbazine arm. A variety of adverse events leading to treatment discontinuation were reported for individual patients on or within each arm. Therefore, no specific safety signals or adverse reactions could be identified as outstanding reasons attributable to treatment discontinuation.

Adverse events or reactions leading to dose reductions occurred more frequently in patients (33%) on the vemurafenib arm than in patient (15.2%) on dacarbazine arm. For patients receiving vemurafenib, most of the adverse events were dermatologic reactions and abnormal hepatic function test results; while for patients receiving dacarbazine, neutropenia and thrombocytopenia led to dose reductions. The following table summarizes adverse events leading to dose reductions in at least 3 patients on each arm.

Adverse Events Leading to Dose Modification (≥3 Patients on Either Arm)

	Vemurafenib N = 336		**Dacarbazine N = 282**	
	Grade 1-4 (%)	Grade3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Rash	36 (10.7)	24 (7.1)	0	0
Arthralgia	22 (6.5)	9 (2.7)	1 (<1)	1 (<1)
Pyrexia	9 (2.7)	0	1 (0.4)	0
Blood Alkaline Phosphatase Increased	9 (2.7)	6 (1.8)	0	0
GGT Increased	9 (2.7)	6 (1.8)	0	0
Rash Maculopapular	9 (2.7)	8 (2.4)	0	0
Nausea	8 (2.4)	2 (<1)	2 (<1)	1 (<1)
Blood Bilirubin Increased[1]	7 (2.1)	5 (1.5)	0	0
Fatigue	6 (1.8)	3 (<1)	1 (<1)	0
ALT Increased	6 (1.8)	3 (<1)	1 (<1)	1 (<1)
Vomiting	6 (1.8)	2 (<1)	0	0
AST Increased	6 (1.8)	2 (<1)	0	0
Pruritus	5 (1.5)	2 (<1)	0	0
SCC of Skin	4 (1.2)	4 (1.2)	0	0
Uveitis	3 (<1)	1 (<1)	0	0
Abdominal Pain Upper	3 (<1)	1 (<1)	0	0
Asthenia	3 (<1)	1 (<1	0	0
Blood Creatinine Increased	3 (<1)	1 (<1)	0	0
Decreased Appetite	3 (<1)	0	0	0
Hyperkeratosis	3 (<1)	2 (<1)	0	0
Photosensitivity Reaction	3 (<1)	2 (<1)	0	0
Neutropenia[2]	2 (<1)	1 (<1)	28 (9.9)	25 (8.9)
Thrombocytopenia	1 (<1)	0	6 (2.1)	3 (1.1)

Adopted from the primary clinical review

- **Significant Adverse Events**

Squamous Cell Carcinoma

See the above Serious Adverse Events about the cuSCC incidence. On the other hand, no cases of non-cuSCC were confirmed on the vemurafenib arm. Whether vemurafenib increases the risk of developing non-cuSCC remains important to monitor and to assess. More information or longer follow-up would be needed from randomized trials in patients with diseases or disease settings that may have long-term use of vemurafenib.

New Primary Malignant Melanoma
Seven patients had 8 new primary melanomas diagnosed by the local investigators. All lesions were resolved by excision, and no dose modifications or interruptions for vemurafenib were undertaken in light of these adverse events. It remains inconclusive whether these new primary melanomas represented preexisting lesions in patients with melanoma or newly developed lesions with vemurafenib treatment.

Uveitis
Five patients on the vemurafenib arm developed uveitis compared to none on the dacarbazine arm. Four cases of the uveitis, graded between Grade 1 and Grade 3, resolved without functional sequelae following appropriate management. One case of Grade 2 uveitis was reported as unresolved at the data cutoff.

QT prolongation
Seven patients on the vemurafenib arm had a QTc prolongation of Grade 3 or 4 compared to none on the control arm. No patients had Torsade de pointes, including patients from the uncontrolled clinical trials. Note that patients with a QTc of >450 msec were excluded from the vemurafenib clinical trials.

Hepatotoxicity
Elevations in hepatic specific parameters such as ALT or bilirubin were detected more frequently in patients on the vemurafenib arm than in patients on the dacarbazine arm. The incidences of Grade 3-4 ALT or bilirubin were approximately 1-2% higher in the vemurafenib arm than in the dacarbazine arm. No Hy's Law cases or hepatic deaths were identified.

- **Common Adverse Events**

The most common adverse events in vemurafenib-treated patients were: arthralgia (54%), rash (37%), alopecia (45%), fatigue (38%), nausea (35%), and photosensitivity reaction (33%). The table below lists adverse events with an incidence rate of >10%.

Common Adverse Events Reported in ≥10% of Patients

	Vemurafenib N=336		Dacarbazine N=287	
	Gr 1-4 (%)	**Gr 3-4 (%)**	**Gr 1-4 (%)**	**Gr 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
Decreased Appetite	60 (17.9)	0	27 (9.4)	2 (<1)
General Disorders				
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)
Musculoskeletal & 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 & Unspecified				
Skin Papilloma	72 (21.4)	1 (<1)	0	0
Squamous Cell Carcinoma of Skin*	58 (17.3)	55 (16.4)	1 (<1)	1 (<1)
Keratoacanthoma*	30 (8.9)	29 (8.6)	0	0
Seborrheic Keratosis	33 (9.8)	1 (<1)	3 (1)	0
Nervous System Disorders				
Headache	78 (23.2)	3 (<1)	30 (10.4)	0
Dysgeusia	48 (14.3)	0	9 (3.1)	0
Skin & 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
**Tabulated together for the overall incidence (24%) of cuSCCs*				

Derived from the clinical review

- **Laboratories**

Important Grade 3-4 laboratory abnormalities detected during the controlled trial were summarized in Table. Note that laboratory parameters that had a difference of <1% in Grade 3-4 toxicity are not included unless considered clinically important to the reviewer.

Important Grade 3-4 Laboratory Abnormalities

	Vemurafenib (N=336)	**Dacarbazine (N=282)**
	Grade 3-4 (%)	**Grade 3-4 (%)**
Increased LDH	9 (2.7)	12 (4.3)
Increased Alkaline Phosphatase	10 (3)	2 (<1)
Increased ALT	9 (2.7)	5 (1.8)
Increased GGT	38 (11.3)	24 (8.5)
Increased Bilirubin	6 (1.8)	0
Hyperkalemia	4 (1.2)	0
Hypercalcemia	7 (2)	3 (<1)
Decreased Neutrophils	2 (<1)	33 (13.3)
Decreased WBCs	3 (<1)	16 (6)
Decreased Platelets	1 (<1)	9 (3.4)

Derived from the clinical review

Post-Marketing Safety Reports

Not applicable.

Safety Summary:

The safety profile demonstrated in this NDA is acceptable for use of vemurafenib in the intended patient population. The most common adverse reactions with a frequency of ≥30% were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, and nausea. Cutaneous squamous cell carcinomas (cuSCC), including squamous cell carcinomas of the skin and keratoacanthomas, were increased with vemurafenib treatment: detected in approximately 25% of vemurafenib-treated patients. However, patients were able to continue vemutafenib without dose adjustment after excision of their CuSCCs. Other severe adverse reactions associated with vemurafenib treatment included hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, uveitis, QT prolongation, and liver enzyme laboratory abnormalities. None of these severe adverse reactions led to deaths with the data cutoff date for the safety database.

10. Advisory Committee Meeting

No Advisory Committee meeting was sought since the benefit/risk profile of vemurafenib demonstrated in this application is clear for the proposed indication. The survival advantage of vemurafenib in patients with advanced melanoma positive for the BRAF V600E mutation outweighs the risks of the product.

11. Pediatrics

Because vemurafenib has an orphan drug designation for the proposed indication, it is exempt from the Pediatric Research Equity Act (PREA) requirement.

It was noted at the NDA filing that the sponsor has proposed a dedicated phase 2 study in pediatric patients.

12. Other Relevant Regulatory Issues

In the clinical inspection summary dated July 28, 2011, the Office of Scientific Investigations (OSI) considered the submitted clinical data reliable except for the identification of incomplete radiographic data documentation and irreproducible target lesion assessments at Study Site 201192, one of four study sites inspected for this NDA. This finding was based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. OSI recommended the review division consider the impact of this finding on the disease progression endpoint assessment.

To assess the effect of the reported radiographic data violations on the co-primary endpoint, a reanalysis of PFS was conducted with exclusion of all patients from Study Site 201192. The reanalysis showed no changes in the PFS results compared to the ITT-based PFS analysis. (See the clinical review and statistical review addendum for details).

The financial disclosures were evaluated by the primary reviewer and found acceptable.

13. Labeling

Please refer to the revised package insert for all important changes as well as to the DEMEPA review for information on carton and container labeling. Key labeling medications included the following

- Modification of the applicant's proposed indication to accurately reflect the studied population of patients in whom the benefit of vemurafenib has been demonstrated
- Specification of the fact that vemurafenib has not been studied in patients with wild-type $BRAF^{V600}$ melanoma
- Addition of severe dermatologic reactions (e.g. Stevens-Johnson syndrome and toxic epidermal necrolysis), ophthalmologic reactions (e.g. uveitis, iritis and retinal vein occlusion), and newly detected primary malignant melanomas as Warnings
- Classification of vemurafenib as a Pregnancy Category D product as it may cause fetal harm based on known mechanism of action
- Clarification of Mechanism of Action based on the submitted preclinical data

14. Recommendations/Risk Benefit Assessment

- ## Recommendations

  Regular approval of vemurafenib for the indication as follows:

  Vemurafenib (ZELBORAF™) is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test.

  Limitation of use: ZELBORAF is not recommended in patients with wild-type $BRAF^{V600}$ melanoma.

- ## Risk Benefit Assessment

  Vemurafenib will provide an effective treatment for approximately 50% of patients with advanced melanoma. Patients eligible for the treatment must have melanoma with the BRAF V600E mutation detected by an FDA approved diagnostic. As shown in the clinical and statistical reviews of this NDA, vemurafenib significantly prolonged overall survival and progression

free survival in patients with BRAF V600E mutation-positive unresectable or metastatic melanoma when compared to dacarbazine, a common cytotoxic therapy for advanced melanoma but not associated with an improvement in overall survival. Vemurafenib also demonstrated consistent antitumor activity in the intended patient population, associated with a response rate of approximately 50%, irrespective of whether patients have received prior systemic therapy for metastatic melanoma.

Vemurafenib's safety profile in the study patients is acceptable despite the increased risk for cuSCCs with vemurafenib treatment. Based on the clinical trials, cuSCCs can be managed with excision without treatment discontinuation or dose adjustment. Nevertheless, cautions should be exercised to monitor and manage other severe adverse reactions that may occur with vemurafenib treatment, including hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, uveitis, QT prolongation, and liver enzyme laboratory abnormalities. These safety issues have been highlighted in the vemurafenib labeling. Clearly, the survival benefit demonstrated with vemurafenib outweighs its risks in the intended patient population.

The totality of the data supports that vemurafenib has a highly favorable benefit-risk profile for the indication-intended patient population. Its benefit-risk profile also appears favorable relative to that of ipilimumab, a recently approved product that is indicated for the treatment of unresectable or metastatic melanoma, regardless of BRAF mutation status. Ipilimumab was associated with a moderate improvement in OS and sometimes with severe or fatal immune-mediated adverse reactions adverse reactions including enterocolitis, hepatitis, dermatitis (e.g. toxic epidermal necrolysis), neuropathy, and endocrinopathy.

Vemurafenib represents the first effective targeted therapy for advanced melanoma containing the intended target BRAF V600E mutation as detected by a genetic-based diagnostic test. Its use should be limited to patients whose melanoma tests positive for this mutation by an FDA approved test and in whom vemurafenib's benefit has been shown.

Vemurafenib should not be used in patients whose melanoma tests negative by an FDA approved test for the BRAF V600E mutation since its safety and efficacy have not been studied in this patient population.

Recommendation for Postmarketing Risk Management Activities

A Medication Guide has been developed primarily to address the increased risk for cuSCC. This will help patients and healthcare providers to understand this risk and to monitor and manage appropriately if cuSCC develops. The Medication Guide will also be helpful in conveying and managing other risks known to vemurafenib treatment. For the intended population, vemurafenib's risk management plans including routine risk management activities, labeling and routine pharmacovigilance are considered adequate at this time.

Reassessment of the adequacy of vemurafenib's risk management activities may be needed if its indications expand in the future to treatment of diseases with a relatively long natural history.

Recommendation for Postmarketing Study Requirements

Postmarketing clinical trials or studies required for the recommended approval are listed below. These requirements have been agreed by the applicant and are intended to assess possible inhibitory effects of vemurafenib on human CYP2C8 and CYP2B6 and to identify unexpected serious risks from longer duration of exposure to vemurafenib, an increase in secondary malignancies with vemurafenib, drug-drug interactions with vemurafenib, and the effect of severe hepatic impairment on the pharmacokinetics of vemurafenib.

1803-1 Perform an *in vitro* screen to determine if vemurafenib is an inhibitor of human CYP2C8 and CYP2B6. Based on results from the *in vitro* screen, a clinical drug-drug interaction trial may be needed.

1803-2 Submit the final analysis of safety in the ongoing trial (Protocol NO25026:BRIM3) to provide the potential for new safety data signals from longer duration of exposure.

1803-3 Submit an analysis of secondary malignancies for the proposed adjuvant melanoma trial [G027826: Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients with Surgically-Resected, Cutaneous BRAF Mutant Melanoma at High Risk for Recurrence] annually and one year after the last patient has completed clinical trial treatment.

1803-4 Follow-up for secondary malignancies from the planned papillary thyroid cancer trial [N025530: An Open-Label, Multi-Center Phase II Study of the BRAF Inhibitor RO5185426 in Patients with Metastatic or Unresectable Papillary Thyroid Cancer (PTC) positive for the BRAF V600 Mutation and Resistant to Radioactive Iodine] annually and one year after the last patient has completed clinical trial treatment.

1803-5 Conduct a drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of vemurafenib.

1803-6 Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of vemurafenib.

1803-7 Conduct a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment to assess the effect of severe hepatic impairment on the pharmacokinetics of vemurafenib.

Recommendation for Postmarketing Study Commitments

1803-8 Submit updated overall survival results from the ongoing trial (Protocol NO25026:BRIM3) with a minimum follow-up of 24 months after the last patient was enrolled into the trial.

1803-9 Develop an Investigational Use Only, Companion Diagnostic (IUO CoDx) that reliably detects V600K BRAF mutation in patients with unresectable or metastatic melanoma and conduct an open-label single arm trial with overall response rate and duration of response as the primary endpoints in this population as determined by the diagnostic test.

1803-10 Assess changes in NRAS mutation status at both baseline and disease progression in biopsy accessible lesions in patients with advanced melanoma positive for the V600E BRAF mutation who have been treated with vemurafenib. This assessment should include all patients with available biopsy specimens and may be derived from completed and ongoing trials [see below for trial ID number and title*] in patients treated with vemurafenib.

*PLX06-02: A Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX4032 in Patients with Solid Tumors

*NP22657: An Open-Label, Multi-Center, Phase II Study of Continuous Oral Dosing of RO5185426 in Previously Treated Patients With Metastatic Melanoma

*NO25026: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving RO5185426 or Dacarbazine

*NP25163: A Phase I, Randomized, Open-label, Multi-center, Multiple Dose Study to Investigate the Pharmacokinetics and Pharmacodynamics of RO5185426 Administered as 240 mg Tablets to Previously Treated BRAF V600E Positive Metastatic Melanoma Patients

*NP25396: A Phase I, Randomized, Open-label, Multi-center, Two Period Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of a Single Oral Dose of RO5185426, Followed by Administration of 960 mg RO5185426 Twice Daily to $BRAF^{V600E}$ Positive Metastatic Melanoma Patients

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/s/

YANGMIN NING
08/10/2011

JOHN R JOHNSON
08/10/2011