CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202429Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202429
Priority or Standard	Priority
Submit Date(s)	April 28, 2011
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Division / Office	DDOP/OODP
Reviewer Name(s)	John Johnson (CTL) Yangmin Max Ning Geoffrey Kim (efficacy) Amy McKee (safety)
Review Completion Date	July 28, 2011
Established Name	Vemurafenib/RO518426
(Proposed) Trade Name	Zelboraf™
Therapeutic Class	Kinase Inhibitor
Applicant	Hoffmann – La Roche Inc.
Formulation(s)	Oral
Dosing Regimen	960 mg BID
Indication(s)	Treatment of BRAF V600E mutation positive unresectable or metastatic melanoma

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the findings described in this clinical review of the new drug application for vemurafenib (NDA 202429), the reviewers recommend regular approval of vemurafenib for the following indication:

ZELBORAF™ is 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 for use in patients with wild-type BRAF melanoma.

1.2 Risk Benefit Assessment

The recommendation for approval is based on the single, randomized clinical trial in which vemurafenib showed statistically significant overall and progression free survival (OS, PFS) advantages over dacarbazine in patients with BRAF V600E mutation-positive unresectable or metastatic melanoma. This trial, which enrolled 675 patients, was stopped at the recommendation of the data safety monitoring board (DSMB) at the time of the first planned interim analysis of overall survival, which occurred approximately one year after the trial was initiated. In the initial dataset provided for this NDA application using a December 30, 2010 data cutoff, the hazard ratio for overall survival was 0.37 (95% CI 0.26-0.54); p<0.0001, favoring vemurafenib, and an updated dataset based on 199 overall survival events using the data cutoff of March 31, 2011, demonstrated a hazard ratio of 0.44 (95% CI 0.33-0.59); p<0.0001. The median OS for the vemurafenib arm has not yet been reached (95% CI 9.6, NR), while the median OS for the dacarbazine arm using the March 31, 2011, data cutoff and censoring patients for crossover was 7.9 months (95% CI 7.2, 9.6). The hazard ratio for progression free survival was 0.26 (95% CI: 0.20, 0.33); p<0.0001. The median PFS for vemurafenib was 5.3 months (95% CI 4.8, 6.6) compared to the median PFS of dacarbazine, which was 1.6 Months (95% 1.5, 1.7).

There are several safety signals that emerged from the randomized clinical trial, including cutaneous squamous cell carcinomas, new primary malignant melanomas, liver toxicity, ophthalmologic adverse events, joint-related adverse events and cardiac events. However, with appropriate monitoring and management, these adverse events do not outweigh the overall survival benefit demonstrated in the trial.

Metastatic melanoma has a grim prognosis. Less than 10% of those that are diagnosed with metastatic melanoma will live beyond 5 years from diagnosis. Since the disease occurs at a younger age compared to other cancers such as prostate cancer, the number of years of life lost per person is amongst the highest of all malignancies. Three agents have been approved for systemic therapy of melanoma. Site-directed therapy such as metastatectomy, radiation therapy, and stereotactic/ablation techniques are also used commonly for isolated metastasis or symptom control.

Vemurafenib represents an important new treatment option with a favorable risk-benefit profile for patients with BRAF V600E mutation-positive unresectable or metastatic melanoma when compared to available treatments. Vemurafenib was shown to be superior to dacarbazine in this population. The risks of secondary malignancies, namely non-melanoma skin cancers, can be managed with appropriate monitoring by clinicians. Further data regarding other secondary malignancies other than skin cancer, the effectiveness of therapy in patients with concurrent RAS mutations or V600K mutations, and long-term survival updates will be addressed in postmarketing commitments and requirements.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

Post Marketing Requirements:

1. To submit the final analysis of safety in the ongoing trial (Protocol NO25026:BRIM3) to provide the potential for new safety data from longer duration of exposure.
2. To follow up for secondary malignancies from the planned papillary thyroid cancer trial [NO25530: 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 for one year after the last patient has completed study treatment.
3. To submit an analysis for secondary malignancies from the proposed adjuvant melanoma trial [GO27826: 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 for one year after the last patient has completed study treatment.

Post Marketing Commitments:

1. To 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.
2. To 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.
3. 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 in patients treated with vemurafenib. These trials are:
   *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

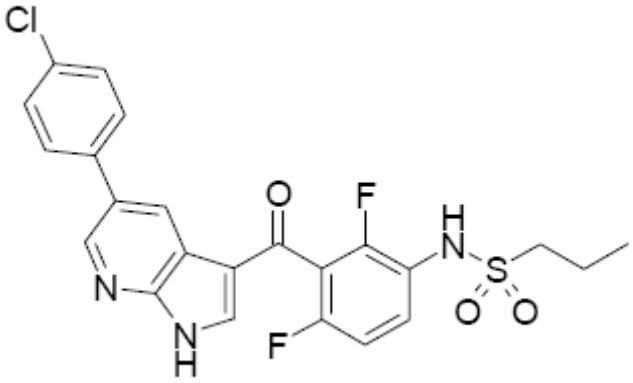
2 Introduction and Regulatory Background

2.1 Product Information

Vemurafenib is chemically designated as Propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide. The molecular formula is $C_{23}H_{18}ClF_2N_3O_3S$ and the molecular weight is 391.55. The structural formula is shown in Figure 1.

Figure 1: Structural Formula of Vemurafenib

STRUCTURAL FORMULA



2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Available Treatments for Metastatic Melanoma

Drug Name	Drug Type	Approval Date	Approval Basis	Survival Benefit?
Dacarbazine (DTIC, DTIC-dome)	Chemotherapy/Cytotoxic	1975	Clinical Responses	NA
IL-2 (Proleukin)	Cytokine/Immunomodulatory	1998	Response Rates	No
Ipilimumab (Yervoy)	Antibody/Immunomodulatory	2011	Overall Survival	Yes

2.3 Availability of Proposed Active Ingredient in the United States

Vemurafenib is not available in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

To date, sorafenib is the only other approved agent that has demonstrated activity against BRAF, but it is a promiscuous inhibitor that targets c-kit, PDGFR, and VEGFR-2. The adverse event profile of sorafenib includes hypertension, gastrointestinal perforation, and wound healing, which is most likely related to the activity against VEGFR. An uncommon adverse reaction associated with sorafenib is the development

of cutaneous squamous cell carcinomas, but many reports of the development of these lesions appeared in the literature well after the drug was approved and made available. It is unknown whether the rate of cutaneous squamous cell carcinomas would increase in clinical trials with sorafenib if there are specific criteria for monitoring of the appearance of these lesions as was done in the clinical trials with vemurafenib. Regardless, the development of cutaneous squamous cell carcinomas appears to be related to targeting the BRAF pathway.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Major regulatory milestones along with key FDA recommendations prior to the NDA submission are summarized in Table 2.

Table 2: Major Regulatory Milestones

Milestone	Time	Key Regulatory Activities Related to Clinical Development
IND-73620 Submission	Sept. 2006	• The IND named PLX4032, claimed as a selective inhibitor of BRAF kinase V600E mutant and intended to be investigated in patients with tumors containing the point mutation, including melanoma. • The Phase 1 protocol was evaluated and found to be safe to proceed.
Phase 1 Study	2007-2009	• Use of new formulations of PLX4032 in the form of a microprecipitated bulk powder (MBP) drug-polymer-matrix was proposed and evaluated during the interim to improve the bioavailability of PLX4032. The original formulation had a poor bioavailability and showed no DLT at a dose schedule of 1600 mg BID. • The FDA evaluation of the safety data determined that PLX4032 in a new formulation could be started at 160 mg BID to continue the Phase 1 study. This dosing schedule appeared equivalent to the original formulation at 800 mg BID in terms of serum levels of the product. • The determined MTD schedule of PLX4032 in the new formulation was 960 mg BID, verified further in an expansion cohort of patients with metastatic melanoma positive for the $BRAF^{V600E}$ mutation.

End-of Phase 1 Meeting	May 2009	• Proposed to develop RO5185426 (PLX4032) in patients with advanced melanoma with the $BRAF^{V600E}$ mutation and to use a response rate of ≥30% or PFS (HR 0.5 and an improvement of 2 months) as regulatory endpoints for accelerated approval. The proposal was based on the encouraging tumor response results from 16 patients with advanced melanoma positive for the $BRAF^{V600E}$ mutation • The Agency recommended the sponsor conduct a randomized Phase 3 trial with overall survival as the primary endpoint given that no evidence showed that PFS is not an adequate surrogate endpoint in metastatic melanoma. • 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". • The Agency also recommended the sponsor initiate a comprehensive long term plan to monitor the safety of the product, including possible incidences of non-cutaneous squamous cell carcinomas • The Agency also discussed issues on the development of a companion diagnostic to detect the BRAF V600E mutation during clinical trials
Special Protocol Assessment	Aug. 2009	• SPA requested for a randomized double-blind, double-placebo controlled, randomized Phase 3 trial in previously untreated patients with unresectable or metastatic melanoma withV600E-positive BRAF mutation receiving RO5185426 or dacarbazine. The proposed primary endpoint was overall survival. • The Agency recommended the sponsor change the proposed trial design to an open-label, randomized study comparing RO5185426 with dacarbazine in the proposed patient population since overall survival was the primary endpoint. The Agency discouraged blinding the proposed trial and using double placebos (oral placebo for patients assigned to the dacarbazine arm and intravenous placebo for patients assigned to the RO5185426 arm).

		• No SPA agreement letter was issued for the proposed trial. The sponsor accepted the Agency's recommendations and specified that no further requests for SPA would be made.
Fast Track Designation	June 2010	• The request for the Fast Track designation was granted on the basis that the product was being investigated to improve overall survival in patients with melanoma containing the $BRAF^{V600E}$ mutation.
Amendment of Statistical Plan for the Phase 3 Trial	Sep.-Oct. 2010	• The Agency recommended the sponsor to amend the statistical plan for the above Phase 3 trial comparing RO5185426 with dacarbazine after more data from early phase trials emerged that suggested consistent, high response rates of RO5185426 treatment (a response rate of 50%-80% by RECIST 1.1 with an estimated median progression-free time of 7 months) in patients with melanoma containing the $BRAF^{V600E}$ mutation. • The projected overall survival hazard ratio was adjusted from the original 0.75 to 0.65 in the amended statistical plan while an estimated median survival of 8 months remained the same in the dacarbazine arm, decreasing the number required for the final overall survival analysis from the originally planned 468 to approximately 196. PFS was added as a co-primary endpoint, and the final analysis of PFS was performed at the time of the interim analysis of OS. *(see FDA Statistical Review for details)*
Expanded Access Protocol	Nov. 2010	• The Agency evaluated and granted the proposed treatment use of R05185426 under the IND for patients with metastatic melanoma with the $BRAF^{V600E}$ mutation
Pre-NDA Meeting	Jan-Feb 2011	• The sponsor proposed to file an NDA for R05185426 to treat patients with advanced melanoma positive for the $BRAF^{V600E}$ mutation under two scenarios, depending on the availability of results from the Phase 3 trial vs from Phase 1 and 2 trials.

		• The Agency was amenable to reviewing an application in either scenario. • The pre-specified interim analysis results from the Phase 3 trial showed an improvement in overall survival with a HR of 0.376 (p<0.001), prompting a rolling NDA submission to seek regular approval. • The Agency agreed to the Data Monitoring Board's recommendation to allow patients in the dacarbazine arm of the Phase 3 trial to crossover to receive R05185426.
NDA-202429 submission	Feb-Apr. 2011	• Priority review designated (6 months of review)

2.6 Other Relevant Background Information

Melanoma is the fifth leading cancer type in men and the sixth leading cancer type in women with an estimated total of 68,130 new cases and 8,700 deaths due to melanoma in 2010 (Jemal 2010). Unfortunately, the incidence of melanoma continues to rise in the U.S. and in the rest of the world (Howlander 2011). Sun exposure, use of tanning beds, fair skin, history of sunburns and immunosuppression all have been associated with an increased risk of melanoma. Germline mutations in CDK2NA, CDK4 and CMM1 are associated with hereditary melanomas and the syndrome of familial atypical mole and melanoma (FAMM). Somatic mutations in BRAF have been identified in melanoma and have a reported frequency of ~40-60%. The most common alteration that occurs is the codon 600 valine to glutamate (V600E) mutation, which represents ~90% of BRAF mutations. The next most common mutation is the codon 600 valine to lysine (V600K) followed by the valine to arginine mutation (V600R). Currently it is hypothesized that V600 mutations constitutively activate BRAF kinase activity leading to ERK activation and aberrant and uncontrolled cell proliferation and survival. Somatic mutations in RAS also have been identified in melanoma. Mutations in NRAS have a reported frequency of 10-20%, while KRAS mutations in melanoma are rare (~2%). Mutations of HRAS are rarely, if ever, found in melanoma. Activating mutations in RAS lock RAS proteins into a GTP-bound state leading to constitutive activation of downstream effector pathways such as the MAPK and PI3K pathways. Although rare, there have been reports of the co-existence of NRAS and BRAF mutations. In a cohort of 19 patients with germline CDK2NA mutations, three patients were found to have concomitant NRAS and BRAF mutations (Jovanovic 2010). There have been other case reports and work with short-term melanoma cell lines that have demonstrated the co-existence of NRAS and BRAF mutations. In addition, Pollock et al. report that three out of 32 dysplastic nevi that were sequenced for mutations had mutations in both BRAF and NRAS (Pollock 2003).

The prognosis of metastatic melanoma is grim with a five-year overall survival rate of less than 10%. There does appear to be a subtype of melanoma that has a relatively

indolent disease course, but there has been no successful determination of biomarkers or clinicopathologic features to identify these patients. Long et al. prospectively observed the clinical outcome of 197 patients with metastatic melanoma (Long 2011). Mutated BRAF (mutBRAF) was found in 95 (48%) of these patients, and 70 (74%) of the patients had the V600E mutation while 19 (20%) had the V600K mutation. The authors did not perform other mutational analysis such as CDK2NA or RAS. The authors found no difference in the time from the diagnosis of melanoma to first distant metastasis between the BRAF mutated and wtBRAF groups, but their data suggested that patients with BRAF mutations do not have a more favorable prognosis and may have a worse prognosis as compared to patients with wtBRAF (Long). Smaller, retrospective studies also have suggested an association with mutBRAF and shorter survival and shorter durations of responses to biochemotherapy, but no definitive conclusions can be drawn from these studies (Kumar 2003, Chang 2004).

Currently, there are three approved drugs for the treatment of advanced melanoma. Dacarbazine (DTIC) was approved over 30 years ago and is a commonly used chemotherapeutic agent either alone or in combination with other biologic or chemotherapy agents. There is a wide range of response rates associated with DTIC which range from 5-20%, but in well-controlled trials with modern methodologies of determining responses, the response rates appear to be in the range of 10%, and median overall survival is approximately 9 months (Patel 2011, Middleton 2000). IL-2 (Proleukin) was approved in 1998 on the bases of eight separate single-arm studies involving 270 patients with metastatic melanoma. Due to the high toxicity associated with IL-2 treatment, these patients were selected carefully for performance status and the absence of concurrent illnesses. The overall response rate in these patients was 16% with a complete response rate of 6%. It is important to note that the median duration of the complete responses is greater than 5 years. Ipilimumab (Yervoy), a monoclonal antibody targeting CTLA-4, was approved in 2011 on the basis of a double-blind, randomized trial comparing Yervoy to Yervoy in combination with Gp100 to Gp100 alone. Overall survival was longer (median = 10 months) in the Yervoy and Yervoy + Gp100 arms as compared to Gp100 alone (median = 6 months). In a recent publication, Yervoy in combination with DTIC was compared to DTIC alone. Overall survival in the Yervoy-DTIC group was 11.2 months as compared with 9.1 months in the DTIC group (Hodi 2010, Robert 2011). Other non-approved therapies that are used for the treatment of metastatic melanoma include temozolomide, paclitaxel, cisplatin, and biochemotherapy regimens involving the combination of dacarbazine, platinum, IL-2, and interferon alfa. Combination chemotherapy regimens have been associated with higher responses, but no studies demonstrating a survival benefit have been reported.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear reasonable.

3.2 Compliance with Good Clinical Practices

Data from this study were monitored by an external DSMB. The DSMB, which reviewed safety data from all RO5185426 trials, consisted of clinicians who are experts in the disease area and one statistician. The DSMB reviewed available safety data from this trial at regularly scheduled intervals specified in the DSMB charter. In addition, for this study the DSMB reviewed the results of the interim analysis of OS and the pre-specified final analysis for PFS performed at the time of the interim analysis for OS.
Following each data review, the DSMB made recommendations to the Sponsor regarding the conduct of this study according to the DSMB charter. All communications between the DSMB and the Sponsor followed the processes described in the DSMB Charter. An independent Data Coordinating Center provided the safety and efficacy results to the DSMB.

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki," or with the laws and regulations of the country in which the research was conducted, whichever afforded greater protection to the individual. The study fully adhered to the principles outlined in the current "Guideline for Good Clinical Practice (GCP)" International Conference on Harmonisation (ICH) Tripartite Guideline (January 1997), or with local law if it afforded greater protection to the patient. Roche and the investigators strictly adhered to the stated provisions in these guidelines. This was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with applicable regulations and law and to follow ICH GCP guidelines. The investigator ensured compliance with the current EU Clinical Trial Directive [2001/20/EC] and was trained according to Roche Standard Operating Procedures. For studies conducted in the USA or under a US IND, the investigator ensured adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators"; part 50, "Protection of Human Patients"; and part 56, "Institutional Review Boards." In other countries where "Guideline for Good Clinical Practice" exist, Roche and the investigators strictly ensured adherence to the stated provisions.

It was the responsibility of the investigator or designee (if acceptable by local regulations) to ensure the informed consent form (ICF) from each patient was signed and dated prior to participation in this study after adequate explanation of the aims,

methods, objectives and potential hazards of the study. It was explained to the patients that they were completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The ICF for the optional specimen donation to the Roche Clinical Repository was incorporated into the main clinical trial ICF and a separate, second signature was required from those patients who consented to participate.

OSI Inspection

Table 3: OSI Inspected Sites

Site # (Name,Address, Phone number, email, fax#)	Number of Enrolled Subjects	Number of Evaluable for Response	Number of Subjects with Best Response	Number of SAEs
Site #201192 Dr. Alessandro Testori, IEO Istituto Europeo di 14 4 0 Oncologia. Via Ripamonti, 435 , Milano, MI, 20141, 39-02-57489459, ITALY	14	11	5 (all with IND treatment)	0
Site #201202 Dr. Carmen Loquai, Universitaetsklinikum Mainz, Mainz, RP, 55131, 49-0-6131-17 ext 0, GERMANY	12	8	5 (all with IND treatment)	3
Site #200991 Dr. Jeffrey Sosman, Vanderbilt University Medical 9 6 4 Center, Nashville, TN, 37232, 1-615-343-6653, USA	9	8	6 (5 with IND treatment; 1 with DTIC)	4
Site #200997 Dr. Kim Margolin, University of Washington, Seattle, WA, 98109, 1-206-288-7341, USA	7	7	4 (3 with IND treatment; 1 with DTIC)	2

The following is excerpted from the OSI review:
Jeffrey Sosman
Site #20091
Assessment of data integrity: The data collected by this site are acceptable to support approval of the pending application.

Kim Margolin
Site #200997
Assessment of data integrity: Although there were lapses in the conduct of the study the lapses were identified early and necessary procedural corrections were made, e.g. collection of oxygen saturation, chemistry and hematology studies. The information missed in patient diaries were sporadic and limited in number. While regulatory violations as noted above occurred at this site, they are unlikely to significantly impact primary efficacy and safety data, nor do they appear to have had a significant impact on the protection of subjects' rights or welfare. Not withstanding the regulatory violations noted above, the data generated at this site are acceptable in support of an approval of the pending application.

Alessandro Testori
Site #201192
Assessment of data integrity: Radiographic data related to assessment of target lesion sizes could not be verified at this site; therefore, OSI can not provide an assessment of reliability of these data submitted in the NDA and the review division may wish to consider the impact of this finding on disease progression endpoint assessment. Survival data from the site appears to have been accurately reported in the NDA. The impact of failure to follow protocol specified PK sample storage/transport procedures should also be considered in assessment of pharmacokinetic data from this site. The balance of data reported for Study BRIM3 from this site appears to have been adequately captured/reported and may be considered reliable in support of the pending application.

Carmen Loquai
Site #201202
Assessment of data integrity: While inspectional observations from this site remain pending, based on preliminary communications from the field investigator, it appears that with the exception several instances of failure to report non-serious adverse events, no regulatory violations were observed and data from this site are acceptable in support of the pending application.

Hoffman LaRoche, Inc
Assessment of data integrity: Not withstanding regulatory violations discussed in prior sections of this review, the data from this Sponsor submitted to the agency as part and in support of NDA 202429 appear generally reliable.

OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS
Based on the review of preliminary inspectional findings for clinical investigators Dr. Loquai, Dr. Margolin, Dr. Testori, Dr. Sosman, and Hoffman LaRoche, Inc., survival data and safety data reported in the NDA appear reliable.

Reviewer's Comments:
Although the radiographic data related to assessment of target lesion sizes could not be verified at site #201192, the Office of Scientific Investigations concludes that the survival data and safety data reported in the NDA is reliable. The lack of verification of radiographic data at site #201192 is of a concern especially in light of the fact that the pivotal trial did not use an independent radiological committee for evaluation of PFS and response rates. This concern is mitigated by the statistically robust and clinically meaningful improvement in overall survival of vemurafenib over dacarbazine seen in the trial. The final conclusion drawn by OSI regarding the validity of the data and the report by the independent CRO (see section 6.1.10.1: Data Integrity) mitigate the concerns of a widespread, systemic problem of radiographic data in other sites. Thus, OS, PFS and response rate data will remain included in the package insert.

3.3 Financial Disclosures

Disclosure of financial interests of the investigators who conducted the clinical trials supporting this NDA was submitted in the FDA form 3454. The disclosure was certified by Judith Siegel, Vice President, Pharma Development Operations for the applicant. One sub-investigator in the key study supporting this NDA was found to have financial conflict of interest, in the form of significant payments from the applicant. There were 104 sites where patients were enrolled on the pivotal, Phase 3 trial.

Reviewer's Comment:
The total number of patients enrolled in the 3 sites (n=12) at which this sub-investigator had a financial conflict of interest did not drive the efficacy or safety data and does not appear to influence the outcome of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to the CMC review.

4.2 Clinical Microbiology

Vemurafenib is administered by mouth and was not reviewed for clinical microbiology.

4.3 Preclinical Pharmacology/Toxicology

Refer to preclinical pharmacology/toxicology review and to section 6.1.9 for a discussion on potential pro-proliferative effects of vemurafenib on RAS mutant cell lines.

4.4 Clinical Pharmacology

Refer to the Clinical Pharmacology review.

4.4.1 Mechanism of Action

From the package insert:
Vemurafenib is a low molecular weight, orally available, inhibitor of some mutated forms of BRAF serine-threonine kinase, including $BRAF^{V600E}$. Vemurafenib also inhibits other kinases *in vitro* such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5 and FGR at similar concentrations. Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib has anti-tumor effects in cellular and animal models of melanomas with mutated $BRAF^{V600E}$.

4.4.2 Pharmacodynamics

Refer to the Clinical Pharmacology review for details.

4.4.3 Pharmacokinetics

Refer to the Clinical Pharmacology review for details.
From the package insert:
The pharmacokinetics of vemurafenib were determined in patients with BRAF mutation-positive metastatic melanoma following 15 days of dosing at 960 mg twice daily with dosing approximately 12 hours apart. The population pharmacokinetic analysis pooled data from 458 patients. A one-compartment disposition model with first-order absorption and first-order elimination adequately describes the vemurafenib concentration-time profile.

At steady state, vemurafenib exhibits linear pharmacokinetics within the 240 mg to 960 mg dose range. The bioavailability of vemurafenib has not been determined. Following oral administration of vemurafenib at 960 mg twice daily for 15 days to patients with metastatic melanoma, the median T_{max} was approximately 3 hours.

Following 15 days of dosing at 960 mg twice daily, the mean (± SD) C_{max} and $AUC_{0\ 12}$ were 62 µg/mL ± 17 and 601 ± 170 µg*h/mL, respectively. The median accumulation ratio estimate from the population pharmacokinetic analysis for the twice daily regimen

is 7.36, with steady state achieved at approximately 15 to 22 days following dosing at 960 mg twice daily. At steady state, the mean vemurafenib exposure in plasma is stable (concentrations before and 2-4 hours after the morning dose) as indicated by the mean ratio of 1.13.

The potential effect of food on vemurafenib absorption has not been studied. In clinical trials, vemurafenib was administered without regard to food.

APPEARS THIS WAY ON ORIGINAL.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Clinical Studies in Support of NDA 202429

Study #	Population	Design	Dose (mg B.I.D.)	# Any Vemurafenib	# Vemurafenib 960 mg B.I.D.
PLX06-02	Metastatic Melanoma and Colorectal Carcinoma	Phase 1 Dose Escalation with BRAF mutation positive melanoma expansion cohort	160-1120	56	32
NP22676	Stage IV BRAF-V600 Mutation-Positive Melanoma	PK Study	960	25	
NP25158	Unresectable Stage IIIc or Stage IV BRAF-V600 Mutation-Positive Melanoma	Mass Balance Study	960	7	7
NP25163	Unresectable Stage IIIc or Stage IV BRAF-V600 Mutation-Positive Melanoma	PK Study	240-960	52	
NP22657/ BRIM2	BRAF-V600 Mutation-Positive Metastatic Melanoma	Phase 2 Single Arm	960	132	132
NO25026/ BRIM3	Unresectable Stage IIIc or Stage IV BRAF-V600 Mutation-Positive Melanoma	Phase 3 Vemurafenib vs. Dacarbazine	960	336	336

5.2 Review Strategy

The clinical review is based on the clinical study report for the randomized trial in unresectable or metastatic melanoma, NO25026, including the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant, study reports for other vemurafenib clinical trials and literature review of melanoma. Efficacy is supported by the single arm study in previously treated metastatic melanoma, NP22657.

5.3 Discussion of Individual Studies/Clinical Trials

This NDA is based primarily on overall survival and progression free survival from a single, randomized, open-label Phase 3 trial, NO25026 (BRIM 3).

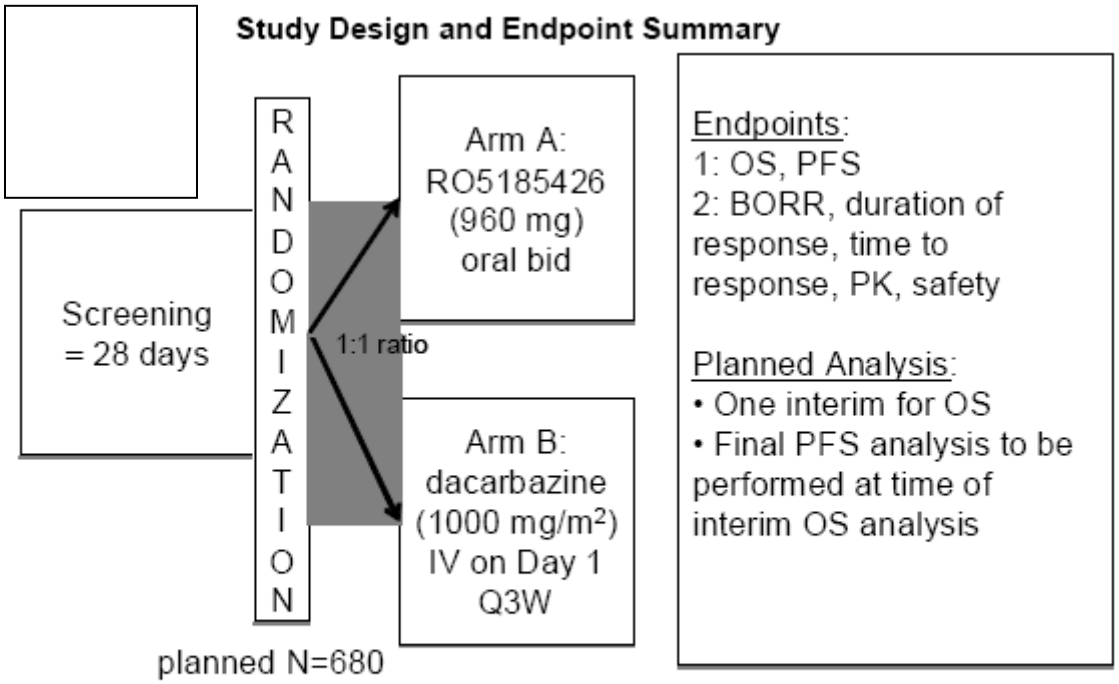
Study Title: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving RO5185426 or Dacarbazine.

Reviewer's Comment: *Vemurafenib is also known as RO5185426*

5.3.1 Study Design

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.

Figure 2: Study Design



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.

Tumor assessments were done at screening, every six weeks for the first 12 weeks, every nine weeks subsequently, and at the final visit. Patients were followed for AEs (with exception of SCC) up to 28 days after the last dose in all patients. All SCC events occurring at any time during the study or follow-up period (every three months until patient death, withdrawal of consent, or lost to follow-up) were collected and reported as a serious adverse event (SAE) to the sponsor.

This study followed the “dual protocol approach” because it was a global study that included investigator sites within the European Union (EU) that, due to conflicts with local regulations, could not necessarily comply with the signature requirements on FDA Form 1572. Therefore, the study was conducted under two identical companion protocols: one for sites in the US and non-EU countries, and the other for sites in EU countries. As proscribed in the protocol, data from two protocols (NO25026-ROW and NO25026-EU) were to be combined into one comprehensive statistical analysis. The study was powered based on this aggregate analysis.

Data from this study were monitored by an external DSMB. The DSMB, which reviewed safety data from all RO5185426 trials, consisted of clinicians who are experts in the disease area and one statistician. The DSMB reviewed available safety data from this trial at regularly scheduled intervals specified in the DSMB charter. In addition, for this

study the DSMB reviewed the results of the interim analysis of OS and the pre-specified final analysis for PFS performed at the time of the interim analysis for OS.

Reviewer's Comment: *Dacarbazine was approved for use in metastatic melanoma in 1975, and has been used as a single agent or in combination since then with reported response rates in the range of 5-20%. The phase I study of vemurafenib reported a response rate of 54% in patients with BRAF V600E mutation-positive melanoma, with some press releases reporting the unconfirmed response rates of ~75%. Both patients and investigators may have been biased to believe that vemurafenib was a better drug than DTIC prior to the start of this open-label trial.*

5.3.2 Study Drug Administration and Schedule

A total of 680 patients were planned to be enrolled at centers in Western Europe, North America, Australia/New Zealand, and Israel. Patients were randomly assigned to treatment in a 1:1 randomization ratio to one of two treatment arms. Following the screening period (of up to 28 days), eligible patients were randomized to receive either:

- Experimental Arm A: oral RO5185426 administered twice daily (bid) at a dose of 960 mg
- Control Arm B: dacarbazine administered intravenously 1000 mg/m2 on Day 1 every 3 weeks (3 week cycle)

The treatment allocation was based on a minimization algorithm using the following balancing factors:

- Geographic region (North America, Western Europe, Australia/New Zealand, others)
- Eastern Cooperative Oncology Group (ECOG) performance status (0 vs.1)
- Metastatic classification (unresectable Stage IIIC, M1a, M1b, and M1c)
- Serum lactate dehydrogenase (LDH) normal vs. LDH elevated

Reviewer's Comment:
Patients were appropriately enrolled in geographic regions of high sun exposure. Stratification by geographic regions may address different genetic profiles of the melanoma other than BRAF mutation status. The other stratification factors are reasonable as well and account for known prognostic factors such as LDH and ECOG performance status.

5.3.3 Study Endpoints

Primary Objective

- The primary objective of this study was to evaluate the efficacy of RO5185426 as a monotherapy compared to dacarbazine in terms of progression-free survival (PFS) and overall survival (OS) in previously untreated patients with *BRAF*V600E mutation-positive metastatic melanoma.

Secondary Objectives

The secondary objectives were as follows:

- To further assess the efficacy of RO5185426 compared to dacarbazine based on best overall response rate (BORR), time to response, and duration of response
- To evaluate the tolerability and safety profile of RO5185426 using the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI CTCAE) (version 4.0)
- To further characterize the pharmacokinetic (PK) profile of RO5185426
- To contribute to the validation of the cobas® 4800 BRAF V600 Mutation Test as a companion diagnostic test for the detection of *BRAFV600* mutations in DNA extracted from formalin-fixed paraffin-embedded tumor (FFPET) samples

Exploratory Objectives

The exploratory objectives were as follows:

- To explore the overall quality of life (QoL) of the treatment groups using the Functional Assessment of Cancer Therapy - Melanoma (FACT-M) (Version 4) questionnaire, and physical symptom improvement outcome (PIO)
- To assess the responsiveness of melanomas carrying certain non-V600E (i.e. V600K and V600D) mutations in codon 600 of the *BRAF* gene to RO5185426
- To evaluate biomarkers that may be relevant:
    - to further predict responsiveness to RO5185426
    - to explain primary or acquired resistance to RO5185426
    - to indicate pharmacodynamic effects of RO5185426
    - to monitor the disease
- To evaluate the molecular characteristics of squamous cell carcinomas (SCCs) that may be observed in patients treated with RO5185426.

Reviewer's Comment:
The exploratory endpoints evaluating relevant biomarkers for response prediction and resistance are important issues that merit further studies. There is non-clinical evidence suggesting that vemurafenib may be pro-proliferative of tumors harboring RAS mutations and that acquired resistance to vemurafenib may be mediated by the appearance of RAS mutations which were not initially present. This issue is discussed further in section 6.1.9 and will be addressed in a post-marketing commitment by the applicant.

5.3.4 Eligibility Criteria

The target population was male or female patients ≥ 18 years of age with histologically confirmed metastatic melanoma who had not received prior systemic anti-cancer treatment and whose melanoma was confirmed to bear the *BRAF*V600E mutation by the cobas® 4800 BRAF V600 Mutation Test.

Inclusion Criteria

Patients had to meet all of the following criteria to be included in the study:

1. Male or female patients ≥ 18 years of age
2. 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.
3. Treatment-naïve, i.e., no prior systemic anti-cancer therapy for advanced disease (Stage IIIC and IV). Only prior adjuvant immunotherapy was allowed.
4. Must have had a *BRAF*V600-positive mutation (by Roche cobas test) prior to administration of study treatment
5. ECOG performance status of 0 or 1
6. Life expectancy > 3 months
7. Measurable disease by RECIST criteria (version 1.1) prior to the administration of study treatment
8. Must have recovered from effects of any major surgery or significant traumatic injury at least 14 days before the first dose of study treatment
9. Cutaneous SCC lesions identified at baseline must be excised. Adequate wound healing was required prior to study entry. Baseline skin exam was required for all patients.
10. Adequate hematologic, renal, and liver function as defined by laboratory values performed within 28 days prior to initiation of dosing:
11. For premeonopausal women, negative serum pregnancy test within 10 days prior to commencement of dosing; women of non-childbearing potential were included if they were either surgically sterile or postmenopausal for ≥ 1 year
12. For fertile men and women, the use of an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician, in accordance with local requirements
13. Absence of any psychological, familial, sociological or geographical condition that would potentially hamper compliance with the study protocol and follow-up schedule; such conditions were discussed with the patient before trial entry
14. A signed informed consent form (ICF) obtained prior to study entry and prior to performing any study-related procedures

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

1. Any active central nervous system (CNS) lesion (i.e., those with radiographically unstable, symptomatic lesions). However, patients treated with stereotactic therapy or surgeries were eligible if patient remained without evidence of disease progression in brain ≥ 3 months. Patients were also required to be off corticosteroid therapy for ≥ 3 weeks. Whole brain radiotherapy was not allowed with the exception of patients who had definitive resection or stereotactic therapy of all radiologically detectable parenchymal lesions.
2. History of carcinomatous meningitis
3. Regional limb infusion or perfusion therapy
4. Anticipated or ongoing administration of anti-cancer therapies other than those administered in this study
5. Pregnant or lactating women
6. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate RO5185426 absorption (patients had to be able to swallow pills)
7. Mean QTc interval ≥ 450 msec at screening
8. NCI CTCAE Version 4.0 grade 3 hemorrhage within 4 weeks of starting the study treatment
9. Any of the following within the 6 months prior to study drug administration:
    a. myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension, cerebrovascular accident or transient ischemic attack, or symptomatic pulmonary embolism
10. Known clinically significant active infection
11. History of allogeneic bone marrow transplantation or organ transplantation
12. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or study drug administration, or could interfere with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry into this study
13. Previous malignancy within the past 5 years, except for basal or squamous cell carcinoma of the skin, melanoma in-situ, and carcinoma in-situ of the cervix (an isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer was allowed)
14. Previous treatment with a BRAF inhibitor
15. Known human immunodeficiency virus (HIV) positivity, AIDS-related illness, active hepatitis B virus, or active hepatitis C virus
16. Randomization to this trial at another participating site

Reviewer's Comments:
These inclusion and exclusion criteria are reasonable for the trial population.

Procedures for Assessing Patients for BRAF V600 Mutations
A sample of formalin-fixed paraffin-embedded tumor consisting of 5 serially cut, unstained sections was submitted for each patient being considered for entry into this trial. DNA from the tumor samples was isolated and tested using the cobas® 4800 BRAF V600 Mutation Test, which was developed as a companion diagnostic test for RO5185426. Patients were eligible for enrollment in the study if they had a positive test result for the mutation and met all other eligibility criteria. The cobas test reports either Mutation Detected or Mutation Not Detected for each tumor specimen analyzed.

As part of the clinical validation of the cobas test, a subset of samples was subjected to bidirectional Sanger sequencing as a reference method in order a) to perform an agreement analysis between the cobas and Sanger test results for the detection of V600E mutations, and b) to identify non-V600E mutations. Discrepancies between the two test methods were resolved using 454 “deep” sequencing as an independent method. Based on a pre-study power analysis, Sanger sequencing was performed on all available tumor specimens obtained in the BRIM-3 trial for patients screened by the cobas test for enrollment as of June 15, 2010. All of these additional DNA tests were performed after patient enrollment in the clinical trial and the results did not influence patient eligibility for study drug treatment.

Bi-directional Sanger DNA sequencing has been viewed as a reference standard for assessing DNA sequence variation, but an in vitro diagnostic Sanger method for BRAF mutation detection has not been approved by the FDA. Sanger sequencing has limited sensitivity for somatic mutation detection, with loss of sensitivity when mutation levels fall below ~20-30%, as compared with the estimated sensitivity of 5% for the cobas test. Thus it was expected that the cobas test would identify mutations that Sanger sequencing would not detect. Furthermore we observed a test failure rate of approximately 10% for Sanger sequencing in the samples from the Phase 2 study, NP22657, as compared to a test failure rate of < 1% for the cobas test. Thus we anticipated that Sanger would fail to detect mutations in a number of samples due to either lack of sensitivity or test failure. Pre-clinical studies indicated that the cobas test also detects *BRAF*V600D mutations and a proportion of *BRAF*V600K mutations. Therefore, it was anticipated that some cases identified by the cobas test as being mutation-positive would in fact harbor *BRAF*V600D or *BRAF*V600K mutations. Sanger sequencing was expected to identify a small percentage (approximately 10%) of cases with *BRAF*non-V600E mutations (e.g., *BRAF*V600D, *BRAF*V600K, or *BRAF*V600R). Since a small number of such cases were likely to be enrolled based on a positive cobas test result, an exploratory objective of this study was to assess the responsiveness of these tumors to RO5185426. It was also anticipated that a small percentage of cases identified by the cobas test as being mutation-negative would harbor *BRAF*V600K, or *BRAF*V600R, or perhaps rarer variant mutations in adjacent codons. Since these patients would not be enrolled into this study, clinical responsiveness of these other *BRAF* mutant tumors was not assessed.

To resolve discordances between Sanger sequencing and the cobas® test results, picotiter plate pyrosequencing on the 454 GS-Titanium platform was used as an independent method. This 454 sequencing is more sensitive (approximately 1% mutant alleles) than either of the other two methods. For Phase 2 study, NP22657 [12], 454 sequencing was performed on all discordant cobas test and Sanger sequencing samples, and on a representative subset of concordant samples (i.e., cobas test and Sanger sequencing *BRAF*V600E-positive or -negative samples). For this study, 454 sequencing was performed on a limited subset of samples.

Reviewer's Comments:
The cobas test performance is discussed further in section 6.1.7. There have been no clinical studies in melanoma patients whose tumors have been tested negative for the BRAF V600E mutation as detected by the cobas test aside from 5 patients who were treated in the dose escalation phase of the early phase clinical trial. These patients were treated with doses lower than the dose used in the pivotal phase 3 study and no responses were demonstrated.

5.3.5 Duration of Treatment

Patients were treated until the development of progressive disease, unacceptable toxicity, and/or consent withdrawal. Patients who withdrew from the study for any reason could start other anti-cancer treatments. Patients randomized to the dacarbazine group were not permitted to receive RO5185426 unless recommended by the DSMB after the interim analysis of OS.

Patients who withdrew from treatment for any reason were to be followed for SCC according to the surveillance plan and for survival until death, withdrawal of consent, or lost to follow-up. The dose of RO5185426 could be interrupted or reduced for toxicity and dacarbazine could be interrupted or discontinued for toxicity.

Dosing beyond progression of the underlying malignancy was considered only under special circumstances, i.e., if the patient could clinically benefit by continued therapy and it was judged by the investigator, in consultation with the sponsor, to be in the best interest of the patient.

5.3.6 Primary Endpoint Evaluation

The co-primary efficacy endpoints for this study were OS and PFS.

Overall Survival

OS was defined as the time from randomization to death from any cause. For patients who were alive at the time of analysis data cutoff, OS time was censored at the last date the patient was known to be alive prior to the clinical cutoff date. The last date the patient was known to be alive was derived as the latest date of contact or study

assessment. Survival time for patients with no post-baseline survival information was censored on the date of randomization.

The primary analysis of OS was a comparison of the two treatment groups using an unstratified log-rank test (two-sided). The hazard ratio for death for RO5185426 relative to dacarbazine and the associated 95% CI were computed using a Cox regression model. Median OS was estimated using the Kaplan-Meier method, with 95% CI calculated using the method of Brookmeyer and Crowley [1]. The Kaplan-Meier estimate of 6-month OS and the associated 95% CI was provided.

Progression-Free Survival
The final analysis for PFS was performed at the time of the interim efficacy analysis for OS. PFS was defined as the time from randomization to the date of disease progression (based on tumor assessment date) or death from any cause, whichever occurred first. The death of a patient without a reported progression was considered as an event on the date of death. Patients who had neither progressed nor died were censored on the date of last evaluable tumor assessment prior to the clinical cutoff date. PFS for patients who had no post-baseline assessment and who did not have an event were censored on the date of randomization.

The primary analysis of PFS was a comparison of the two treatment groups using an unstratified log-rank test (two-sided). The hazard ratio for progression or death for RO5185426 relative to dacarbazine and the associated 95% CI were computed using a Cox regression model. Median PFS was estimated using the Kaplan-Meier method, with 95% CI calculated using the method of Brookmeyer and Crowley [1]. The Kaplan-Meier estimate of 6-month PFS and the associated 95% CI was provided.

5.3.7 Secondary Endpoint Evaluation

Best Overall Response Rate (Confirmed)
A hierarchical approach was to be used to evaluate the statistical significance of best overall response rate (BORR) (confirmed). If either of the co-primary endpoints of OS or PFS met the respective criteria for statistical significance, BORR (confirmed) was evaluated for statistical significance at the 0.05 level (two-sided). Best overall response (confirmed) was defined as a complete response (CR) or partial response (PR) which was confirmed per RECIST version 1.1. The best overall response of CR or PR was determined on the basis of confirmed response at the next tumor assessment. Evaluable patients who did not meet these criteria were considered non-responders; this included patients who never received study treatment and treated patients for whom a post-baseline tumor assessment was not performed.

The BORR and the associated 95% Clopper-Pearson CI were calculated for each treatment group. The difference in BORR between treatment groups and the associated

95% Hauck-Anderson CI were calculated. BORR was compared between treatment groups using a Chi-squared test with Schouten correction.

Duration of Response
Duration of response was evaluated for patients who satisfied the criteria for best overall responses (confirmed). Duration of response was defined as the time from the date of the earliest qualifying response to the date of disease progression or death from any cause. For patients who were alive without progression following the qualifying response, duration of response was censored on the date of last evaluable tumor assessment before the data cutoff date.

Time to Response
Time to response was evaluated for patients who satisfied the criteria for best overall response (confirmed). Time to response was defined as the time from randomization to the date of the earliest qualifying response. Time to response was summarized using descriptive statistics (median, 25% and 75% quartiles minimum, maximum). No formal hypothesis testing was performed for time to response.

5.3.8 Major Protocol Amendments
As of the cutoff date for this CSR, the original protocol, dated September 1, 2009, was amended twice. Each amendment was implemented after the first patient was randomized. Changes that had a major impact on the *conduct* of the study are summarized below.

Amendment B, first implemented June 8, 2010:

- Added text that the BRAF mutation analysis must be done after informed consent is obtained but before other screening procedures, and that all subsequent screening procedures should be performed only if the cobas test is positive.
- Clarified that all SCC events should be reported as SAEs.

Amendment C, first implemented November 1, 2010, before the interim analysis for OS:

- 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 planned; with the change in the type 1 error rate (see bullet 4 below), this resulted in a reduction in the number of deaths required for final analysis from 468 to approximately 196 (note, the planned power to detect a treatment effect [80%] was not changed)
- Changed the number of interim analyses for OS from two (at 50% and 75%) to one (at 50% information) and the method of determination of the efficacy boundary from O'Brien-Fleming to the Pocock method

- Added PFS as a co-primary endpoint and as part of the study's primary objective, hence adding it as a co-primary endpoint to OS was done to strengthen the collective evidence of a RO5185426 treatment effect; specified that the final analysis of PFS was to occur at the time of the interim analysis of OS
- Changed the type 1 error rate for the study from 0.025 (two-sided) to 0.05 (two-sided) as the type 1 error rate of 0.05 (two-sided) was considered by the Sponsor to be adequate for this study; implemented type 1 error for the co-primary endpoints as 0.045 (two-sided) for OS and 0.005 (two-sided) for PFS in order to maintain the overall type 1 error rate for the study as 0.05 (two-sided)

After the database closure for this study report an additional amendment was implemented.

Amendment D, first implemented February 16, 2011

- Added allowance for crossover from the dacarbazine group to the RO5185426 group for all patients (including those who had received subsequent systemic therapy upon disease progression and those with asymptomatic brain metastases) on dacarbazine with a wash-out period of 14 days. Crossover from the RO5185426 group to the dacarbazine group was disallowed.
- Added cautions for concomitant medications: for potential drug-drug interactions with any concomitant medications that are primarily metabolized by the CYP450 1A2, 3A4 and 2C9, those that strongly inhibit or induce CYP3A4, and for medications and supplements that may affect QT interval prolongation.
- Increased monitoring of ECG and electrolytes before initiating treatment with RO5185426 and during treatment, as well as recommendations to manage potential QTc prolongation.
- Added evaluation and assessment of molecular characteristics of suspicious lesions in addition to the evaluation of cuSCC.

Changes to Planned Analyses

The planned analyses for this study were described in the SAP dated November 4, 2010.

The following analyses were specified in the SAP but were not performed for the reasons stated:

- The analysis of BORR for which confirmation was not required was not performed; analysis of BORR which required confirmation was performed as it was considered a more meaningful measure of clinical benefit.
- A sensitivity analysis of OS censored for subsequent anti-cancer therapy was not performed due to the compelling OS results observed at the time of this analysis.
- A sensitivity analysis of PFS in which data were to be censored for non-protocol anti-cancer therapy received without disease progression was not performed. Because there were so few patients evaluable for PFS who received anti-cancer therapy without disease progression (7 RO5185426 and 15 dacarbazine), the

Sponsor considered that this sensitivity analysis would not differ in its conclusion from the primary analysis of PFS.

- A sensitivity analysis of PFS in which censoring was to account for missed visits was not performed because there was only one patient (200998/1004, dacarbazine) who satisfied the criteria for missed visits (2 or more consecutive missed visits prior to death or progression).
- Summary of RO5185426 concentration values at the time of progression, biopsy of progressive lesion and at time of treatment termination will be provided in a subsequent report with the biomarker analysis.

Reviewer's Comment:
The rationale behind not performing these analyses is reasonable and acceptable.

6 Review of Efficacy

Efficacy Summary

This application is based on the co-primary endpoints of overall survival (OS) and progression free survival (PFS) in a single, randomized, open-label study comparing vemurafenib with dacarbazine in 675 patients with locally advanced or metastatic BRAF V600E mutation-positive melanoma.

- The applicant reports an improvement in OS in patients treated with vemurafenib as compared to placebo with a hazard ratio of 0.37 (95% CI: 0.26, 0.55); p<0.0001.
- With longer follow-up and with 199 OS events, which fulfills the protocol specified number of OS events required for the final OS evaluation, the applicant reports an improvement in OS in patients treated with vemurafenib as compared to placebo with a hazard ratio of 0.44 (95% CI: 0.33, 0.59); p<0.0001.
- The median survival for patients treated with dacarbazine is 7.89 months (95% CI: 7.20-9.63) whereas the median survival for patients treated with vemurafenib has not been reached (95% CI: 9.59-NR)
- The applicant reports an improvement in PFS in patients treated with vemurafenib as compared to placebo with a hazard ratio of 0.26 (95% CI: 0.20, 0.33); p<0.0001. The Kaplan-Meier estimate of median PFS is 5.32 months for patients treated with vemurafenib as compared to 1.61 months for patients treated with dacarbazine.
- The applicant reports a confirmed overall response rate of 48.4% in patients treated with vemurafenib compared to 5.5% in patients treated with dacarbazine, with a median duration of response of 5.49 months (95% CI 3.98, 5.72).

6.1 Indication

The proposed indication is: (b) (4)

Reviewer's Comments:
The proposed indication is not reflective of the population studied in the pivotal trial. The PCR-based test used to select patients in the trial was designed to specifically detect the BRAF V600E mutation, but is cross reactive with other V600E mutations such as V600K. Based on the reference method of Sanger sequencing, approximately 10% of the patients who tested positive by the test had V600K mutations by sequencing (see section 6.1.7 for detailed discussion). The test has not detected V600R or V600D mutations, although the incidence of these mutations is low. Vemurafenib has not been studied in other V600 mutations and the safety and efficacy for patients with tumors that bear other V600 mutations has not been demonstrated. The revised indication is:

ZELBORAF™ is 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 for use in patients with wild-type BRAF melanoma.

6.1.1 Methods

Clinical review is based primarily on the CSR for study NO25026, the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant and literature review of melanoma.

6.1.2 Demographics

Demographic data is summarized in Table 4. Enrollment occurred in 11 different countries. 21% of the patients were enrolled in the United States.

Reviewer's Comments:
There was no substantial imbalance between treatment arms with respect to the demographic characteristics of age, gender, and race. The overwhelming majority of the patients were Caucasian.

Table 5: Patient Demographics

		Vemurafenib (n=337)	Dacarbazine (n=338)	Total (n=675)
Baseline Characteristics:				
Age (years):				
	Mean:	55.2	52.6	53.9
	SD:	13.8	13.9	13.9
	Median:	56.0	52.5	54.0
	Min:	21	17	17
	Max:	86	86	86
Gender:				
	Male:	200 (59.0)	181 (54.0)	381 (56.4)
	Female:	137 (41.0)	157 (46.0)	294 (43.6)
Race:				
	White:	333 (98.8)	338 (100.0)	671 (99.4)
	Other:	4 (1.2)	0 (0.0)	4 (0.5)

Table 6: Region of Enrollment

	Vemurafenib (n=337)		Dacarbazine (n=338)		Total (n=675)	
Region:						
Australia/New Zealand	39	(12)	38	(11)	77	(11)
North America	86	(26)	86	(25)	172	(25)
Western Europe	205	(61)	203	(60)	408	(60)
Other	7	(2)	11	(3)	18	(3)

Baseline Disease Characteristics
The majority of the patients enrolled on this trial had distant metastasis (M1C). Almost 70% of the patients enrolled had a history of melanoma that was resected /treated but

returned as metastatic disease. The median time from diagnosis of metastatic disease to enrollment on trial was 10.6 months.

Reviewer's Comment:

Most series in the literature report that the median survival of metastatic melanoma is 9 months, so this trial may have enrolled a higher percentage of melanoma patients who have a more indolent disease compared to that found in the US community population.

Table 7: Baseline Disease Characteristics

	Vemurafenib (n=337)		Dacarbazine (n=338)		Total (n=675)	
Melanoma Stage at Randomization:						
Unresectable IIIC	15	(4.5)	14	(4.1)	29	(4.3)
M1a	37	(11.0)	38	(11.2)	75	(11.1)
M1b	63	(18.7)	60	(17.8)	123	(18.2)
M1c	222	(65.9)	226	(66.9)	448	(66.4)
Melanoma Stage at Diagnosis:						
Stage 0	9	(2.7)	9	(2.7)	18	(2.7)
Stage I	68	(20.2)	79	(23.4)	147	(21.8)
Stage II	76	(22.6)	88	(26.0)	164	(24.3)
Stage III	76	(22.6)	65	(19.2)	141	(20.1)
Stage IV	99	(29.4)	87	(25.7)	186	(27.6)
Unknown	9	(2.7)	10	(3.0)	19	(2.8)
Adjuvant therapy:						
Yes	68	(20.2)	59	(17.5)	127	(18.8)
No	269	(79.8)	279	(82.5)	548	(81.2)
Time from Diagnosis of Metastatic Disease to Enrollment on Trial (months):						
Mean	11.1		10.1		10.6	
SD	21.1		21.1		21.1	
Median	3.5		3.1		3.25	
SEM	1.2		1.1		0.8	
Min-Max	0-160.3		0-186.6		0-186.6	

Baseline Tumor Characteristics

Five patients on each arm had no measurable disease at baseline. The mean number of metastatic sites at baseline for each patient was 2.6 and the sum of the longest diameter of target lesions at baseline is depicted in table 7 below.

Reviewer's Comments:
Overall, patients enrolled on this trial had several sites of metastasis and tumors of notable sizes that justified treatment with systemic therapy.

Table 8: Baseline Tumor Characteristics

Sum of Longest Diameter of Target Lesions at Baseline (cm)			
Mean	8.8	7.9	8.4
SD	9.6	5.7	7.9
Median	6.6	6.6	6.6
SEM	5.3	3.1	3.1
Min-Max	9.0-131.0	9-29.5	9-131.0
N	332	333	665
N Greater Than Mean	133	123	256

6.1.3 Subject Disposition (Data Cutoff 12-30-10)

Between January 4, 2010 and December 16, 2010, a total of 2107 patients were screened at 104 centers in 12 different countries. The reasons for screen failure are depicted in the figure below. Out of 2107 patients screened, 1021 patients tested positive for the BRAF mutation by the Cobas V600E mutation test (48.5%).

Reviewer's Comment:
The number of BRAF mutations is consistent with prior published literature regarding the frequency of a BRAF V600E mutation in melanoma.

Table 9: Summary of Reasons for Screen Failure

NO25026 Summary of Reasons for Screen Failure

Screen Failure Reason	Number of Patients	Percent of Patients
BRAF negative	1086	75.84%
Brain mets	110	7.68%
Deterioration/ECOG/death	46	3.21%
WDC	32	2.23%
Insufficient tumour	27	1.89%
Unmeasurable lesion/disease	26	1.82%
Other	18	1.26%
Patient decision	14	0.98%
Cardiac function	12	0.84%
Elected other therapy/trial	10	0.70%
PD	10	0.70%
Tissue issue	9	0.63%
Other cancer	8	0.56%
Liver function	7	0.49%
Previously treated with ACT	5	0.35%
HIV+/HBV/HBC	4	0.28%
Investigator decision	3	0.21%
Surgery/Surgical complications	3	0.21%
Lab Values	2	0.14%
TOTAL	**1432**	**100%**

A total of 675 patients were randomized to this study: 337 patients to RO5185426 and 338 patients to dacarbazine. A total of 37 patients who were initially randomized to dacarbazine withdrew consent or refused treatment before receiving any therapy. An additional 11 patients randomized to dacarbazine never received treatment for reasons such as progressive disease or the discovery of brain metastases compared to only 2 patients on the vemurafenib arm who did not receive treatment due to a negative BRAF test and for anemia.

Reviewer's Comments:
The 11 patients who were randomized to dacarbazine but never received treatment for reasons such as progressive disease or discovery of brain metastasis raise questions as to whether there was an imbalance of "sicker" patients randomized to the dacarbazine arm, as no patients who were randomized to receive vemurafenib withdrew prior to receiving treatment. Also, a key eligibility requirement for trial entry is an ECOG performance status of 0 or 1 so these patients who became ineligible for treatment represents a rapid deterioration of their condition. Concerns regarding the imbalance of patients on each arm are addressed in the sensitivity analyses described in section 6.1.4.

Table 10: Subject Disposition

	Vemurafenib	Dacarbazine
Screened	**2107**	
Randomized	**337**	**338**
Treated	**336**[1]	**289**
Refused Treatment/Withdrew Consent	0	37
Never Received Treatment (other reasons)	2[2]	11[3]
Ongoing Randomized Treatment	**223**	**83**
Continuing despite progression	7	6
Discontinued Randomized Treatment	**113**	**206**
Progressive Disease or Death	95	181
Lost to Follow Up/Patient Decision	6	12
Adverse Event[4]	12	10
Other		3[5]

[1] One patient was randomized to Dacarbazine but was mistakenly given Vemurafenib
[2] 1 patient was discontinued form trial due to anemia prior to starting treatment; 1 patient was randomized in error and did not have BRAF mutation and was not treated.
[3] 5 patients had progressive disease prior to starting treatment; 2 patients found to have brain metastasis and were not treated; 1 patient with pulmonary embolus found prior to starting treatment; 1 patient with no measurable disease and was not treated; 2 patients have no records available.
[4] In absence of death or progressive disease.
[5] 2 patient stopped per PI discretion; 1 patient stopped after it was discovered that patient was randomized in error (No Braf mutation but patient received 1 dose of dacarbazine).

6.1.4 Analysis of Primary Endpoint(s)

Overall Survival

The primary analysis of overall survival is shown in table 12, and the Kaplan Meier curves are depicted in figure 3. The median survival times for both the vemurafenib and dacarbazine arms are not considered reliable as < 10% of randomized patients had > 7 months of follow up at the time of analysis. The FDA requested updated OS data based on the pre-specified number of death events (190). The applicant provided updated OS data based on 199 events using a data cutoff date of March 31, 2011 and the analysis is depicted in table 10 and figure 4. Upon recommendation of the DSMB to close accrual to the trial and to allow crossover, all patients who were initially randomized to dacarbazine were allowed to receive vemurafenib. Patients who received other systemic therapy following dacarbazine were not permitted to receive vemurafenib until February 16, 2011.

Reviewer's Comments:
Based on this randomized trial, vemurafenib has demonstrated a statistically significant improvement in OS as compared to dacarbazine in BRAF V600E mutation positive melanoma. The hazard ratio of 0.44 (using the updated OS data) represents a 56% reduction in the risk of death as compared to dacarbazine, but the estimates of how long this survival advantage actually is cannot be estimated at this point as the median survival of those treated with vemurafenib has not been reached. The lower limit of the 95% confidence interval of the Kaplan-meier estimates of OS for the vemurafenib arm is 9.6 months, thus one can say that the difference in median OS as compared to dacarbazine is at least 1.7 months, but this most likely underestimates the actual difference in survival times. In spite of not being able to estimate the precise median differences in survival, the overall hazard ratio and the separation of the Kaplan-meier curves give confidence that the prolongation of OS as seen with vemurafenib is of a clinically significant magnitude and represents direct evidence of clinical benefit.

Table 11: Primary Analysis: OS; Full ITT Population*

Study NO25026-FDA (Data Cutoff 12-30-10)

Overall Survival	Vemurafenib N = 337	Dacarbazine N = 338
Number of Events	43 (12.8)	75 (22.2)
Censored	294 (87.2)	63 (18.6)
Median OS**	**9.2 months (8.03, NE[2])**	**7.7 Months (6.2, NE[2])**
Hazard Ratio[1] (95% CI)		**0.37 (0.26-0.54)**
p-value (logrank test)		**<0.0001**
Duration of Follow Up	**3.75 months**	**2.33 Months**
UPDATED OS ANALYSIS		
Number of Events	78 (23.1)	121 (35.8)
Censored	259 (76.9)	217 (64.2)
Median OS	**NE[2] (9.59-NE[2])**	**7.89 Months (7.20-9.63)**
Hazard Ratio[1] (95% CI)		**0.44 (0.33-0.59)**
p-value (logrank test)		**<0.0001**
Duration of Follow Up	**6.21 months**	**4.46 months**

*The Applicant has conducted the OS analysis with an enrollment cutoff of 12/15/10. This excludes 2 patients on the dacarbazine arm and 1 patient on the vemurafenib arm. This data cut off point yielded the same hazard ratio as using the data cutoff point 12 30 10.
**K M estimates of median OS are considered unreliable as <10% of the randomized patients had >7 months of follow up at the time of the survival analysis.
[1]Cox proportional hazards model [2]Not estimable

Figure 3: Kaplan-Meier OS Estimates: Data cutoff 12/30/2010

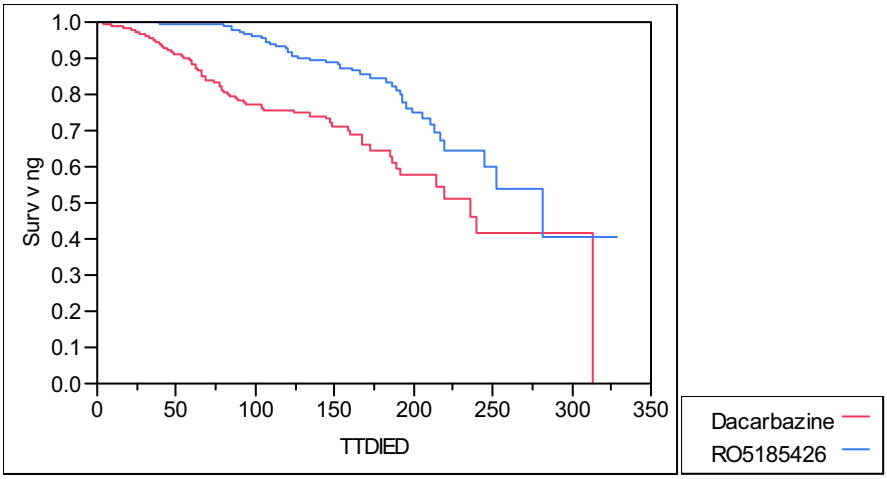
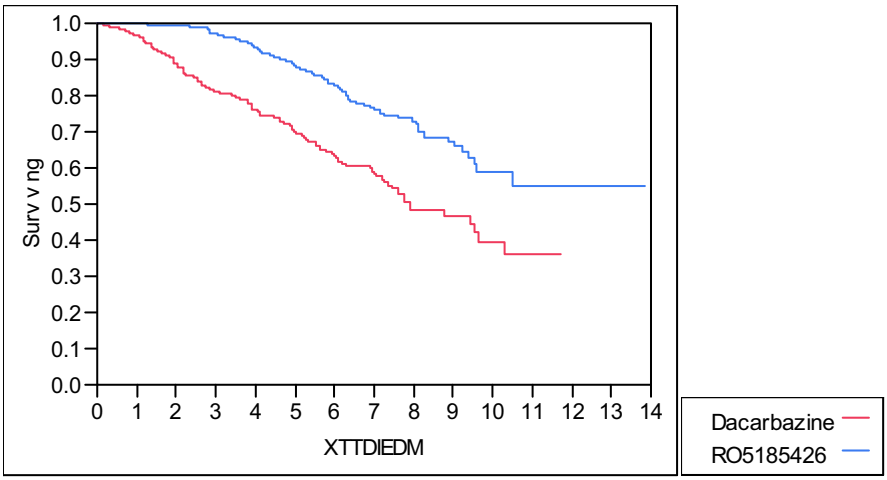


Figure 4: Kaplan Meier OS Estimates: Data Cutoff 3/31/11



Progression Free Survival

The primary analysis of progression free survival in the intent-to-treat population is shown in table 11 and the Kaplan Meier estimates are depicted in figure 5. PFS was derived by investigators assessment. A clear separation of the curves occurs early and is maintained signifying that the treatment effect of vemurafenib is statistically robust and will be maintained over time. In the analysis of PFS conducted by the sponsor, an enrolled cutoff of 10/27/10 was used to perform the analysis. As depicted in table 12, the hazard ratio and the p-value using this enrollment cutoff date did not change significantly.

Reviewer's Comments:
These PFS results are supportive of the OS benefit seen with vemurafenib therapy. This was an open-label trial and did not use an independent radiological committee to assess PFS. There was also some evidence of bias in the form of the 37 patients who refused treatment with dacarbazine suggesting that many patients believed vemurafenib therapy was superior to dacarbazine before the trial was conducted. Whether this bias carried over to the investigators is unknown, but the sensitivity analyses conducted and the lack of missing data (see below) give evidence that data integrity remained intact and the median difference in PFS of 3.7 months is a reliable estimate of the treatment effect of vemurafenib. This magnitude of PFS effect is somewhat disappointing in light of the ~50% response rate seen with vemurafenib, and again underscores the need for further study on the mechanisms of primary and secondary resistance to this form of therapy. In addition, PFS has not been demonstrated as a reliable surrogate for clinical benefit in this disease setting as both clinical trials involving ipilimumab demonstrated an overall survival benefit in the absence of PFS benefit (Korn 2008, Hodi 2010, Robert 2011)

Table 12: Primary Analysis: PFS; Full ITT Population

Study NO25026-FDA (Data Cutoff 12-30-10)

Progression Free Survival	Vemurafenib N = 337	Dacarbazine N = 338
Number of Events	106 (31.5)	198 (58.6)
Censored	231 (68.5)	140 (41.4)
Median PFS	**5.3 months (4.8, 6.3)**	**1.6 Months (1.5, 1.7)**
Hazard Ratio[1] (95% CI)		**0.25 (0.20-0.32)**
p-value (logrank test)		**<0.0001**

[1]Cox proportional hazards model

Figure 5: Kaplan-Meier PFS Estimates – ITT Population

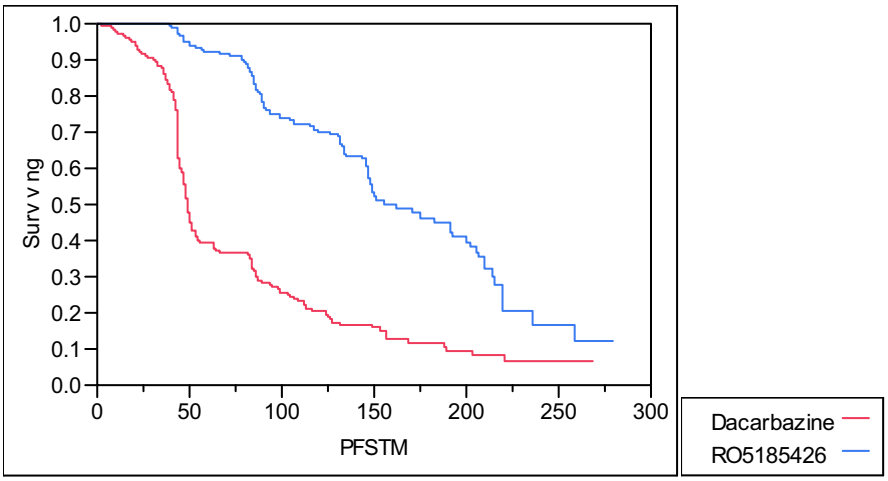


Table 13: Primary Analysis: PFS; Randomized before 10/27/10

Study NO25026-FDA (Data Cutoff 12-30-10)

Progression Free Survival	Vemurafenib N = 275	Dacarbazine N = 274
Number of Events	104 (37.8)	182 (66.4)
Censored	171 (62.2)	92 (33.6)
Median PFS	**5.3 months (4.8, 6.6)**	**1.6 Months (1.5, 1.7)**
Hazard Ratio[1] (95% CI)		**0.26 (0.20-0.33)**
p-value (logrank test)		**<0.0001**

Missing Data

The OS variable was derived from the Last Known Day Alive (LKDA) variable, which in turn was derived from study assessment dates or from survival status evaluations which are specified by the protocol to occur every 3 months. There were a total of 4 patients, who did not withdraw consent for the study and thus should have been followed every 3 months for survival, whose LKDA were outside the 3 month window from the date of the data cutoff (dacarbazine, n=3, vemurafenib, n=1). These patients were censored for OS at the date of the last contact and have no significant impact on the OS analysis.

The PFS variable is calculated by RECIST assessments which were specified by the protocol to occur every 2 cycles (6 weeks) for the first 2 cycles and every 8 weeks thereafter +/- 2 weeks. A total of 6 patients had tumor assessments outside the protocol specified window (dacarbazine n=2, vemurafenib n=4) and only one patient missed more than 2 consecutive scheduled visits (dacarbazine arm). These protocol deviations and missed visits did not affect the PFS analysis,

Reviewer's Comment:
The overall follow-up time for this trial was short as most of the patients enrolled within 6 months of the data cutoff, so one would expect that there should not be an excess of missing data. Regardless, the data surrounding the key efficacy variables was well organized and there were few missing data.

Sensitivity Analysis
A sensitivity analysis was performed in which the 48 patients who were randomized to receive dacarbazine but were not actually treated were censored for progression and death at the date of the data cutoff regardless of the patients known clinical outcome. The Kaplan-Meier estimates for overall survival is depicted in figure 6 and demonstrates an initial separation of the curves. The curves cross, but at the time points where the data is unreliable for K-M estimates due to the low number of patients found at these time points. Similarly, the sensitivity analysis for PFS demonstrates initial separation of the curves with the curves crossing at late time points.

Reviewers Comment:
These data demonstrate the robustness of the OS and PFS data in the setting of a "best case" scenario for those patients who were randomized but not treated with dacarbazine and give some measure of evidence that potential biases were minimized.

Figure 6: Overall Survival Sensitivity Analysis

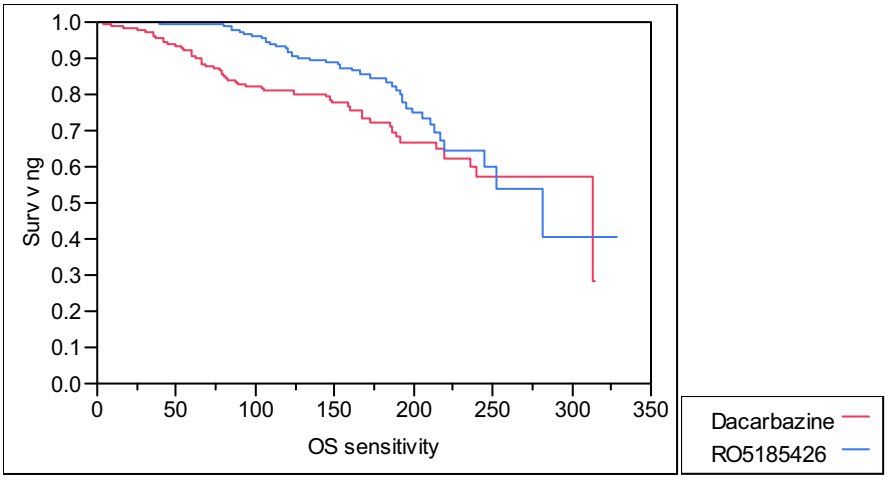
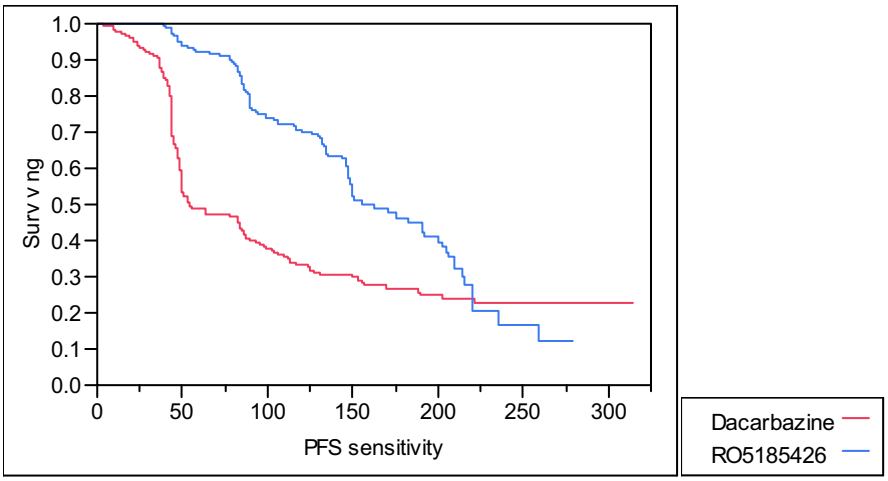


Figure 7: Progression Free Survival Sensitivity Analysis



In an additional sensitivity analysis using the data cutoff date of 3/31/2011, patients who were initially randomized to dacarbazine but crossed over to receive vemurafenib were not censored at the time of cross over. Only one patient who crossed over to receive vemurafenib was censored at the time of crossover and subsequently died. The hazard ratio obtained in this analysis was 0.47 (95% CI 0.35, 0.62) in favor of vemurafenib.

Reviewer's Comment:
Only 50 patients who were randomized to dacarbazine crossed over to receive vemurafenib even though over 200 patients were still alive. The provision for patients who have received subsequent therapy to cross over to vemurafenib was not made until February 16, 2011 and thus many patients may have opted to start other systemic therapies. Since only one patient who crossed over to receive vemurafenib subsequently died, it is not surprising to see that this sensitivity analysis yields similar OS results.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints for this study were best overall response (confirmed), duration of response and time to response. Best overall response (confirmed) was defined as a complete response (CR) or partial response (PR) that was confirmed per RECIST version 1.1. The best overall response of CR or PR was determined on the basis of confirmed response at the next tumor assessment. Evaluable patients who did not meet these criteria were considered non-responders; this included patients who never received study treatment and treated patients for whom a post-baseline tumor assessment was not performed.

The analysis population for BORR consisted of all ITT patients randomized by

September 22, 2010 (at least 14 weeks prior to the clinical cutoff date of December 30, 2010). The interval of 14 weeks was chosen because it was the minimum time needed to observe an overall response that could have been confirmed, according to the protocol-specified schedule for the first two tumor assessments (every 6 weeks, +/- 7 days).

Table 14: Response Rate Study NO25026 (Patients Randomized Prior to 9/22/10; Data Cutoff 12/30/10)

Response Rate (CR+PR)	Vemurafenib N = 219	Dacarbazine N = 220
Response Rate	**106 (48.4%)**	**12 (5.5)%**
CR	2 (0.9%)	0
PR	104 (47.4%)	12 (5.5%)
Median Duration of Response[1]	5.49 Months (4.0, 5.7)[2]	NR[3] (3.9, NR)
RR in treated patients	**106/217 (48.8%)**	**12/191 (6.3%)**
Time to Response[4]	**2.72 months (median)**	**1.45 months (median)**

[1] Kaplan-Meier Estimates
[2] 79 out of the 106 patients who responded to Vemurafenib have not progressed at the time of data cutoff.
[3] 10 out of 12 of the patients who responded to dacarbazine have not progressed at the time of data cutoff. NR = Not reached
[4] Of the patients who had a response (vemurafenib n = 106; DTIC n=12)

Reviewer's Comment: It is reasonable to use a cutoff date of 9/22/10 to assess response rates as the inclusion of patients enrolled past this date would lead to an inaccurate assessment of the true response rates. The investigator assessed response rate is consistent with the response rate determined by an independent radiological committee (IRC) in the Phase 2 study (see section 6.1.10.1 for details of the phase 2 study).

6.1.6 Other Endpoints

The sponsor has several exploratory endpoints associated with study NO25026. Due to the exploratory nature of the endpoints, the lack of data quality associated with these endpoints, the lack of labeling claims associated with these endpoints, and the lack of statistical power to support the findings from these endpoints, a thorough review was not performed.

6.1.7 Subpopulations

The treatment effect of RO5185426 across subgroups was examined using estimates of the hazard ratio for death and by display of Kaplan-Meier curves by treatment group within each subgroup. The subgroups were pre-specified in the SAP. An additional post-

hoc subgroup analysis was performed based on the time between diagnosis of metastatic disease and enrollment on trial and baseline sums of the longest diameters of target lesions.

Reviewer's Comment:
A treatment effect in favor of RO5185426 treatment was observed across subgroups: in all cases, the 95% CI of the HR estimate in the subgroup included the HR estimate for the overall population (HR = 0.37).

Figure 8: Forest Plot OS Hazard Ratios in Pre-Specified Subgroups (from applicant's CSR)

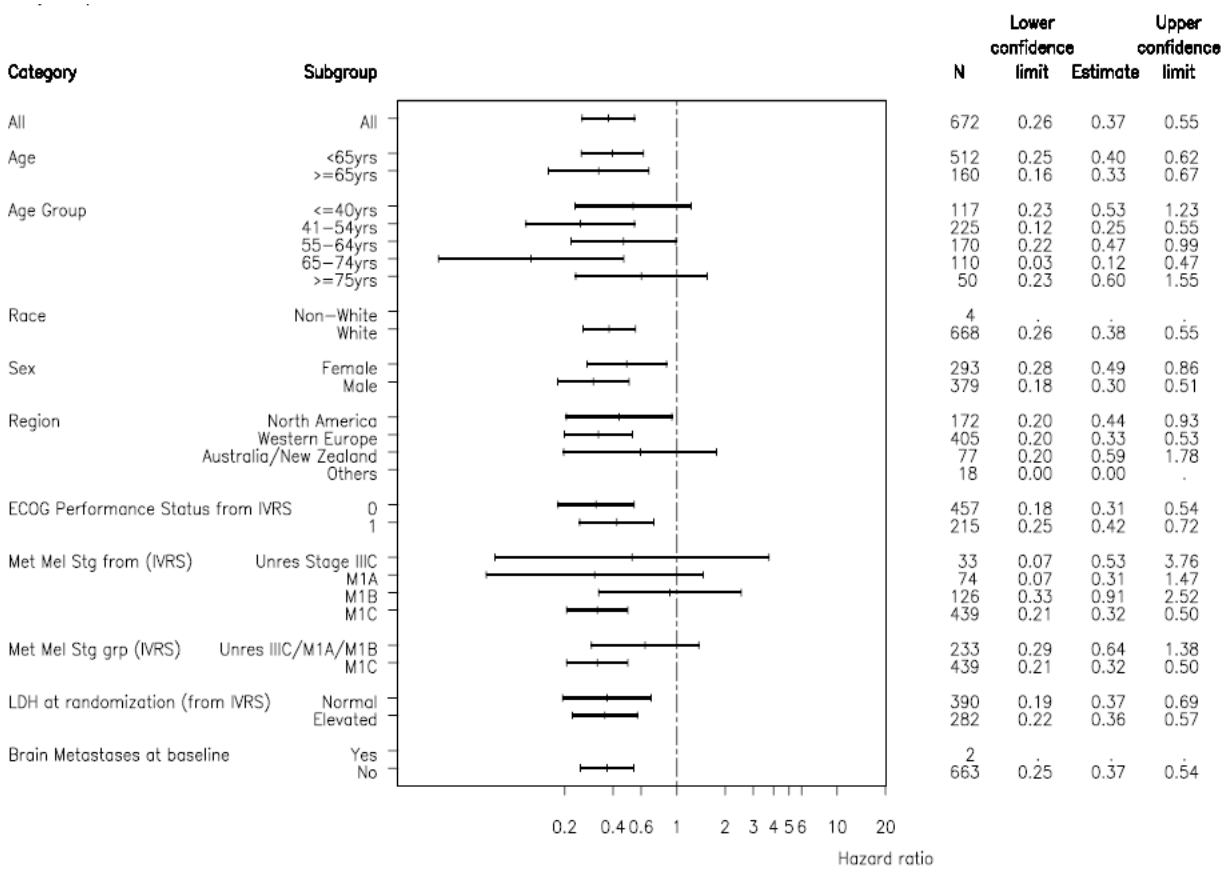
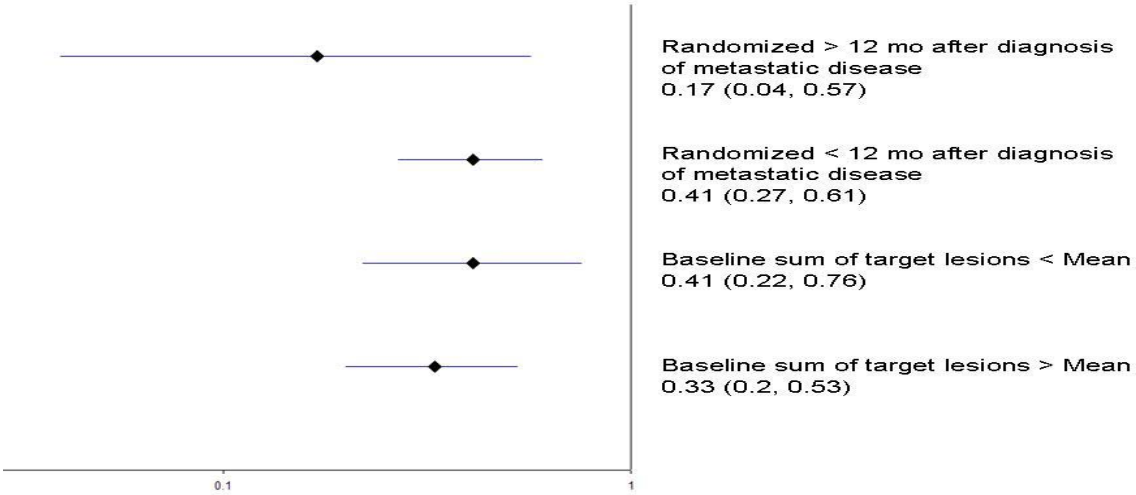


Figure 9: Post-Hoc Subgroup Analysis



Non-V600E Mutations

Pre-clinical studies indicated that the cobas test also detects a proportion of *BRAFV600E2, BRAF*V600K and *BRAF*V600D mutations. Therefore, it was anticipated that some cases (approximately 10%) identified by the cobas test as being mutation-positive would in fact harbor *BRAFV600E2*, *BRAF*V600D or *BRAF*V600K mutations. Since a small number of such cases were likely to be enrolled based on a positive cobas test result, an exploratory objective of this study was to assess the responsiveness of these tumors to vemurafenib. It was also anticipated that a small percentage of cases identified by the cobas test as being mutation-negative would harbor *BRAF*V600K, or *BRAF*V600R, or perhaps rarer variant mutations in adjacent codons. In their initial submission package, sequencing data on 542 patients were submitted, consisting of 328 screened patients from the phase 2 trial and 214 patients from the phase 3 trial. Of these screened patients 132 out of the 328 screened patients were enrolled onto the phase 2 trial and 85 out of 214 screened patients were enrolled onto the phase 3 trial. Based on the reference standard Sanger sequencing results the following table was generated to demonstrate the analytical sensitivity and specificity of the test.

Table 15: Analytical Sensitivity and Specificity of the V600 Mutation Test

Sensitivity TP/(TP + FN)		95.80%
Specificity TN/(TN+FP)		82.43%
False positive rate = FP / (FP + TN)		17.57%
False negative rate = FN / (TP + FN)		4.20%
Positive predictive value	TP/(TP+FP)	84.44%
Negative predicitive value	TN/(TN+FN)	95.17%

Of the 542 patients that were screened and had sequencing data submitted for review, there were 26 patients who were identified as having a positive cobas test and V600K by Sanger sequencing, while 14 patients had a negative cobas test and V600K mutation by Sanger sequencing. It is important to note that the sponsor of the premarketing authorization application for the companion diagnostic is not seeking a claim for the detection of V600K mutation.

Of the patients in the phase 3 trial whose sequencing information was submitted in the initial submission package, a total of 19 patients were determined to have a V600K mutation by Sanger sequencing (DTIC = 9; Vem = 10) and 9 patients were identified as having a V600K mutation in the phase 2 trial. Seven out of 16 (43.8%) patients identified as having a V600k mutation who were treated with vemurafenib had a confirmed response which is similar to the response rate seen in the V600E population. Non-clinical data indicates that similar IC50 concentrations are seen in all V600 mutations.

For the premarketing authorization approval of the cobas® 4800 BRAF V600 Mutation test, test accuracy was evaluated using 449 evaluable specimens from 596 consecutive specimens from Phase III trial for which clinical, demographic, and Sanger sequencing data were collected.
The following is excerpted from CDRH's review:
The agreement analysis between the cobas test results and 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%. There were a total of 35 mutation detected by cobas which were not identified as V600E mutations by Sanger. Eight (8) of these were wild type, 25 were V600K and 2 were V600-other. Additionally, 6 specimens were identified as mutation not detected by cobas but were identified as V600E by Sanger. The cross-reactivity of the cobas® 4800 BRAF V600 Mutation test for V600K was 65.8% (25 of 38 samples). The distribution of discrepant results within the evaluable sample population is comparable to that observed with the evaluable phase II samples.

Reviewer's Comment:
The cobas test is able to detect V600E mutations with a higher sensitivity than the reference method of Sanger sequencing, but it is not as specific. The test cross reacts with other V600 mutations and does not appear to cross react with wild-type BRAF V600. Patients who have a V600K mutation that are detected by the cobas test appear to have similar response rates to the other patients that test positive, but there are no safety or efficacy data available for those who have a non-V600E BRAF mutation that do not test positive by the cobas test, and thus it would be inappropriate to make the indication for vemurafenib to the V600 (unspecified) population. Since the V600K population represents ~10% of the melanoma population and since pre-clinical evidence suggests that vemurafenib should be active in the V600K population, we have asked the applicant to develop a test for the V600K mutation and to conduct a trial in this population (see post marketing commitments).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Of the 336 patients in the vemurafenib group, 159 (47%) had a dose modification for any reason. Of these 159 patients, 112 had at least one dose reduction, with the mean number of dose reductions per patient of 1. Below, a table depicting the response rates in the patients who were treated with vemurafenib that had a dose reduction compared to those that did not require a dose reduction.

Reviewer's Comment:
Reasons for dose reductions will be discussed in the safety section of this review. Although the response rates were similar, there was an exposure-response relationship for progression free survival but not for overall survival as discussed below. Even with dose reductions and lower steady state concentrations, treatment with vemurafenib is superior to dacarbazine in terms of OS, PFS, and BORR.

Table 16: Response Rates of Patients Randomized to Vemurafenib Who Required Dose Reduction

Response Rate (CR+PR)	Dose Reduction N = 159	No Dose Reduction N = 176
Response Rate	**60 (37.7%)**	**53 (30.1)%**
CR	2 (0.9%)	0
PR	58 (36.5%)	53 (30.1%)
Median Duration of Response	5.49 Months (3.8, 5.7)	5.32 (3.8, NR)

Exposure-Response for Effectiveness (Excerpted from the Clinical Pharmacology Review)

Exposure Metric: Time-Normalized Cmin

Time-normalized C_{min} ($C_{min,tn}$) was determined by the observed AUC normalized by the duration of treatment. Only pre-dose concentrations were used. The concentration from the last sample until the patient's last dose date was assumed to remain constant (LOCF).

Overall Survival

Overall survival (OS) data from trial 25026 were reviewed to determine if there was a significant exposure-response relationship. Kaplan-Meier curves were plotted by low and high exposure as an initial examination of the relationship between $C_{min,tn}$ and OS. Figure 10 shows the Kaplan-Meier plots for the low and high exposure groups.
A Cox-proportional hazards analysis was conducted to determine the effect of risk factors on the probability for OS. A multivariate analysis was conducted with forward inclusion (p=0.1) and backward elimination (p=0.05) for the selection of model covariates. Covariates tested included $C_{min,tn}$, $\ln(C_{min,tn})$, baseline melanoma classification, baseline ECOG score, and baseline LDH status. Table 17 shows the results of the proportional hazards analysis. No significant exposure-response relationship was identified for overall survival. The p-value for $\ln(C_{min,tn})$ was 0.39. Elevated LDH and ECOG score were significant factors in the multivariate analysis that decreased the probability for survival.

Figure 10: Kaplan-Meier plots of overall survival data from trial 25026. Low and high vemurafenib exposure were defined by patients with $C_{min,tn}$ values < or = 39.0 ng/mL.

Proportion for Survival

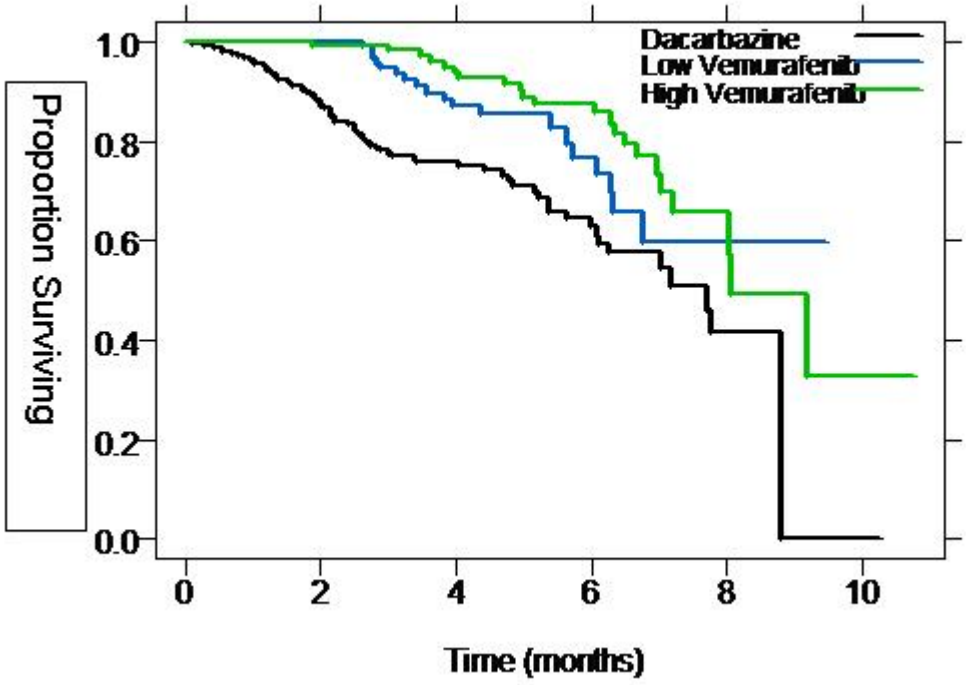


Table 17: Results of proportional hazards analysis indicate no significant exposure-response relationship for overall survival.

Parameter	Hazard Ratio	95% CI	p-value	Included in Final Model?
ln(Cmin,tn)	0.821	(0.525 - 1.29)	0.39	No
LDH Elevated	3.11	(1.54 - 6.28)	0.0015	Yes
ECOG Score (0)	0.411	(0.212 - 0.798)	0.0086	Yes

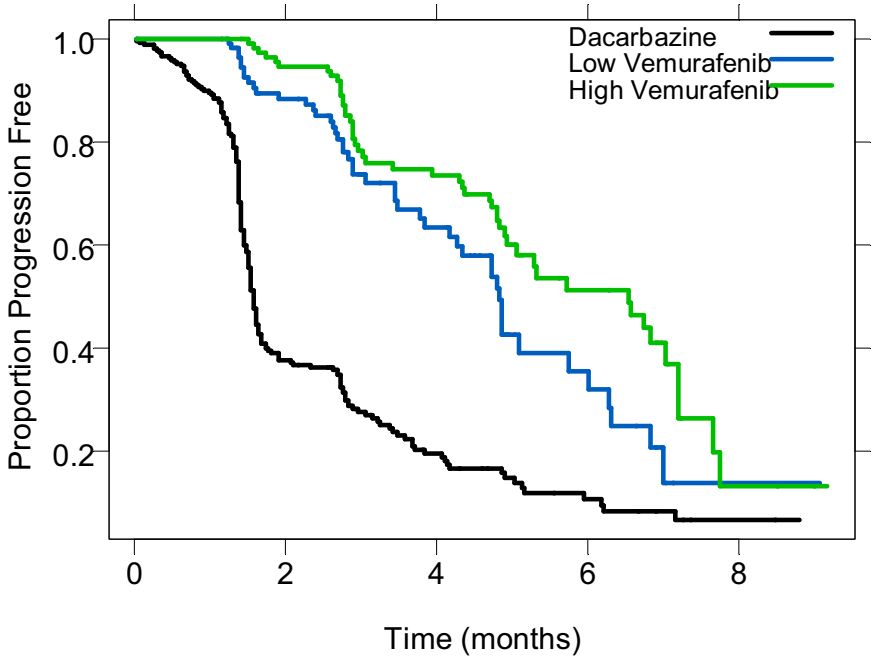
Regardless of the lack of exposure-response for OS there is a clear survival benefit for the vemurafenib treatment group. It remains a possibility that a maximal effect was reached at the studied doses and that exposure-response could be observed for overall survival across a broader range of vemurafenib exposures.

Progression-Free Survival

Progression-free survival data from trial 25026 were reviewed to determine if there was a significant exposure-response relationship. Both disease progression and deaths were considered events. Kaplan-Meier curves were plotted by low or high exposure as

an initial examination of the relationship between $C_{min,tn}$ and PFS. Figure 11 shows that a trend for exposure-response for PFS may exist.

Figure 11: Kaplan-Meier plots of PFS data from trial 25026 are suggestive of a trend for exposure-response. Low and high vemurafenib exposure were defined by patients with $C_{min,tn}$ values < or = 39.0 ng/mL.



6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Vemurafenib has demonstrated significant antitumor effect in the setting of test positive metastatic melanoma; however, the effects do not last and ultimately, the disease develops resistance to the drug. Vemurafenib has not been studied in the setting of cobas test negative BRAF V600E except for 5 patients in the dose escalation portion of the phase 1 trial. Non-clinical data suggest that the drug is less effective in terms of inhibition of cell line proliferation, inhibition of ERK phosphorylation and inhibition of tumor growth in xenograft models in the wtBRAF setting (figure12, table 17:From Applicant's Submitted Nonclinical Studies).

Figure 12: Non-clinical Effects of Vemurafenib on wt-BRAF Cell Lines

Figure 1.

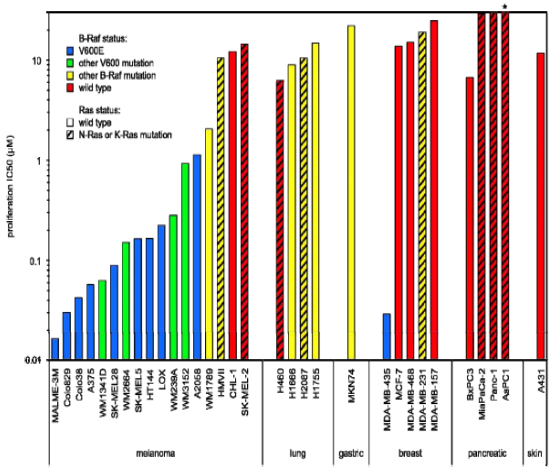


Figure 8 RO5185426 Exhibited No Anti-tumor Activity in the HCT116 Xenograft Model Expressing Only Wild-type BRAF.

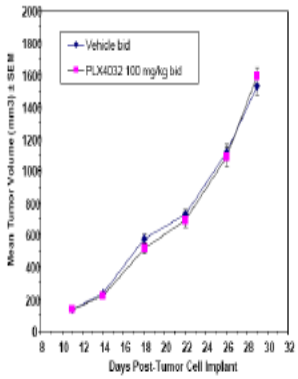


Table 18: Inhibition of ERK Phosphorylation in Cell Lines

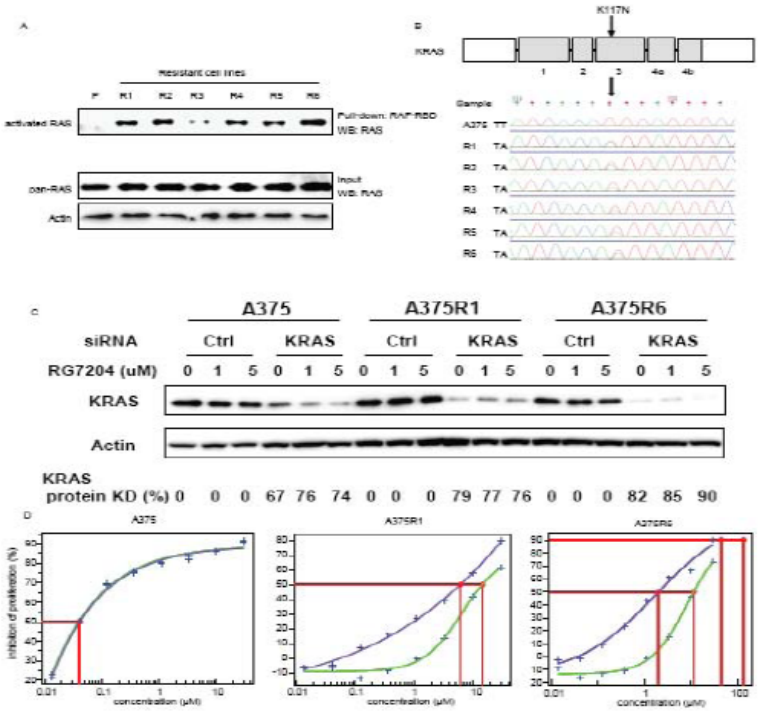
Table 2 Inhibition of ERK Phosphorylation: IC_{50} of RO5185426 in Several Representative Cancer Cell Lines

Tumor	Melanoma			Colorectal	
Oncogene	$BRAF^{V600E}$		$NRAS^{Q61R}$	$BRAF^{V600E}$	$KRAS^{G12V}$
Cell line	A375	COLO829	SK-MEL2	COLO205	SW620
IC_{50} (nM)	11	16	>40,000	32	>40,000

The mechanism of resistance has been discussed in the scientific literature, and to date there are no reports of the development of secondary mutations of B-RAF that mediate drug resistance such that occur in the epidermal growth factor receptor (EGFR) in the setting of anti-EGFR tyrosine kinase therapy in lung cancer and the bcr-abl fusion protein in the setting of imatinib therapy in chronic myelogenous leukemia. There are data that suggest that resistance is mediated by acquired mutation of RAS, upregulation of other receptor tyrosine kinases or growth factors, or by a mechanism that has yet to be determined (figure 13, From Applicant's Submitted Nonclinical Studies).

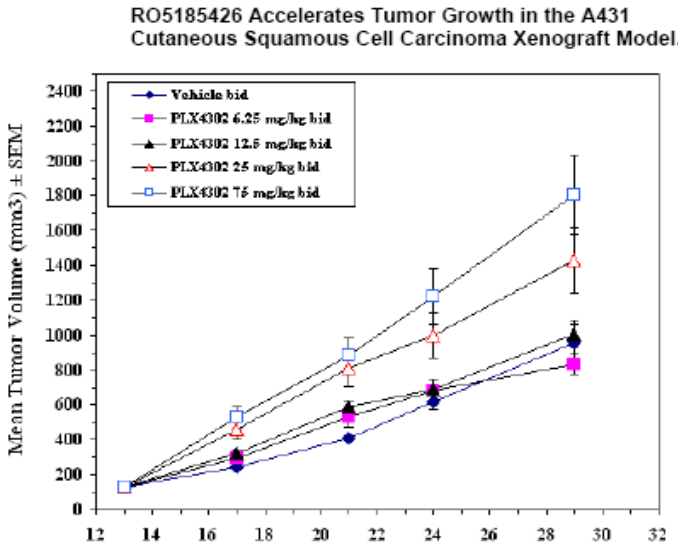
Figure 13: Acquired Activating KRAS Mutation in Vemurafenib Resistant Cell Lines

Figure 3. RO5185426-resistant cell lines display elevated RAS–GTP levels and harbor an acquired activating KRAS mutation. (*A*) Whole cell lysates of the parental sensitive and the six RO5185426-acquired resistant cell lines were subjected to RAS–GTP analysis. RAS–GTP complex was revealed by immunoblotting with RAS antibody. (*B*) Whole exome sequencing identified a single nucleotide mutation (T->A) resulting in K117N substitution within exon 3 of KRAS in all six resistant cell lines but not in the parental line, and this was confirmed by Sanger sequencing. (*C–D*) Sensitive (A375) or resistant (A375R1 and A375R6) cells were transfected with scrambled (Ctrl) or KRAS siRNA. Western blot analysis was performed with whole cell lysates collected 72 hours post-transfection. Transfectants were treated with various concentrations of RO5185426 for 4 days, and cell viability was measured to plot growth curves.



Most concerning is the non-clinical data suggesting that treatment with vemurafenib and other B-Raf inhibitors in the setting of a RAS mutation is pro-proliferative (Figures 14, From Applicant's Submitted Nonclinical Studies; Hatzivassiliou 2010).

Figure 14: Pro-proliferative Effects of Vemurafenib and Other BRAF Inhibitors in Non-Clinical Models



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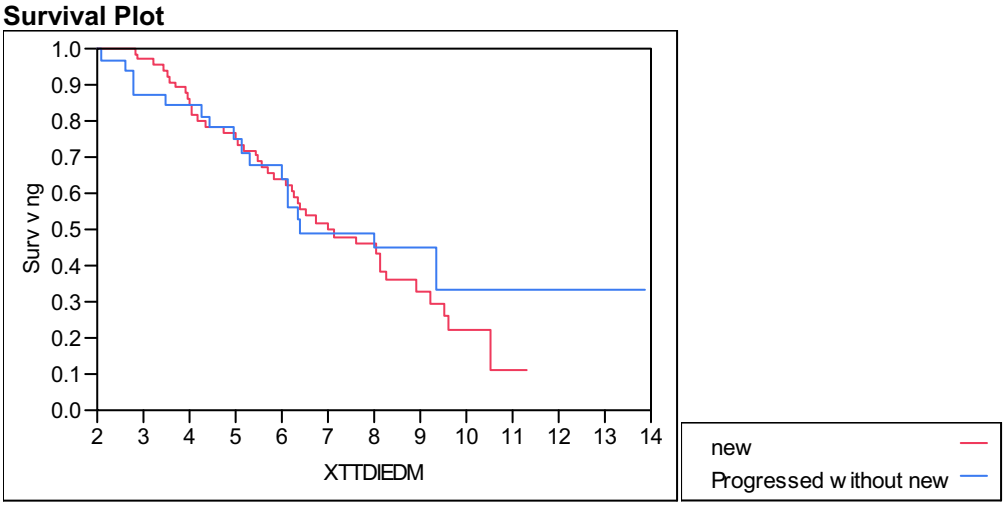
A post-hoc exploratory analysis was conducted in which patients who had a reduction in target lesion size but had a progressive event with a new lesion were identified and overall survival was compared to those patients who had progressive disease with no

evidence of tumor response. Conceivably, the tumors of those patients who developed new lesions in the setting of their target lesions decreasing in size developed an acquired resistance to therapy while the tumors of those patients who did not have a response had a primary resistance to therapy. It is interesting to see that there is no difference in survival for the two groups, suggesting that the patients who had an initial response in their target lesions did not have a survival benefit compared to the patients who were primarily resistant to the tumor (figure 15).

Figure 15: Kaplan-Meier OS Estimates: Patients with Responses but New Lesions vs. Patients with No Tumor Response



Reviewer's Comment:
This analysis is severely limited, but may raise the question of whether there are other factors, such as baseline RAS mutations, that can predict either primary or secondary resistance to therapy. The applicant has collected biopsy samples at baseline and at progression of patients who were treated with vemurafenib. We have asked the applicant for a post marketing commitment to analyze these samples for RAS mutations in order to elucidate mechanisms of primary and secondary resistance.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Supportive Studies

Study NO22657 administered 960 mg of vemurafenib twice daily to 132 patients with previously treated BRAF mutation-positive, metastatic melanoma in a single-arm, multi-center, phase 2 study. The baseline disease characteristics of the patients enrolled onto this study was similar to that of study NO25026, except that 51% of the patients had 1 prior therapy regimen and the remaining 49% had 2 or more prior regimens. The majority of patients were male (61%) and Caucasian (99%). The primary endpoint of

this study was best overall response rate (BORR) as determined by an Independent Radiologic Committee (IRC). The median time to response was 1.4 months with 75% of responses occurring by month 1.6 of treatment. Updated response rate and duration of response data based on a data cutoff of January 31, 2011 is shown in Table 18

Table 19: Phase II: Study NO22657

Response Rate (CR+PR)[1]	Vemurafenib 960 mg BID N = 132
Response Rate	**69 (52.2%)**
CR	3 (2.3%)
PR	66 (50.0%)
Median Duration of Response	6.5 Months (5.6, NR)
Updated Results[2]	
Response Rate	**70 (53%)**
CR	7 (5%)
PR	63 (48%)
Median Duration of Response	6.7 months (5.6, 9.8)

[1] data cutoff September 27, 2010
[2] data cutoff January 31, 2011

Study PLX06-02 was a phase 1 dose escalation study with an expansion cohort of 32 patients with BRAF V600E mutation-positive melanoma who were treated at the dose of 960 mg BID. The confirmed response rate (CR+PR) was similar to that seen in the phase 2 and phase 3 studies.

Table 20: Phase I Extension Cohort: Study PLX06-02

Response Rate (CR+PR)	Vemurafenib 960 mg BID N = 32
Response Rate	**18 (56.2%)**
CR	3 (16.7%)
PR	15 (46.9%)
Median Duration of Response	7.6 Months

Reviewer's Comment:
The IRC confirmed BORR seen in the phase 2 trial was similar to that seen in the phase 3 pivotal trial as is the duration of response. It is unclear and probably unlikely that durable complete responses, as is seen with IL-2 therapy will be seen with single agent treatment. Combination strategies are underway in an attempt to improve both response rate and response duration.

Data integrity:

There were a total of 37 protocol violations that were considered major. A total of 23 (6.8%) patients randomized to the dacarbazine arm and 13 (4.2%) randomized to the vemurafenib arm had a major protocol violation. The majority (23, 62%) of major protocol deviations were receiving non-protocol anti-cancer therapy without documented disease progression. The sponsor has also provided a listing of protocol deviations provided by the CRO which is consistent with the reported protocol violations.

Table 21: Protocol Violations:

	Vemurafenib (n=337)	Dacarbazine (n=338)	Total (n=675)
Major Violations	14 (4.2)	23 (6.8)	37 (5.5)
Cobas Test Negative	1 (0.3)	1 (0.3)	2 (0.3)
Prior Anti-cancer Therapy	3 (0.3)	1 (0.9)	4 (0.6)
No Measurable Disease	5 (1.5)	5 (1.5)	10 (1.5)
Received incorrect study drug	0 (0)	1 (0.3)	1 (0.1)
Anti-cancer therapy without Progression	7 (2.1)	16 (4.7)	23 (3.4)

The CRO has reported the identification of additional protocol violations concerning a number of sites using RECIST v1.0 criteria instead of the protocol specified RECIST v1.1 criteria. According to RECIST v1.1, the short axis of lymph nodes should be measured, recorded, and used in the summation of the target lesions which differs from RECIST v1.0 which uses the long axis of lymph nodes for summation. The CRO surveyed the 104 sites participating and found that 5 sites were using RECIST v1.0 criteria (3 sites did not respond to the survey). Reassessment of scans at 3 of these 5 sites did not significantly change response rates or eligibility (one patient had an upgrade from stable disease to partial response)

Reviewer's Comment:
Overall, it is believed that these protocol violations should not impact the overall integrity of site-generated data as related to primary safety and efficacy analyses. See also section 3.2: Compliance of Good Clinical Practice.

APPEARS THIS WAY ON ORIGINAL.

7 Review of Safety

Safety Summary

7.1 Methods

The Phase 3 trial NO252026 included safety assessments at baseline, on day 1 ± four days of every 21-day cycle, and at the end of treatment (within 28 days of last dose). Serious adverse events that had not recovered completely by the end of treatment were to be followed until resolution.

At baseline, safety assessments included medical, oncologic, and surgical history, vital signs, physical exam, laboratories (hematology, chemistries, liver function), assessment of ECOG PS, ECG, and dermatology evaluation. Safety assessments performed at the start of each cycle were the same as at baseline, except ECGs were required prior to every other cycle and dermatology evaluation occurred at cycle 2 and every four cycles thereafter. Post-treatment follow-up was to occur every 3 months and included dermatology evaluation.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The three trials for which the applicant submitted safety data are summarized in Table 22. These three trials (PLX06-02, NP22657 and NO25026) were included in the integrated summary of safety (ISS), while data from NO25026 also were presented separately.

Table 22: 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**
ISS Melanoma					**500**

The ISS included a total of 500 patients treated with vemurafenib. Among these 500 patients, all received the same dose and schedule as used in the Phase 3 trial NO25026.

Reviewer's Comment:
The majority of patients with melanoma who received vemurafenib on the 960 mg twice daily dosing schedule were treated on the Phase 3 trial NO20506. For this reason, the safety analyses, other than those provided in section 7.1.3 below, will focus primarily on data from this trial.

7.1.2 Categorization of Adverse Events

MedDRA terminology (version 13.1) was used to characterize all adverse events in the Phase 3 trial NO25026. Adverse event grading was done according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event data from three trials were included in the integrated safety database (see Section 7.1.1, Table 22 above). The rates of the most common (>15% of patients) treatment-emergent adverse events in vemurafenib-treated patients on NO25026 were compared to event rates in the entire ISS database. This analysis is presented in the table below.

Table 23: Incidence of Most Common Treatment-Emergent Adverse Events (>15%) in the ISS Database

	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)

The above information was verified using the ISS AE (NP22657 PL00602 NO25026 AE for SCS) and AEEXT (AE Analysis) datasets.

The incidences of the most common treatment-emergent adverse events occurring in vemurafenib-treated patients in the Phase 3 trial were similar to the incidences in the integrated safety database.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to vemurafenib and comparator therapy in the phase 3 trial NO25026 is summarized in Table 24 below.

Table 24: Exposure

	Vemurafenib N = 336	Dacarbazine N = 293
Number of Months on treatment Median	4.2	0.8
Total Cumulative Dose Median	211.2 g	2000 mg/m^2
Dose Per day (Vemurafenib) or Cycle (Dacarbazine) Median	Planned: 1920 mg 1804 mg	Planned: 1000 mg/m^2 1000 mg/m^2
Relative Dose Intensity (%) Median	94	95.7

The above information was verified using the MEDTEXT (Trial Medications Analysis) dataset.

Vemurafenib arm patients had a longer duration of treatment than did comparator arm patients. The relative dose intensity was close to 100% on both arms.

At the time of the cut-off for the three-month safety update (approximately one-and-a-half months earlier than the final overall survival analysis reported above), there were 37 patients who had crossed over from dacarbazine treatment to vemurafenib treatment after the interim overall survival analysis. For these 37 patients, the median relative dose intensity for vemurafenib is similar (100%), while the median number of months on treatment and total cumulative dose is smaller (0.7 months and 36.5 g), as would be expected.

Dose modifications, interruptions, and reductions are summarized in the table below.

Table 25: Dose Modifications

	Vemurafenib N = 336	Dacarbazine N = 289
Any Modification	159 (47.3%)	44 (15.2%)
Reduction	112 (33.3%)	44 (15.2%)
Number of dose reductions		
1	81	34
2	29	8
3	0	0
4	1	2
5	1	0
Interruption	147 (43.8%)	5 (1.7%)

The above information was verified using the MEDTEXT (Trial Medications Analysis) dataset.

Three times as many patients on the vemurafenib arm required a dose modification. One hundred twelve (33.3%) vemurafenib-treated patients and 44 (15.2%) dacarbazine-treated patients underwent dose reduction. The majority of patients who required an initial dose reduction on both arms did not require further dose reduction.

Adverse events leading to dose modification in ≥3 patients on either arm are summarized in Table 26 below. In addition, discontinuations due to adverse events occurred in 5.7% of vemurafenib arm patients and 4.3% of dacarbazine arm patients (see section 7.3.3, Table 33).

Table 26: 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)

[1]Includes hyperbilirubinemia.
[2]Includes neutrophil count decreased.
The above information was verified using the AEEXT (AE Analysis) dataset.

Dermatologic adverse events and increased liver enzymes accounted for the majority of dose modifications on the vemurafenib arm, while dacarbazine patients more often had dose modifications for bone marrow suppression adverse events such as neutropenia and thrombocytopenia. Rash, both generalized and maculopapular, increased GGT, increased blood alkaline phosphatase, vomiting, increased AST, increased blood bilirubin, pruritus, SCC of the skin, uveitis, upper abdominal pain, asthenia, increased blood creatinine, decreased appetite, hyperkeratosis and photosensitivity reaction each accounted for dose modification in at least 3 patients on the vemurafenib arm but none on the comparator arm.

7.2.2 Explorations for Dose Response

There is evidence of an exposure-response relationship for cuSCCs. See Section 7.5.1 of this review and the Clinical Pharmacology Review.

7.2.3 Special Animal and/or In Vitro Testing

See the summary of the pharmacology/toxicology review in section 4.3.

7.2.4 Routine Clinical Testing

See sections 7.4.2-7.4.4.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of the clinical pharmacology review in section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This NME is the first in the class of BRAF inhibitors for which an NDA has been submitted.

7.3 Major Safety Results

7.3.1 Deaths

More total deaths occurred on the comparator dacarbazine arm than in the vemurafenib arm, and approximately 1% of deaths on both arms were associated with treatment-emergent adverse events. Deaths that occurred within 30 days of the start of treatment include nine deaths in the dacarbazine group and none in the vemurafenib group. Deaths within 28 days of last drug dose were 8.3% on the vemurafenib arm and 5.9% on the dacarbazine arm. All deaths occurring in the safety population are included in the table below.

Table 27: All Safety Population Deaths on NO20506

	Vemurafenib N = 336	Dacarbazine N = 293
Total Deaths	63 (18.8%)	99 (33.8%)
TEAE[1]	4 (1.2%)	3 (1%)
Progression	53 (15.8%)	94 (32.1%)
Other[2]	6 (1.8%)	2 (<1%)
Unknown	3	0
Other Events	3	2
Deaths within 28 Days of Last Dose	28 (8.3%)	17 (5.9%)
TEAEs[1]	3 (<1%)	2 (<1%)
Progression	23 (5.6%)	14 (5%)
Other[2]	2 (<1%)	1 (<1%)
Unknown	1	0
Other Events	1	1
Deaths within 60 Days of Last Dose	29 (8.6%)	39 (13.8%)
TEAEs[1]	3 (<1%)	1 (<1%)
Progression	24 (7.1%)	37 (13.1%)
Other[2]	2 (<1%)	1 (<1%)
Unknown	1	0
Other Events	1	1

[1] Includes 201249/7901 on the vemurafenib arm, coded as other cause of death (cardiopulmonary failure), but with adverse event-related death.
[2] Excludes 201249/7901 on the vemurafenib arm, coded as other cause of death (cardiopulmonary failure), but with adverse event-related death.
The above information was verified using the DIEDEXT (Extension Died) dataset.

Four vemurafenib-treated patients experienced a grade 5 TEAE other than disease progression within 28 days of the last dose of study drug. Details for these four patients are provided in the table below.

Table 28: All Grade 5 Treatment-Emergent Adverse Events Excluding Disease Progression and Occurring Within 28 Days of Last Dose on the Vemurafenib Arm

Patient ID	Grade 5 AE Preferred Term	Last Dose (Day)	Onset AE (Day)	Death (Day)	Days from Last Dose to Death	Cycle #
200991/2404	Cerebrovascular Accident	211	215	215	4	10
201217/4203	Pneumonia	187	187	190	3	9
201249/7901	Cardiopulmonary Failure	92	92	92	0	5
201055/7505	Aortic Aneurysm Rupture	43	63	63	20	3

None of these deaths were considered related to study drug. Patient 200991/2404 was a 69 year-old female with a history of hypertension who underwent wide excision of residual disease and was hospitalized post-operatively when she suffered a cerebrovascular accident. Patient 201217/4203 was a 57 year-old female with a history of underlying chronic obstructive pulmonary disease and asthma on prophylactic Augmentin and steroids who died of pneumonia. Patient 201249/7901 was a 76 year-old female with a history of pericardial effusion and hypertension who had been hospitalized for several weeks prior to her death with deteriorating clinical condition and ECOG status declining from 0 to 3. Patient 201055/7505 was a 48 year-old male with a history of thoracic aortic aneurysm who temporarily discontinued vemurafenib for elevated GGT and ALT on C3D1; the patient suffered a ruptured aortic aneurysm leading to death.

Reviewer's Comment:
This reviewer agrees with the applicant's assessment that none of these deaths were related to study drug. They all were more likely related to underlying medical conditions and interventions and possibly to disease progression in the case of Patient 201249/7901.

Two dacarbazine-treated patients experienced Grade 5 TEAEs other than disease progression within 28 days of the last dose of study drug. Details for these patients are provided in the table below.

Table 29: All Grade 5 Treatment-Emergent Adverse Events Excluding Disease Progression and Occurring Within 28 Days of Last Dose on the Dacarbazine Arm

Patient ID	Grade 5 AE Preferred Term	Last Dose (Day)	Onset AE (Day)	Death (Day)	Days from Last Dose to Death	Cycle #
201190/6201	Leukopenia Neutropenia Thrombocytopenia Shock	1	6 8 15 17	17	16	1
203183/2251	Cardiac Arrest	104	119	119	15	5

Patient 201190/6201 was a 35 year-old female who developed pancytopenia after her first dose of dacarbazine. She was initially admitted to the hospital for intravenous antibiotics but discharged to home. She died at home two days after discharge secondary to shock. Patient 203183/2251 was a 55 year-old male who had no significant past cardiac medical history who died of a cardiac arrest.

Deaths not attributed to disease progression or a TEAE are summarized in the table below.

Table 30: Deaths not Attributed to Disease Progression or TEAE

Patient ID	Treatment arm	Cause of Death	Last Dose (Day)	Death (Day)	Days from Last Dose to Death
201055/7503	Vemurafenib	Unknown	82	86	4
201156/1602	Vemurafenib	Unknown	125	252	127
201156/1605	Vemurafenib	Pleural Effusion	84	193	109
201244/1205	Vemurafenib	Peritonitis	160	208	48
201191/1808	Dacarbazine	General Physical Health Deterioration	1	39	38
201198/3706	Dacarbazine	Cerebrovascular Accident	1	74	73

Patient 201055/7503, a 52 year-old female, was admitted to the hospital for pain ten days prior to death and developed symptoms consistent with brain metastases or intracranial hemorrhage. Computed tomography could not be achieved due to the patient's clinical condition, thus cause of death is unknown.

There have been no deaths among the patients who crossed over from dacarbazine treatment to vemurafenib treatment.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events occurred in 42.9% of patients on the vemurafenib arm and 17.8% on the dacarbazine arm. SAEs that occurred in ≥1% of patient on either arm are summarized in the table below.

Table 31: Nonfatal Serious Adverse Events (≥1% on Either Arm)

	Vemurafenib N = 336		Dacarbazine N = 287	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Any SAE	144 (42.9)	124 (36.9)	51 (17.8)	33 (11.5)
SCC of Skin	58 (17.3)	55 (16.4)	1 (<1)	1 (<1)
Keratoacanthoma	29 (8.6)	29 (8.6)	0	0
Malignant Melanoma	7 (2.1)	6 (1.8)	0	0
Pyrexia	4 (1.2)	2 (<1)	4 (1.4)	3 (1)
Thrombosis	0	0	3 (1)	2 (<1)

The above information was verified using the AEEXT (AE Analysis) dataset.

Squamous cell carcinomas (SCC) of the skin and keratoacanthomas were the most common serious adverse events on the vemurafenib arm. SCC of the skin occurred in one patient on the dacarbazine arm, and keratoacanthoma was not observed on the dacarbazine arm.

7.3.3 Dropouts and/or Discontinuations

Reasons for treatment discontinuation are summarized in the table below. Disease progression was the most common reason for treatment discontinuation on both arms. More patients discontinued treatment due to adverse events on the vemurafenib arm than on the comparator arm (7.1% vs. 4.2%, respectively).

Table 32: Reasons for Treatment Discontinuation

	Vemurafenib N = 336	Dacarbazine N = 293
Disease Progression	119 (35.4%)	191 (65.1%)
Adverse Event	24 (7.1%)	9 (4.2%)
Other Reason[1]	4 (1.2%)	29 (9.9%)
Withdrawal of Consent	3 (<1%)	5 (1.7%)
Refuse Treatment	4 (1.2%)	6 (2%)
Protocol Violation	1 (<1%)	1 (<1%)
Death[2]	9 (2.7%)	13 (4.4%)
Remain on Treatment	172 (52.7%)	39 (13.3%)

[1] "Other" reasons for discontinuation included: For vemurafenib, all were disease progression, one of which was also in combination with an unresolved Grade 3 AE of elevated GGT; for dacarbazine the reasons were mainly due to medical discretion/decision (4 patients), disease progression (3 patients), surgery for metastases, withdrawal of consent due to an AE, patient opted to withdraw and adverse event (1 each).
[2] Death was captured as a reason for discontinuation on the "Treatment Completion" page and would only occur if the patient died before the study drug was stopped.
The above information was verified using the EXIT dataset.

Specific adverse events leading to treatment discontinuation are summarized in the table below.

Table 33: Discontinuations due to Adverse Events

	Vemurafenib N = 336	Dacarbazine N = 287
Any Adverse Event	34 (7.1%)	12 (4.2%)
Arthralgia	2	0
Dysphagia	2	0
Pneumonia	2	0
Metastases to CNS	1	1
Dyspnea	1	1
Pneumonia	1	1
Thrombocytopenia	1	1
Abdominal Pain	1	0
Aortic Aneurysm Rupture	1	0
Ascites	1	0
Atrial Fibrillation	1	0
Blood Alkaline Phosphatase Increased	1	0
Blood Bilirubin Increased	1	0
Chest Pain	1	0

Choking	1	0
Cognitive Disorder	1	0
Conjunctiva Hyperemia	1	0
Dehydration	1	0
Diplopia	1	0
Dyspepsia	1	0
Esophageal Pain	1	0
Fatigue	1	0
Gait Disturbance	1	0
GGT Increased	1	0
Gastroesophageal Reflux	1	0
Hepatitis Acute	1	0
Hyponatremia	1	
Intracranial Tumor Hemorrhage	1	0
Myocardial Infarction	1	0
Pain	1	0
Pancreatitis	1	0
Rash	1	0
Renal Impairment	1	0
Stevens-Johnson Syndrome	1	0
Thrombocytopenia	1	0
Toxic Skin Eruption	1	0
Vomiting	0	1
Abdominal Pain Lower	0	1
Cardiopulmonary Failure	0	1
Cerebrovascular Accident	0	1
Dyspnea	0	1
Febrile Neutropenia	0	1
Gastrointestinal Hemorrhage	0	1
Hypotension	0	1
Leukopenia	0	1
Musculoskeletal Pain	0	1
Myelitis Transverse	0	1
Nausea	0	1
Neutropenia	0	1
Pleural Effusion	0	1
Pulmonary Embolism	0	1
Shock	0	1
Thrombosis	0	1

The above information was verified using the AEEXT (AE Analysis) dataset.

The rate of discontinuation due to adverse event was low on both arms. There was little overlap in the adverse events that led to discontinuation both between the two treatment arms and within each treatment arm.

7.3.4 Significant Adverse Events

Cutaneous Squamous Cell Carcinoma

There were 79 events of cutaneous squamous cell carcinomas (cuSCCs) in the vemurafenib arm compared to one event in the dacarbazine arm, including both keratoacanthomas and SCCs of skin. The median time to onset in the vemurafenib arm was 7.1 weeks, and no dose interruptions or reductions were undertaken in response to these events. No cases were reported after 28 days off treatment. Patients had between one and eight lesions, and there with six patients with greater than or equal to five lesions. All cuSCCs resolved with excision except in two patients, for whom the outcome was not reported before the data cutoff for this trial.

Reviewer comment:
Given the patient population for this application, this reviewer does not view cuSCCs as a safety concern if appropriate monitoring is employed to manage these events.The overall benefit of vemurafenib in this advanced melanoma population outweighs the risks of cuSCCs given the overall survival benefit and after examining the details and outcome of patients who were diagnosed with cuSCCs in this trial.

New Primary Malignant Melanoma

Seven patients had eight lesions that were identified by the local investigators as new primary melanomas; one patient (201249/7905) was identified in the serious adverse event dataset as melanoma, but this patient had progression of a pre-existing lesion. All lesions were resolved by excision, and no dose modifications or interruptions for vemurafenib were undertaken in light of these adverse events.

Table 34: New Primary Malignant Melanoma Adverse Events

Patient ID	AE Description by Investigator	Grade	Outcome	Dose modification/ Interruption	Disposition
200997/3505	Primary Melanoma, Left Upper Back	2	Resolved	None	On study at C15 with PR
201186/1902	Primary Substernal Melanoma	3	Resolved	None	PD at C10, alive with progression
201187/3202	New primary melanoma, Back	3	Resolved	None	PD at C17, alive with progression
201187/3204	Primary Melanoma, Right Flank	3	Resolved	None	PD at C14, alive with progression
	Primary Melanoma, Left Shoulder	3	Resolved	None	
201187/3208	New Primary Melanoma, Left Forearm	3	Resolved	None	On study at C11 with PR
201187/3209	New Primary Melanoma, Right Forearm	3	Resolved	None	On study at C10 with PR
201204/5502	Primary Melanoma, Right Shoulder	2	Resolved	None	On study at C17 with PR
201249/7905[1]	Melanoma Progression	2	Unresolved	Discontinued	PD at C6, died of PD

[1]Patient 201249/7905 clearly did not have a new primary melanoma but disease progression in a previously identified lesion and will be excluded from further discussion here.

The applicant undertook an independent review of five of these cases in four patients from one study site: patients 201187/3202, 201187/3204, 201187/3208 and 201187/3209. Tissue blocks were submitted for independent review by two dermatopathologists who were blinded to patient treatment. A report was written by a third dermatopathologist summarizing the results and discussing the field of dermatopathology in diagnosing very early melanoma lesions versus benign melanocytic lesions. One lesion was unanimously considered to be a keratoacanthoma. Three lesions were noted to have subtle or unusual changes that were atypical, but on the whole the lesions were deemed benign due to the narrow width and lack of invasion into deeper tissue. For one lesion, the dermatopathologists agreed that early melanoma in situ would be in the differential diagnosis; however, the opinion of all three dermatopathologists was that this lesion was a benign lentiginous junctional nevus

based on the narrow width as well as lack of extension to intact deep margins of the biopsy.

Reviewer's Comment:
There is discussion in the literature regarding diagnosis of malignant melanoma in situ versus a benign melanocytic lesion and the difficulties in defining features that would clearly categorize benign and malignant lesions, with discordance between experienced dermatopathologists ranging from26% to 38% (Corona 1996, Farmer 1996). More recent literature suggests these diagnostic difficulties persist;(Shoo 2010, Scolyer 2010) prediction of biological behavior from pathology alone may not be reliable, and molecular diagnostics are neither validated nor widely available to assist in diagnosis. The current management recommendations suggest that for lesions for which a clear diagnosis is not reached, complete excision with close follow-up is indicated.

One hypothesis for the cases identified above is that vemurafenib may be driving growth of melanocytic cells that have pre-malignant changes into a melanoma in situ. Given the applicant's in vitro data for accelerated growth of Ras-mutated cells upon exposure to vemurafenib, an additional hypothesis would be that these de novo melanomas may have Ras mutations. However, there is no evidence to support this hypothesis at this time. The risk:benefit ratio for vemurafenib remains favorable for this advanced melanoma population despite this finding, but the tolerance for such a risk may be lower in the adjuvant setting or in an indication apart from melanoma. Furthermore, this adverse event should be more explicitly described in the label.

Liver toxicity

Liver enzyme elevations on this trial were more frequent on the vemurafenib arm compared to the dacarbazine arm (see table below). However, this reviewer did not identify any Hy's Law cases. Additionally, there were no cases of acute liver failure. There was one discontinuation secondary to elevated GGT, one discontinuation secondary to increased bilirubin and one discontinuation secondary to increased alkaline phosphatase.

Table 35: Liver Enzyme Elevations

	Vemurafenib N=336		Dacarbazine N=282	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Increased LDH	219 (65.2)	9 (2.7)	159 (56.4)	12 (4.3)
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

There was one case of acute hepatitis and two cases of cytolytic hepatitis. Patient 201244/1205 is a 62 year-old female with past medical history significant for systemic lupus erythematosus and chronic obstructive pulmonary disease who was on chronic steroid medication. She had normal ALT, AST, GGT and total bilirubin levels through six cycles of vemurafenib. On cycle 7 day 1, she had a Grade 2 elevation GGT accompanied by worsening abdominal pain, elevated transaminases and hemodynamic instability that developed through cycle 7 and was discontinued from the study. Patient 201186/1903 is a 38 year-old male with normal liver enzymes on entry to the trial; on cycle 2 day 1, he had a Grade 2 elevation of ALT and AST that resolved with dose modification; he discontinued from the trial after seven cycles secondary to disease progression. Patient 201186/1952 is a 54 year-old female with normal liver enzymes at baseline who began to have elevated ALT, AST and bilirubin during cycle 3; on cycle 5 day 1, liver enzymes increased precipitously and resolved over the next two cycles. Study drug was not interrupted, nor was the dose reduced; the patient remains on study at cycle 13 with a partial response.

Reviewer's Comment:
Despite the frequency of liver enzyme elevations, drug-induced liver injury was not evident in the Phase 3 trial. Management with dose modification and/or interruption appears to have sufficiently addressed the event in most patients, except the three who discontinued study drug. Given the inclusion of liver enzyme abnormalities in the Warnings and Precautions section of the label with monitoring recommended at baseline and monthly during treatment, I do not have any specific labeling changes in regard to this group of adverse events.

Uveitis
There were five patients on the vemurafenib arm (including "Intermediate uveitis") and none on the dacarbazine arm who developed uveitis (see table below). In addition, on the vemurafenib arm there were five patients with blurry vision (three Grade 1, one

Grade 2 and one Grade 3), five patients with iritis (all Grade 2) and six patients with photophobia (three Grade 1, two Grade 2).

Table 36: Uveitis Adverse Events

Patient ID	Grade	Intervention	Outcome	Dose modification/ Interruption	Disposition
201232/1152	2	Steroid and dilating ophthalmic drops	Resolved with residual scarring	Dose interrupted	PD at end of C7, died of PD
201214/2701	3	Steroid and dilating ophthalmic drops	Resolved without sequelae	Dose interrupted	SD at C14
201247/2506	2	Steroid and dilating ophthalmic drops	Unresolved	Dose interrupted	On study at C16 with PR
201204/5501	1	Steroid and antibiotic ophthalmic drops	Resolved without sequelae	None	PR at C17
201249/7903	2	Steroid ophthalmic drops	Resolved without sequelae	None	On study at C13 with PR

Reviewer's Comment:
Vemurafenib causes an inflammatory response in the eye that may resolve with steroid treatment. Given the potential serious nature of the adverse event, it should be more fully described in the label.

Arthralgia/Arthritis

The incidence of arthralgia and arthritis were both higher on the vemurafenib arm, as well as several other joint-related adverse events, shown in Table 37 below. The mechanism of arthralgia is not known in this patient population but is likely related to vemurafenib treatment, given the low rate of arthralgia and other joint-related AEs on the dacarbazine arm.

Table 37: Joint-Related Adverse Events

	Vemurafenib N=336		Dacarbazine N=287	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Arthralgia	180 (53.6)	15 (4.5)	19 (6.6)	2 (<1)
Arthritis	8 (2.4)	1 (<1)	0	0
Joint Effusion	2 (<1)	1 (<1)	0	0
Joint Range of Motion Decreased	2 (<1)	0	0	0
Joint Stiffness	8 (2.4)	0	0	0
Joint Swelling	12 (3.6)	0	2 (<1)	0

Cardiac Disorders

There are three cardiac disorders that occurred more frequently in the vemurafenib arm than the dacarbazine arm and had at least one Grade 3-4 event but were not included in the common AE table due to low frequency. These events are displayed in Table 38 below. Furthermore, QTprolongation/Torsades de Pointes was designated an AE of special interest due to the preclinical and early clinical safety signal observed. There were no cases of torsade de pointes in any vemurafenib-treated patients in the clinical trials conducted to date. Details for the thorough QT_c study are noted in Section 7.4.4 below.

Table 38: Cardiac Adverse Events

	Vemurafenib N=336		Dacarbazine N=287	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Atrial fibrillation	9 (2.7)	2 (<1)	2 (<1)	1 (<1)
Myocardial infarction	3 (<1)	3 (<1)	0	0
Pericarditis	3 (<1)	2 (<1)	0	0
QT prolongation/ Torsades de Pointes	36 (10.7)	7 (2.1)	0	0

Reviewer's Comment:
There were no deaths associated with the adverse events in Table 38*, though one patient discontinued vemurafenib secondary to atrial fibrillation and one secondary to a myocardial infarction. QT prolongation already is addressed in the label; atrial fibrillation should be added to Section 6.1.*

7.3.5 Submission Specific Primary Safety Concerns

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

More patients on the vemurafenib arm experienced grade 1-4 and grade 3-4 adverse events. The most common grade 1-4 treatment-emergent adverse events are included in the table below. The most common grade 1-4 treatment-emergent adverse events in vemurafenib-treated patients on NO20506 were: arthralgia (49.1%), rash (36%), alopecia (33.3%), fatigue (32.1%), nausea (30.1%), photosensitivity reaction (29.8%), diarrhea (25%), pruritus (21.4%), headache (21.3%), hyperkeratosis (19%), pyrexia (17.9%), skin papilloma (17.6%), and decreased appetite (15.8%).

Table 39: Grade 1-4 TEAEs (≥5% of Patients on Either Treatment Arm)

	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)
Blood & Lymphatic Disorders				
Anemia	19 (5.7)	3 (<1)	22 (7.7)	7 (2.4)
Neutropenia	2 (<1)	1 (<1)	34 (11.8)	26 (9.1)
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
Upper Abdominal Pain	26 (7.7)	2 (<1)	8 (2.8)	0
Abdominal Pain	23 (6.8)	5 (1.5)	14 (4.9)	2 (<1)
General Disorders & 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)
Pain	22 (6.5)	3 (<1)	15 (5.2)	2 (<1)
Chills	21 (6.3)	0	3 (1)	0
Infections and Infestations				
Nasopharyngitis	22 (6.5)	0	10 (3.5)	0
Folliculitis	20 (6)	1 (<1)	3 (1)	0

Investigations				
Blood alkaline phosphatase increased	30 (8.9)	9 (2.7)	0	0
ALT increased	26 (7.7)	6 (1.8)	5 (1.7)	1 (<1)
Blood bilirubin increased	22 (6.5)	4 (1.2)	1 (<1)	1 (<1)
AST increased	21 (6.3)	3 (<1)	3 (1)	0
GGT increased	18 (5.4)	11 (3.3)	3 (1.1)	0
Weight decreased	26 (7.7)	1 (<1)	7 (2.4)	0
Metabolism & Nutrition Disorders				
Decreased Appetite	60 (17.9)	0	24 (8.3)	1 (<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
Musculoskeletal Pain	26 (7.7)	0	11 (3.8)	1 (<1)
Back Pain	27 (8)	1 (<1)	14 (4.9)	1 (<1)
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)				
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
Dizziness	26 (7.7)	2 (<2)	14 (4.9)	0
Psychiatric Disorders				
Insomnia	23 (6.8)	0	15 (5.2)	0
Respiratory, Thoracic & Mediastinal Disorders				
Cough	28 (8.3)	0	20 (6.9)	0
Dyspnea	32 (9.5)	5 (1.5)	26 (9.1)	7 (2.4)

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
Sunburn	33 (9.8)	0	0	0
Rash Maculo-papular	30 (8.9)	8 (2.4)	2 (<1)	0
Palmar-Plantar Erythrodysaesthesia Syndrome	26 (7.7)	1 (<1)	4 (1.4)	0
Actinic Keratosis	28 (8.3)	0	11 (3.8)	0
Skin Lesion	29 (8.6)	1 (<1)	2 (<1)	0
Keratosis Pilaris	21 (6.3)	0	2 (<1)	0

The above information was verified using the AEEXT (AE Analysis) dataset.

Increased AST, increased bilirubin, increased creatinine, popular rash, chest pain, influenza-like illness, folliculitis, increased GGT, melanocytic nevus, cry mouth, acanthoma, hypokalemia, acneiform dermatitis, skin exfoliation, atrial fibrillation, conjunctivitis, dypshagia, joint swelling, dermal cyst, arthritis, edema and papilloma each occurred more commonly in vemurafenib-treated patients (≥2% difference between arms) but are not included in the table above because they occurred in <5% of patients on either arm.

The most common grade 3-4 treatment-emergent adverse events are included in the table below. The most common grade 3-4 treatment-emergent adverse events in vemurafenib-treated patients on NO20506 were: SCC of the skin (11.3 %), rash (8.3%), keratoacanthoma (6%), arthralgia (3.3%), increased GGT (2.7%), photosensitivity reaction (2.7%), maculopapular rash (2.4%) and increased blood alkaline phosphatase (2.1%).

Table 40: Grade 3-4 TEAEs (≥1% of Patients on Either Arm)

	Vemurafenib N=336	Dacarbazine N=287
	Grade 3-4 (%)	Grade 3-4 (%)
Any Adverse Event	197 (58.6)	96 (33.4)
SCC of Skin	55 (16.4)	1 (<1)
Rash	28 (8.3)	0
Keratoacanthoma	29 (8.6)	0
Arthralgia	15 (4.5)	2 (<1)
GGT Increased	11 (3.3)	0
Photosensitivity Reaction	9 (2.7)	0
Rash Maculopapular	8 (2.4)	0
Blood Alkaline Phosphatase Increased	9 (2.7)	0
Fatigue	7 (2.1)	7 (2.4)
Dyspnea	7 (2.1)	7 (2.4)
Nausea	7 (2.1)	5 (1.7)
ALT Increased	6 (1.8)	1 (<1)
Pain in Extremity	5 (1.5)	5 (1.7)
Pruritus	5 (1.5)	0
Vomiting	4 (1.2)	3 (1)
Pain	4 (1.2)	2 (<1)
Blood Bilirubin Increased	4 (1.2)	1 (<1)
Hyperkeratosis	4 (1.2)	0
Anemia	3 (<1)	3 (1)
Thrombocytopenia	2 (<1)	8 (2.8)
Neutropenia[1]	1 (<1)	33 (11.7)

[1] Includes Neutrophil Count Decreased
The above information was verified using the AEEXT (AE Analysis) dataset.

Among the 37 patients who crossed over from the dacarbazine treatment to vemurafenib treatment, the rate and type of adverse events were similar to patients who had been treated initially with vemurafenib.

7.4.2 Laboratory Findings

Laboratory adverse events are summarized in the table below. Laboratory parameters where post-baseline increases to Grade 3 or 4 occurred in ≥ 5% of patients included:
• decreased neutrophils: <1% vemurafenib, 13% dacarbazine
• increased GGT: 11.3% vemurafenib, 8.5% dacarbazine
• decreased WBC: <1% vemurafenib, 6% dacarbazine
• decreased lymphocytes: 8% vemurafenib, 7% dacarbazine

Table 41: Laboratory Grade 1-4 Adverse Events in ≥10% in Either Arm

	Vemurafenib N=336		Dacarbazine N=282	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
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)
Hyperkalemia	47 (14)	4 (1.2)	39 (13.8)	0
Hypercalcemia	41 (12.2)	7 (2)	26 (9.2)	3 (<1)
Decreased Hemoglobin	94 (34)	9 (3.7)	111 (35.5)	12 (3.4)
Decreased Lymphocytes	149 (51.6)	24 (8.3)	83 (36.6)	17 (7.5)
Hypoalbuminemia	44 (13.9)	4 (1.3)	49 (19.2)	3 (1.2)
Hypophosphatemia	94 (29.9)	11 (3.5)	34 (13.5)	8 (3.2)
Hypocalcemia	27 (8.3)	0	45 (17)	0
Decreased Neutrophils	24 (8.2)	2 (<1)	94 (37.8)	33 (13.3)
Decreased WBCs	56 (17.2)	3 (<1)	90 (33.7)	16 (6)
Decreased Platelets	18 (5.5)	1 (<1)	74 (27.9)	9 (3.4)

The above information was verified using the LABTXT (Laboratory Analysis) dataset from the initial NDA submission.

7.4.3 Vital Signs

Vital signs recorded during the active treatment period were examined for extreme abnormalities. Among 336 vemurafenib-treated patients in the safety population, none had a recorded temperature >39°C. Aberrations in heart, either tachycardia or bradycardia, were not reported. Elevated systolic blood pressures were commonly reported, with systolic BP ≥150 mm Hg reported for 166 (83%) patients. Elevated diastolic blood pressures were also commonly reported, with diastolic BP ≥90 mm Hg reported for 83 (25%) patients. Hypertension was the most commonly reported concurrent disease at baseline in both treatment groups (vemurafenib 28%, dacarbazine 26%), and persistent elevations of SBP >160 mmHg or DBP >90 mmHg were uncommon. Eight cases were reported as hypertension AEs, with six in vemurafenib-treated patients versus two in dacarbazine-treated patients. None of these events were serious AEs; none resulted in dose modification or discontinuation; and none of these cases were considered by the investigator to be related to study treatment.

7.4.4 Electrocardiograms (ECGs)

A thorough QTc study was conducted as a sub-study within the single-arm Phase 2 trial of vemurafenib and was submitted with this application.

The following is extracted from the Interdisciplinary Review Team for QT Studies consult:

No large changes in QTc interval (i.e., >20 ms) were detected in the trial following the treatment of vemurafenib (RO5185426) 960 mg twice daily, even though vemurafenib appears to prolong QTc interval in a concentration-dependent manner (P <0.0001). The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean change from baseline was 14.8 ms, observed at 6 hours post-dose on Day 15 (i.e., at steady state) in Cycle 1.

Labeling changes in blue recommended by the IRT-QT team include the following:

Section 5.4: QT Prolongation

(b) (4)

Section 12.2 Pharmacodynamics:
The effect of vemurafenib 960 mg administered twice daily on QTc interval was evaluated in a multi-center, open-label, single-arm study in 132 previously treated patients with BRAF V600 mutation-positive metastatic melanoma. No large changes in QTc interval (i.e., >20 ms) from baseline were detected in the trial. Vemurafenib is associated with concentration-dependent QTc interval prolongation. The largest upper bound of the 2-sided 90% confidence interval (CI) on Day 15 in Cycle 1 for the mean change from baseline was 14.8 ms, observed at 6 hours post-dose.

7.4.5 Special Safety Studies/Clinical Trials

No organ dysfunction studies have been conducted to date. Patients were required to have total bilirubin ≤1.5 x ULN, AST/ALT ≤2.5 x ULN, and creatinine ≤1.5 x ULN in order to enroll.

Of vemurafenib arm patients with total bilirubin levels reported between study day -7 to study day 1, four had a total bilirubin value >1.5x ULN. Patient 201059/9401, a 63 year-old male, entered the trial with a baseline Grade 2 elevation of bilirubin. His bilirubin remained elevated at Grade 2 throughout the study period, and he discontinued treatment due to the adverse event of choking on food. Patient 201062/8804 had an

isolated elevated bilirubin at screening that did not recur throughout his study treatment. Patient 201186/1957, a 40 year-old male, had Grade 2 elevation of bilirubin at baseline and intermittently throughout the study period. He remains on treatment after four cycles with a partial response. Patient 201219/1759, a 74 year-old female, had a Grade 2 elevation of bilirubin on Cycle 1 Day1 that persisted through three cycles of treatment. She remains on treatment with a partial response.

Among vemurafenib arm patients with AST or ALT reported between study day -7 to study day 1, one patient had a reported AST or ALT value >2.5x ULN. Patient 201202/6105, a 52 year-old male, had Grade 2 elevations of both ALT and AST on Cycle 1 Day 1 that continued intermittently during his treatment course. He discontinued treatment during Cycle 3 for progressive disease.

Reviewer's Comment:
No conclusions regarding the use of vemurafenib in patients with hepatic impairment can be drawn from the Phase 3 trial NO20506, as the trial included only four patients with bilirubin elevations >1.5x ULN within 7 days of the start of study treatment and only 3 patients with AST or ALT elevations >2.5x ULN within 7 days of the start of study treatment.

Among vemurafenib arm patients with serum creatinine reported between study day -7 to study day 1, one patient had a reported serum creatinine value >1.5x ULN. Patient 201198/3705, a 45 year-old male, had a Grade 2 elevation of serum creatinine on Cycle 1 Day 1. The patient's screening level had been normal and improved to Grade 1 for the remainder of the study. This patient remains on treatment in Cycle 14 with a partial response.

Reviewer's Comment:
No conclusions regarding the use of vemurafenib in patients with renal impairment can be drawn from the Phase 3 trial NO20506, as the trial included only one patient with serum creatinine elevation >1.5x ULN within 7 days of the start of study treatment.

7.4.6 Immunogenicity

The following adverse event preferred terms were considered possibly related to immunogenicity: chills, drug hypersensitivity, hypersensitivity, hypotension, pruritis, rash, rash erythematous, respiratory failure, swelling face, wheezing and Stevens-Johnson syndrome. For each of these preferred terms, events that occurred within three days of vemurafenib administration were reviewed. Thirteen patients experienced events within three days of study drug administration, as detailed in the table below. In addition, one patient also experienced Stevens-Johnson syndrome and one patient experienced toxic epidermal necrolysis.

Table 42: Adverse Events Possibly Related to Immunogenicity

Patient ID	AE Preferred Term	Grade	First Dose (Day)	AE Start (Day)	Time from First Dose to AE (Days)	Action with Study Drug
201217/4211	Rash	1	1	3	2	None
201217/4212	Rash	1	1	1	0	None
201219/1758	Pruritus	1	1	3	2	None
201233/3401	Rash	2	1	3	2	Dose modified/ Interrupted
201237/1501	Rash	1	1	4	3	None
201237/1502	Rash	1	1	3	2	None
201238/3603	Pruritus	.	1	1	0	None
201240/5310	Pruritus	1	1	1	0	None
201241/1552	Pruritus	1	1	3	2	None
202616/5404	Rash	2	1	3	2	None
202618/9801	Pruritus	1	1	4	3	None
203236/2952	Rash Erythematosus	1	1	2	1	None
201193/6805	Stevens-Johnson Syndrome	3	1	18	17	Discontinued permanently
201165/6404*	Toxic epidermal necrolysis	3	1	27	26	Discontinued permanently

* Patient 201165/6404 initially was randomized to the dacarbazine arm and crossed over to vemurafenib after progression.

Additionally, one patient in the PK Study NP25163 developed shock associated with delayed hypersensitivity reaction to vemurafenib, which was described as a constellation of symptoms, including sinus tachycardia, eye swelling, pyrexia, flushing, and hypotension. The patient was hospitalized and fully recovered. Upon rechallenge with a single dose of 240 mg vemurafenib, the patient became hypotensive but responded to resuscitation and was discharged from the hospital; study drug was permanently discontinued.

The pharmacology-toxicology review identified that in the dog study, eosinophilia with counts increased up to 343% and 478% in the females and males, respectively. The Phase 3 trial in humans had 28 instances of eosinophilia in 13 patients on the dacarabazine arm and 32 instances in 20 patients on the vemurafenib arm. The majority of the instances on the vemurafenib arm were 2-3 times the upper limit of normal and noted as not clinically significant by the investigator.

Reviewer's Comment:
Rash and pruritus were common adverse events with vemurafenib, thus the patients in the table above who experienced this without additional signs or symptoms of immunogenicity likely were experiencing these AEs independent of an allergic-type reaction to vemurafenib. However, the patient with Stevens-Johnson syndrome that appeared 17 days after initiation of treatment, the patient with toxic epidermal necrolysis that appeared after 26 days after initiation of treatment and the patient from the PK study who experienced the delayed hypersensitivity reaction all demonstrate that vemurafenib has the potential to cause severe hypersensitivity reactions. The labeling includes severe hypersensitivity reactions under Warnings & Precautions, and this reviewer does not believe that more restrictive labeling is required.

7.5 Other Safety Explorations

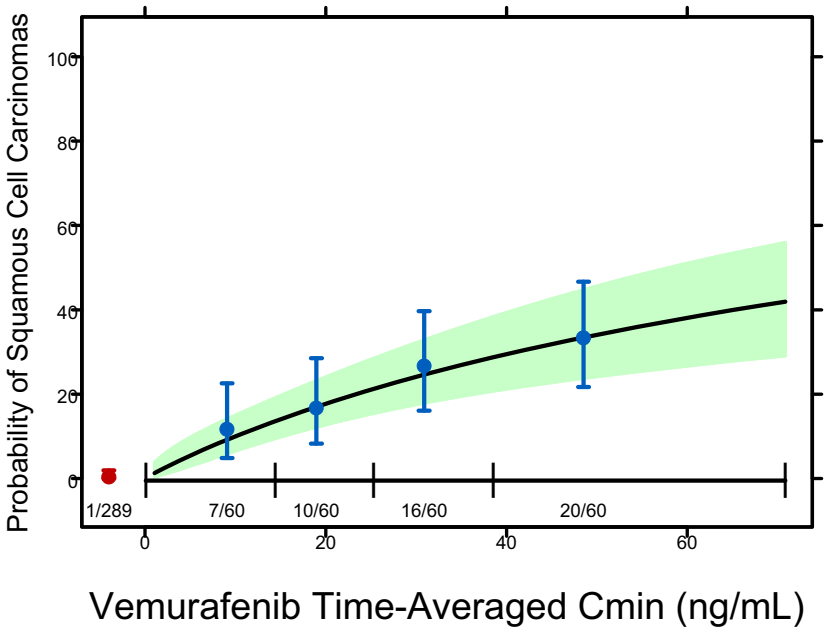
7.5.1 Dose Dependency for Adverse Events

There is a clear relationship between exposure and the incidence of cuSCCs with an increase in the probability of squamous cell carcinomas for higher exposures. The following is extracted from the Clinical Pharmacology Review:

A logistic regression was performed to determine if the exposure-response relationship was significant. The results are shown in Figure 16 below and indicate a significant exposure-response relationship for squamous cell carcinomas (p-value of <0.0001). The model coefficient for $\ln(C_{min,saf})$ was 0.956 with a relative standard error of 15%.

Refer to the Clinical Pharmacology Review for further details.

Figure 16: Exposure-Response Relationship for cuSCCs



7.5.2 Drug-Demographic Interactions

Rates of grade 1-4 adverse events were examined by age (<65 years of age versus ≥65 years of age) and are presented in Table 43 below. Overall, grade 1-4 adverse event rates were similar in patients <65 years old and ≥65 years old. However, several grade 1-4 adverse events occurred more frequently (≥5% difference) in older patients, while others occurred more frequently in the younger patients. The grade 1-4 events that occurred more frequently in patients ≥65 years old were: decreased appetite, squamous cell carcinoma of the skin, nausea, depression, peripheral edema, atrial fibrillation and keratoacanthoma. The adverse events that occurred more frequently in patients <65 years old were arthralgia, alopecia, hyperkeratosis, dry skin, erythema, maculo-papular rash, keratosis pilaris, photosensitivity reaction, constipation, pyrexia, myalgia, and headache.

Table 43: Grade 1-4 Adverse Events by Age

	Age	
	<65 yrs N = 242	≥65 yrs N = 94
Nausea	67 (27.7%)	35 (37.2%)
Decreased Appetite	31 (12.8%)	23 (24.5%)
Squamous Cell Carcinoma of Skin	21 (8.7%)	19 (20.2%)
Oedema Peripheral	32 (13.2%)	18 (19.1%)
Keratoacanthoma	16 (6.6%)	11 (11.7%)
Depression	3 (1.2%)	7 (7.4%)
Atrial Fibrillation	2 (0.8%)	6 (6.4%)
Arthralgia	129 (53.3%)	37 (39.4%)
Photosensitivity Reaction	81 (33.5%)	20 (21.3%)
Pyrexia	49 (20.2%)	11 (11.7%)
Constipation	28 (11.6%)	4 (4.3%)
Myalgia	33 (13.6%)	6 (6.4%)
Hyperkeratosis	53 (21.9%)	14 (14.9%)
Rash Maculo-papular	25 (10.3%)	4 (4.3%)
Dry Skin	43 (17.8%)	11 (11.7%)
Keratosis Pilaris	16 (6.6%)	1 (1.1%)
Alopecia	88 (36.4%)	29 (30.9%)
Erythema	31 (12.8%)	7 (7.4%)

Overall, grade 3-4 adverse event rates were similar in patients <65 years old and ≥65 years old. Among the grade 3-4 adverse events, several occurred more frequently (≥2% difference) in older patients, including SCC of the skin, rash, pruritus, increased GGT and keratoacanthoma. Photosensitivity reaction occurred more frequently in patients <65 years old.

Table 44: Grade 3-4 Adverse Events by Age

	Age	
	<65 yrs N = 242	≥65 yrs N = 94
Squamous Cell Carcinoma of Skin	20 (8.3%)	18 (19.1%)
Rash	16 (6.6%)	12 (12.8%)
Pruritus	2 (0.8%)	3 (3.2%)
GGT Increased	5 (2.1%)	4 (4.3%)
Keratoacanthoma	13 (5.4%)	7 (7.4%)
Photosensitivity Reaction	9 (3.7%)	0

Overall, Grade 1-4 adverse event rates were similar in male and female patients. Several Grade 1-4 adverse events occurred more frequently (≥5% difference) in female patients, including: arthralgia, alopecia, nausea, diarrhea, rash, peripheral edema, maculo-papular rash, vomiting, decreased appetite, dry skin, erythema and flushing. Events of keratoacanthoma, folliculitis and pruritus were more common in males.

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Table 45: Grade 1-4 Adverse Events by Sex

	Sex	
	Female N=137	Male N=199
Arthralgia	85 (62%)	81 (40.7%)
Alopecia	61 (44.5%)	56 (28.1%)
Nausea	54 (39.4%)	48 (24.1%)
Diarrhea	46 (33.6%)	38 (19.1%)
Rash	58 (42.3%)	63 (31.7%)
Edema Peripheral	28 (20.4%)	22 (11.1%)
Rash Maculo-papular	19 (13.9%)	10 (5%)
Vomiting	27 (19.7%)	23 (11.6%)
Decreased Appetite	28 (20.4%)	26 (13.1%)
Dry Skin	28 (20.4%)	26 (13.1%)
Erythema	21 (15.3%)	17 (8.5%)
Flushing	11 (8%)	4 (2%)
Keratoacanthoma	7 (5.1%)	20 (10.1%)
Folliculitis	2 (1.5%)	13 (6.5%)
Pruritus	25 (18.2%)	49 (24.6%)
Increased Creatinine	28 (20.4%)	72 (36.2%)
increased Total Bilirubin	32 (23.4%	87 (37.7%)
Keratoacanthoma	7 (5.1%)	20 (10.1%)
Folliculitis	2 (1.5%)	13 (6.5%)
Pruritus	25 (18.2%)	49 (24.6%)
Increased Alkaline Phosphatase	79 (57.7%)	89 (44.7%)
Increased AST	61 (44.5%)	68 (34.2%)
Increased ALT	66 (48.2%)	79 (39.7%)
Increased GGT	61 (44.5%)	75 (37.7%)

Overall, grade 3-4 adverse event rates and laboratory adverse events rates were similar in male and female patients. Among the grade 3-4 adverse events or laboratory events that occurred more frequently in females (≥2% difference) in females were rash, arthralgia and increased creatinine. Grade 3-4 adverse events or laboratory events that occurred more frequently in males were keratoacanthoma and increased alkaline phosphatase (see Table 46 below).

Table 46: Grade 3-4 Adverse Events by Sex

	Sex	
	Female N=137	Male N=199
Rash	17 (12.4%)	11 (5.5%)
Arthralgia	7 (5.1%)	4 (2%)
Increased Creatinine	4 (2.9%)	1 (0.5%)
Keratoacanthoma	4 (2.9%)	16 (8%)
Increased Alkaline Phosphatase	2 (1.5%)	8 (4%)

7.5.3 Drug-Disease Interactions

See Clinical Pharmacology review.

7.5.4 Drug-Drug Interactions

See Clinical Pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

CuSCCs developed in approximately 24% of all patients treated with vemurafenib. Overall, all cases resolved with excision. The applicant also monitored for non-cuSCCs, and three were noted. Additionally, a number of cases of new primary malignant melanomas also were identified by investigators in the Phase 3 trial. The difficulties in diagnosing early malignant melanoma *in situ* are noted above. Again, all cases were managed with complete excision. This drug amy accelerate the growth of a subset of cells with changes favorable for development of cuSCC, SCC or melanoma. However, in the advanced melanoma population proposed in this NDA, proper monitoring for and treatment of these potential adverse events is adequate given the overall survival benefit that is observed with vemurafenib.

No vemurafenib-treated patients developed acute myeloid leukemia or myelodysplastic syndrome. See Pharmacology-Toxicology review.

7.6.2 Human Reproduction and Pregnancy Data

There are no data in humans at this time. See Pharmacology-Toxicology review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Vemurafenib has not been studied in a pediatric population. (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose, drug abuse potential, withdrawal, and rebound are not relevant to this application.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

As this application is for a new molecular entity with no prior approval history, there is no postmarket experience.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Please refer to the package insert of Zelboraf.

9.3 Advisory Committee Meeting

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEOFFREY S KIM
08/01/2011

AMY E MCKEE
08/01/2011

JOHN R JOHNSON
08/01/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202249 **Applicant: Hoffmann La Roche** **Stamp Date: 4/28/11**

Drug Name: Vemurafenib **NDA/BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Efficacy Data is submitted as data from separate clinical trials
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: NO25026: The proposed indication is: (b) (4)	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	(b) (4) Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and				

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		The sponsor has proposed a dedicated phase 2 study in pediatric patients.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Amy McKee; Geoffrey Kim 5/23/11

Reviewing Medical Officer Date

Clinical Team Leader Date

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/s/

GEOFFREY S KIM
07/19/2011