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APPLICATION NUMBER:

202429Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA # Supplement #	NDA 202429
Applicant Name	Hoffman-La Roche
Date of Submission	4/28/11
PDUFA Goal Date	10/28/11
Proprietary Name / Established (USAN) Name	ZELBORAF vemurafenib
Dosage Forms / Strength	Film-coated tablet, 240 mg
Proposed Indication(s)	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.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Geoffrey Kim (efficacy), Amy McKee (safety)
Statistical Review	Qiang Xu, Shenghui Tang, Rajeshwari Sridhara
Pharmacology Toxicology Review	W. David McGuinn, Robeena M. Aziz, Whitney Helms
CMC Review/OBP Review	Anne Marie Russell, Richard Lostritto
Microbiology Review	N/A
Clinical Pharmacology Review	Jeanne Fourie Zirkelbach
DDMAC	Marybeth Toscano
DSI	Robert Young
CDTL Review	Yangmin Max Ning, John R. Johnson
OSE/DMEPA	Lubna Merchant
OSE/DDRE	N/A
OSE/DRISK	Latonia Ford, Joyce Weaver
Other: QT-IRT	Joo Leon Lee

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

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1. Introduction

The NDA for Zelboraf (vemurafenib) tablets was submitted on 4/28/11 for the proposed indication of "treatment of unresectable or metastatic BRAF mutation-positive melanoma by the cobas® 4800 V600 Mutation Test." The application was given a priority review designation, with a PDUFA date of 10/28/11, because of the improvement in overall survival. This application was given an expedited review due to the scarcity of effective therapies for patients with this disease. The only other treatment which has demonstrated a survival improvement in this disease is ipilimumab which was approved earlier this year. This memo will summarize the regulatory history, the clinical trial results which were submitted in support of this application, and the recommendations of each review discipline.

2. Background

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 $BRAF^{V600E}$.

The IND for vemurafenib (also known as PLX4032, RG7204 and RO51585426) was submitted in 9/06. The phase 1 trial with an extension phase in patients with metastatic melanoma with the BRAF V600E mutation was conducted between 11/06 and 6/10. In 5/09, at an end of phase 1 meeting, the sponsor proposed to develop vemurafenib in patients with advanced melanoma with the $BRAF^{V600E}$ mutation using a response rate of ≥30% or PFS (HR 0.5 and an improvement in medial PFS of 2 months) as regulatory endpoints for accelerated approval. The proposal was based on tumor responses in 11 of 16 patients (69%) with advanced melanoma positive for the $BRAF^{V600E}$ mutation in the phase 1 trial. At that meeting the FDA recommended that the sponsor conduct a randomized phase 3 trial with overall survival as the primary endpoint but expressed willingness to discuss use of their single-arm phase 1 and 2 trials to support accelerated approval once they had more data suggesting impressive activity. During the meeting, the FDA also discussed issues regarding the development of a companion diagnostic to detect the $BRAF^{V600E}$ mutation.

A phase 2 trial in 132 patients with metastatic melanoma with the BRAF V600E mutation was conducted from 9/09 to 9/10. The applicant shared the preliminary results of this trial with the Agency in August 2010. The objective response rate was reported to be approximately 50%. Also, the results of the extension phase of the phase 1 trial were reported in the 8/26/10 issue of the New England Journal of Medicine. Twenty-six of 32 patients (81%) had an objective response.

The BRIM3 trial was a randomized phase 3 trial of vemurafenib vs. DTIC in patients with previously untreated unresectable or metastatic melanoma with the BRAF V600E mutation. The following excerpt from the Statistical Division Director's Memo summarizes the design and evolution of the trial.

> The phase 3 randomized, controlled, multicenter clinical trial was originally designed (September 2009) with 680 patients (468 events) to detect a difference in median overall survival of 10.7 months in the vemurafenib arm vs. 8 months in the DTIC arm and HR of 0.75 with 80% power and two-sided 2.5% level of significance, accounting for 2 interim analyses with 50% and 75% of information. Overall survival was the primary efficacy endpoint.

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> In August of 2010 the Agency became aware of the preliminary results of the Phase 2 study as well as the published results of the Phase 1 study. At this time both studies showed impressive objective response rates of > 50% in the targeted population of patients with metastatic melanoma whose tumors harbored BRAF V600E mutation. It was also reported[1] that in the extension phase of the Phase 1 trial, the median progression-free survival among the 32 patients was greater than 7 months. Literature review[2] suggested that the objective response rates ranged from 11% to 24% in metastatic melanoma patients treated with a variety of chemotherapy agents. Given these results the Agency proactively communicated with the applicant multiple times to modify the statistical analysis plan of the phase 3 trial (which had accrued approximately 400 patients at that time and about 300 more patients had been screened to enter the study), adapting with the impressive observed activity of vemurafenib in the phase 1 and phase 2 studies. Specifically the Agency advised the applicant to (1) increase overall study alpha level to two-sided 5% from two-sided 2.5%, (2) set up alpha spending rule with higher probability to cross at interim analysis, (3) less conservative target HR (0.65 instead of 0.75) to be detected, and (4) add progression-free survival as a second primary endpoint. The applicant accordingly revised the statistical analysis plan to conduct final progression-free survival analysis with 187 events at which time an interim survival analysis was to be conducted with 98 deaths (50% information per modified estimates). Although patients were enrolled into the study within a very short period of time at an unexpected high rate of accrual and hence could not reduce the actual number of patients enrolled with the adaptation, the applicant was able to successfully conduct the analysis early in a planned manner with the timely adaptation of the clinical trial…

The following is a chronology of interactions between the FDA and sponsor regarding the phase 3 trial and is based on excerpts from a summary provided from Roche:

- Teleconference regarding Phase 3 trial (August 11, 2010):
  - Agency's position on the Phase 3 trial:
    - The original design of the Phase 3 trial was appropriate based on the preliminary Phase 1 data.
    - Emerging data from the Phase 1 melanoma extension cohort (BORR of 81% suggests unprecedented activity of vemurafenib in metastatic melanoma.
  - Agency questioned whether the Phase 3 trial should be continued <u>as originally designed</u>, based on new evidence of vemurafenib activity.
    - Requested earlier interim analysis (IA) of OS
  - Agency requested that Roche keep them informed of when they plan to open an Early Access Program (EAP).
- Teleconference regarding Phase 3 trial (August 18, 2010):
  - Agency requested the interim Phase 3 response rate and duration results, and the number of deaths in each treatment arm to be included in the NDA (based on Phase 2 study).
  - Results of the planned interim OS analysis (based on 50% of accrued events) should be submitted during the NDA review period.
  - Based on plans to publicly release results of Phase 2 trial in early November, FDA recommended that Roche prepare an expanded access program (EAP).
- Teleconference regarding Phase 3 trial (September 14, 2010):
  - Agency requested a meeting with Roche on September 23, 2010 to discuss continuing the Phase 3 trial <u>as currently designed</u>.
  - Agency wants to work with Roche to ensure that they have an organized plan that will capture efficacy data in all patients treated to date.
    - The Agency suggested that the current treatment effect size in the Phase 3 trial is too conservative.

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        - The Agency requested that Roche present different scenarios for estimating treatment effect in overall survival based on new information from the Phase 1 and Phase 2 trials. These analyses would not incur a statistical penalty.
        - The Division requested that Roche work on implementing an EAP as soon as possible.
- Teleconference regarding Phase 3 trial (September 20, 2010):
    - The Agency recommended that Roche include an analysis of Phase 3 data including progression-free survival, response rate, and overall survival in the NDA. Based on the data seen to date, the PFS effect should be large enough to support full approval and that an OS benefit would not be needed.
    - The Agency recommended that Roche consider several scenarios for giving patients access to vemurafenib (options are not mutually exclusive):
        - Close enrollment of the Phase 3 (BRIM3) trial in US sites and allow patients in the control arm to crossover to the RO5185426 arm
        - Reopen enrollment of the Phase 2 (BRIM2) trial
        - Change the primary endpoint of the Phase 3 trial to PFS and allow patients in the control arm to crossover to vemurafenib
- Meeting regarding Phase 3 trial (September 23, 2010):
    - Dr. Pazdur and the review team expressed their desire to work with Roche on a proposal that would allow gathering the data necessary to ensure patient access.
    - FDA agreed to Roche's proposal for an early interim analysis, but requested that the statistical assumptions be relaxed to increase the probability of a positive first interim analysis.
    - FDA strongly advocated opening an expanded access protocol with a broader patient population and/or reopening BRIM-2 to ensure patient access as soon as possible.
    - Post-meeting notes: FDA requested a teleconference to discuss a new SAP with relaxed statistical assumptions on September 28, 2010, and a follow-up teleconference on September 29, 2010.
- Teleconference regarding new Phase 3 Statistical Analysis Plan (September 28, 2010):
    - Agreement on statistical assumptions for OS analyses.
    - Requested that patients in the control arm be allowed to crossover upon progression to active treatment at the time of the projected clinical cutoff for the interim analysis.
- Teleconference regarding Phase 3 Statistical Analysis Plan and EAP (September 29, 2010):
    - Discussion focused on the regulatory path for full approval if the first interim analysis for OS does not cross the statistical boundary, and whether crossover of patients in the control arm to vemurafenib would be a data driven decision based on the results of the IA.
    - The Agency suggested changing the primary endpoint to PFS, which could support full approval assuming a clinically meaningful PFS benefit. Patients in the control arm would be allowed to crossover upon progression.
    - The Agency agreed to review a counter proposal by Roche with hierarchical analysis of the co-primary endpoints of PFS and OS. A significant effect demonstrated in PFS would trigger an IA analysis of OS. If OS does not cross the boundary in the IA, a second and final OS analysis would be conducted earlier than originally proposed. Crossover of patients in the control arm would be contingent upon a positive outcome of the OS analysis.
    - The Agency also requested submission of the draft EAP protocol.
- Submission of BRIM3 revised SAP (October 1, 2010)
- FDA comments on BRIM3 revised SAP received (October 13, 2010)
- Teleconference regarding plans for the BRIM3 Interim Analysis and opening of the US Early Access Protocol (EAP) (November 3, 2010):
    - FDA was in agreement with the Phase 3 Statistical Analysis Plan (SAP), protocol amendment and DSMB Charter, the latter having been revised to reflect guidelines for recommending crossover of patients from the dacarbazine arm to the vemurafenib arm based on statistical

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criteria for PFS and OS. The Division asked that the SAP and protocol amendment cross-reference the DSMB Charter for the crossover criteria.

- FDA indicated that they did not expect any further comments on the EAP and agreed to confirm this in the next couple of days. Roche communicated that they were working to finalize the EAP, including incorporation of comments, and will submit the final protocol shortly after receiving confirmation of the end of the review. Roche also communicated that they were working diligently to open an EAP site as soon as possible.

A treatment protocol was submitted on 10/11/10 and was allowed to proceed on 11/5/10.

At the pre-NDA meeting on 1/21/11, the sponsor proposed to submit an application for accelerated approval based objective response rates from the phase 1 and 2 trials or an application for full approval based on final PFS and interim OS results from the randomized trial. *The Agency agreed to review the application under either scenario.*

3. CMC/Device

Chemistry reviewers recommend approval of this NDA with acceptability of the manufacturing of the drug product and drug substance.

Manufacturing site inspections were acceptable. There are no outstanding issues.

The cobas® 4800 V600 Mutation Test is a companion diagnostic that has been reviewed by CDRH and will be approved at the same time as Zelboraf.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewers recommend approval of this NDA and there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology and biopharmaceutics reviewers recommend approval of this NDA and there are no outstanding issues that preclude approval. Clinical Pharmacology is also recommending PMRs for this NDA. Please refer to the action letter for these PMRs.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The efficacy and safety of vemurafenib is based primarily on an international, randomized, open-label trial in patients with previously untreated metastatic or unresectable melanoma with the $BRAF^{V600E}$ mutation as detected by the cobas® 4800 BRAF V600 Mutation Test (Roche Molecular Systems, Inc.). This companion diagnostic test was approved by the FDA concurrently with vemurafenib's approval.

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The trial enrolled 675 patients; 337 patients were assigned to vemurafenib, 960 mg orally twice daily, and 338 were assigned to dacarbazine, 1000 mg/m^2 intravenously, every three weeks. Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. All patients had an ECOG performance status of 0 or 1, and 95% of patients had metastatic disease. The major efficacy outcome measures of the trial were overall survival (OS) and investigator-assessed progression-free survival (PFS). Other outcome measures included confirmed investigator-assessed best overall response rate.

The median follow-up at the time of the overall survival analysis was 6.2 and 4.5 months for the vemurafenib and dacarbazine arms, respectively. Overall survival was significantly improved in patients receiving vemurafenib compared to those receiving dacarbazine (HR=0.44; 95% CI: 0.33, 0.59; p< 0.0001, log-rank test). The median survival of patients receiving vemurafenib had not been reached (95% CI: 9.6 months, not reached) and was 7.9 months (95% CI: 7.3, 9.6) for those receiving dacarbazine.

Progression-free survival (PFS) was also significantly improved in patients receiving vemurafenib (HR=0.26; 95% CI: 0.20, 0.33; p<0.0001, log-rank test). The median PFS was 5.3 (95% CI: 4.9, 6.6) and 1.6 months (95% CI: 1.6, 1.7) in the vemurafenib and dacarbazine arms, respectively. Overall response rate (complete plus partial response rates) was 48.4% (95% CI: 41.6%, 55.2%) and 5.5% (95% CI: 2.8%, 9.3%) in the vemurafenib and dacarbazine arms, respectively. Efficacy results are summarized in the table and figure below.

Efficacy of ZELBORAF in Treatment Naive Patients with BRAF^{V600E} Mutation-Positive Melanoma[a]

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

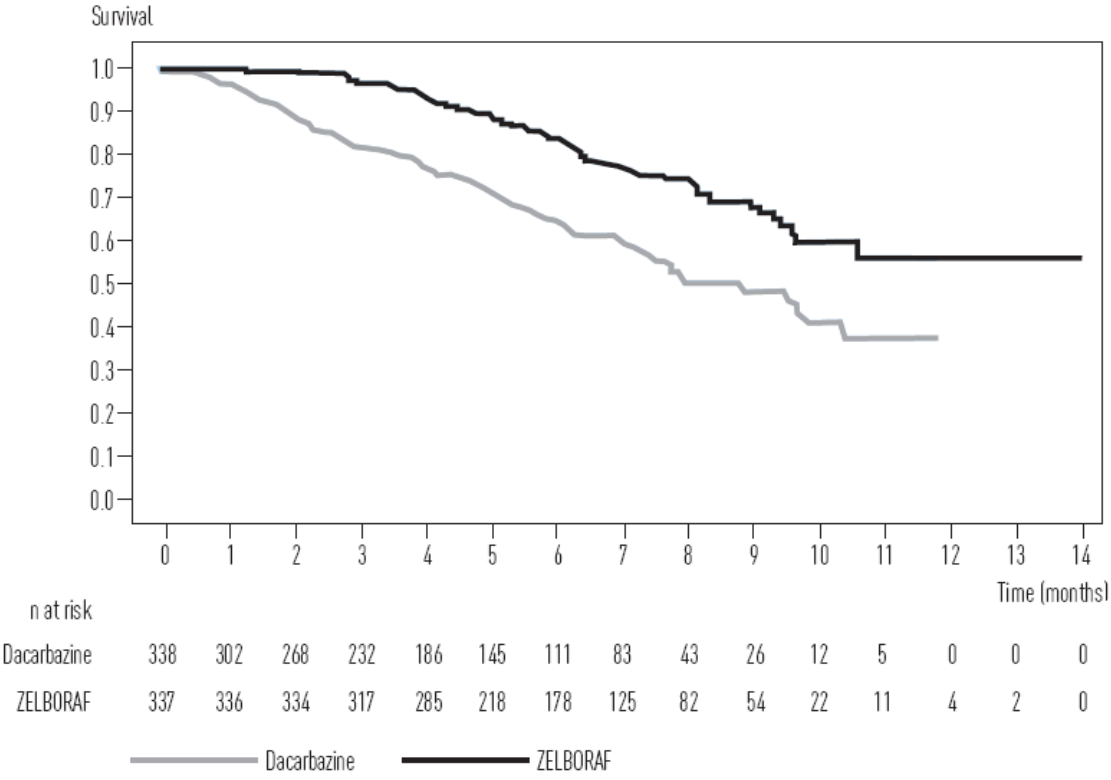
[a] As detected by the cobas® 4800 BRAF V600 Mutation Test

[b] Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors ZELBORAF

[c] Kaplan-Meier estimate

[d] Unstratified log-rank test

Kaplan-Meier Curves of Overall Survival – Treatment Naive Patients



Vemurafenib was also evaluated in a single-arm, multicenter trial that enrolled 132 patients with $BRAF^{V600E}$ mutation-positive metastatic melanoma who had received at least one prior systemic therapy. An independent review of treatment responses demonstrated a confirmed best overall response rate of 52% (95% CI: 43%, 61%), with a median response duration of 6.5 months (95% CI: 5.6, not reached).

Vemurafenib has not been studied in patients with wild-type BRAF melanoma.

8. Safety

The most common adverse reactions (≥30%) in patients treated with vemurafenib were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, and nausea. Cutaneous squamous cell carcinomas (cuSCC), including squamous cell carcinomas of the skin and keratoacanthomas, were detected in approximately 24% of patients treated with vemurafenib. CuSCCs were managed with excision in clinical trials, and patients were able to continue treatment without dose adjustment. Other adverse reactions, sometimes severe, reported in vemurafenib-treated patients included hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, uveitis, QT prolongation, and liver enzyme laboratory abnormalities.

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9. Advisory Committee Meeting

The application was not referred to an FDA advisory committee because the benefit/risk profile of vemurafenib is clearly favorable for the proposed indication.

10. Pediatrics

Vemurafenib is exempt from the requirement for pediatric studies because of orphan drug designation.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proprietary name ZELBORAF was found to be acceptable.
- Physician labeling: Agreement has been reached on the physician labeling. The final indication reflects the population studied.

  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.
- Carton and immediate container labels: Agreement has been reached on carton and container labels.
- Patient labeling/Medication guide: Agreement has been reached on the MedGuide.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.
- Risk Benefit Assessment

  Until the approval of ipilimumab earlier this year, no treatment had been shown to improve overall survival in advanced malignant melanoma. Although the median survival has not yet been reached for vemurafenib in the randomized study, the overall survival in the vemurafenib arm is clearly superior to that in the dacarbazine arm. Additional follow-up will provide a better estimate of the survival with vemurafenib treatment. The improvement in survival is supported by clinically and statistically significant improvements in progression-free survival and objective response rate. The toxicity profile is better than that of most cytotoxic chemotherapeutic agents and is clearly acceptable for a disease that has a dismal prognosis.

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The benefits and risks of vemurafenib were discussed in the Division Director's Summary Review, the CDTL and Clinical Reviews. The review team found the risk-benefit assessment to be acceptable. In conclusion, I concur with the review team's recommendation for approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
  Routine postmarketing surveillance is recommended.

- Recommendation for other Postmarketing Requirements and Commitments: Please refer to action letter.

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/s/

TAMY E KIM
08/16/2011

RICHARD PAZDUR
08/16/2011