CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	April 29, 2013
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK)
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Subject:	Review evaluates the need for a risk evaluation and mitigation strategy (REMS)
Drug Name(s):	Dabrafenib (Tafinlar™)
Therapeutic Class:	Kinase inhibitor
Dosage and Route:	150 mg (tablets) orally, twice daily
Application Type/Number:	NDA 202-806
Submission Number:	3
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2012-1789

CONTENTS

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) dabrafenib (Tafinlar™). The proposed indication for dabrafenib is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA-approved test; it is not recommended for use in patients with wild-type BRAF melanoma. At the time of this review, dabrafenib has not been approved in any other country.

GlaxoSmithKline has submitted a risk management plan which consists of professional labeling. The Applicant did not submit a proposed REMS.

1.1 BACKGROUND

Melanoma, a malignant tumor of melanocytes, is the most serious type of skin cancer. Melanocytes are derived from the neural crest, thus melanomas not only arise from the skin but may also arise from other tissues to which neural crest cells migrate. About 76,250 persons were expected to be diagnosed with melanoma in 2012; 9,180 melanoma-related deaths were also projected for the same year.[1]

The mitogen-activated protein kinase (MAPK) pathway is a primordial signaling system which controls cellular processes such as proliferation, differentiation, survival, and apoptosis. The MAPK pathway consists of a chain of proteins in the cell that communicate a signal from a receptor in the cell membrane to the DNA in the nucleus resulting in cell changes such as cell division. The pathway includes a G-protein working upstream of a core module including three kinases: MAPK Kinase Kinase (MAPKKK), MAPK Kinase (MAPKK), and MAPK. The RAF (acronym for **R**apidly **A**ccelerated **F**ibrosarcoma) kinase family (ARAF, BRAF, CRAF) is part of the MAPK pathway. BRAF mutations have been identified in about 30 to 60% of melanomas. Dabrafenib is potent and selective RAF kinase inhibitor of the mutated forms BRAF V600E, BRAF V600K and BRAF V600D as well as human wild type BRAF and CRAF enzymes.

Available therapies for advanced and metastatic melanoma include the following:

- *Dacarbazine (dimethyl triazene imidazole carboxamide or DTIC).* First approved therapy for metastatic melanoma. Although dacarbazine is still in use, its efficacy is limited (observed responses from 10 to 12%, median progression-free survival (PFS) of ~ 1.5 months, and median overall survival (OS) of 6.4 months).[2]
- *Interleukin-2 (IL-2).* The response rate with IL-2 ranges from 15 to 20% with few durable complete responses and substantial adverse effects. (CRs). Because the adverse effects associated with IL-2 are substantial.

[1] American Cancer Society: Cancer Facts and Figures 2012. Atlanta, GA: American Cancer Society, 2012. Available online at: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf. Last accessed January 3, 2012.

[2] Dabrafenib, Clinical Overview, GlaxoSmithKline, 2012, page 7.

- *Ipilimumab (Yervoy™).* Approved by FDA on March 25, 2011 for the treatment of unresectable or metastatic melanoma. Ipilimumab is a human monoclonal antibody to cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) approved for the treatment of metastatic melanoma in 2011. Treatment with ipilimumab alone significantly improved median survival compared with the glycoprotein100 vaccine (10.1 months *vs.* 6.4 months; hazard ratio [HR]: 0.66; P = 0.003). The overall response rate for the ipilimumab monotherapy arm was low, at 10.9% (95% confidence interval [CI]: 6.3–17.4) with significant immune-related adverse events (rate of Grade 3/4 AEs was 46%, rate of treatment-related death for the ipilimumab alone arm was 3.1%). Treatment with ipilimumab in combination with DTIC showed a significant survival benefit when compared with DTIC alone in the first line treatment of unresectable melanoma.[2]
- *Vemurafenib (Zelboraf™).* Was approved in August 2011 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test; it is not recommended for use in patients with wild-type BRAF melanoma. Vemurafenib is a selective BRAF inhibitor which demonstrated significant PFS (Hazard Ratio 0.26, 95% CI 0.20, 0.33, p <0.0001) and overall survival (Hazard Ratio 0.44, 95% CI, 0.33-0.59, p<0.0001) as compared with DTIC chemotherapy in treatment naïve patients with metastatic melanoma, harboring a V600E BRAF mutation.[3]

Dabrafenib is proposed for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA-approved test; it is not recommended for use in patients with wild-type BRAF melanoma.

The recommended dose is 150 mg orally twice daily administered one hour before or two hours after meals. Management of symptomatic adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation of TAFINLAR. Dose reductions resulting in a dose below 50 mg twice daily are not recommended. It comes in 50 and 75 mg hydroxypropyl methylcellulose (HPMC) hard capsules.

The sponsor anticipates an estimated population of 150 to 200 patients receiving monotherapy dabrafenib in the United States.

On August 3, 2012, GlaxoSmithKline submitted an NDA for trametinib with a proposed indication (indication includes modifications from DOP-2) of the treatment of unresectable or metastatic melanoma with BRAF V600E (b) (4) mutations, as detected by an FDA approved test, who have not received BRAF inhibitor therapy. A single randomized, open-label, active-controlled Phase 3 study (**MEK114267**) in 322 patients with unresectable or metastatic BRAF V600 mutation-positive melanoma, conducted in North America, South America, Europe, Australia, and New Zealand is the basis for approval. GlaxoSmithKline submitted a risk management plan which consists of professional labeling. The Applicant did not submit a proposed REMS.

1.2 REGULATORY HISTORY

The regulatory history of dabrafenib, in pertinent part, is as follows:

- **June 26, 2009:** IND 105032 for dabrafenib (GSK2118436) was submitted to the FDA with the first time-in-human phase 1 study BRF112680.

[3] Robert Justice, MD, MS, Zelboraf, Division Director Review, August 16, 2011.

- **July 24, 2009:** GSK received notification from the FDA that the proposed study was allowed to proceed
- **January 12, 2011:** Orphan designation for treatment of BRAF V600 mutation positive Stage IIb through IV melanoma
- **February 11, 2011:** Fast Track designation granted for treatment of patients with BRAF (V600E (b) (4)) mutation positive advanced melanoma.
- **July 30, 2012:** GSK submitted an original NDA for dabrafenib capsules to FDA.

2 MATERIALS REVIEWED

- Dabrafenib, Risk Management Plan, GlaxoSmithKline, 2012
- Dabrafenib, Clinical Overview, GlaxoSmithKline, 2012
- Dabrafenib, Product Label, GlaxoSmithKline, 2012
- Alexander H. Putman, Ph.D., Division of Hematology Oncology Toxicology, Pharmacology/Toxicology NDA Review and Evaluation, April 11, 2013
- Marc Theoret MD, Medical Officer, Division of Oncology Products 2, Clinical Review draft, April 25, 2013

3 CLINICAL DEVELOPMENT PROGRAM

The primary efficacy of dabrafenib in advanced metastatic BRAF V600 mutation-positive melanoma derives from the pivotal randomized Phase III study of dabrafenib compared to DTIC (BREAK-3, only BRAF V600E mutation positive melanoma, n=250), the key Phase II study in subjects with brain metastases (BREAK-MB, BRAF V600E or BRAF V600K mutation, n=172), and the supportive Phase II study (BREAK-2, BRAF V600E or BRAF V600K mutation, n=92). The efficacy data of these trials was not integrated because of differences in primary endpoints, study designs, assessment schedules, and study populations across the clinical trials. Most subjects across these studies were diagnosed with Stage IV melanoma and a majority had M1c, indicative of a poorer prognosis. See Table 1 in the Appendix for a summary of the 3 main clinical trials.

The safety assessment was based primarily on data from the pivotal study BREAK-3. Additional safety analyses were performed on a dataset that integrated the results from BREAK-3 from 4 supportive studies: BREAK-MB, BREAK-2, BRF113220 [dabrafenib monotherapy arm], and BRF112680 [subset of cohort 1 and cohort 2]. The integrated dataset included 578 subjects. See Table 2 in the Appendix. Also, serious adverse events (SAEs) were evaluated for subjects in the 5 clinical studies mentioned above and Study BRF113771 (pharmacokinetic study) following the data cut-off dates through 30 March 2012, along with important events from other ongoing studies of dabrafenib monotherapy (i.e., compassionate use Study BRF115252, advanced non-small cell lung cancer Study BRF113928, and roll-over Study BRF114144).

3.1 EFFICACY FINDINGS REPORTED BY THE SPONSOR

Dabrafenib demonstrated clinical efficacy in the 3 trials, regardless of the type of BRAF mutation, the presence or absence of metastases, and prognosis. Tables 3, 4, and 5 in the Appendix present the key findings from the pivotal trial BREAK-3, study BREAK-2, and study BREAK-MB in

support of dabrafenib's efficacy for the treatment of unresectable or metastatic melanoma with BRAF V600 mutations.

Efficacy in Subjects with BRAF V600E Mutation Positive Melanoma (no brain metastases). [4] The primary evidence of dabrafenib's efficacy in subjects with BRAF V600E mutation-positive melanoma is provided by BREAK-3. In BREAK-3, dabrafenib demonstrated a statistically significant and clinically meaningful improvement in PFS compared to treatment with DTIC (HR 0.30 [95% CI: 0.18, 0.51; p<0.0001]) in subjects with newly diagnosed BRAF V600E mutation-positive melanoma; this represents a 70% reduction in the risk of progression or death compared with DTIC. The median PFS was 5.1 months for subjects treated with dabrafenib and 2.7 months for subjects treated with DTIC. The overall response rate (ORR) with dabrafenib treatment was consistent between BREAK-3 (53%) and BREAK-2 (59%). The magnitude of the HR for PFS of dabrafenib in BREAK-3 compared with DTIC was consistent between the investigator and independent reviewers and similar to the HR demonstrated for vemurafenib. Preliminary data suggest there is an improvement in OS with dabrafenib over DTIC; the estimated 6 months survival for subjects treated with dabrafenib in BREAK-3 was 87% (HR 0.61 [95% CI: 0.25, 1.48]). In BREAK-2, the response rate and PFS observed in subjects with BRAF V600E mutation-positive melanoma was consistent with findings in the BREAK-3 study.

Efficacy in Subjects with Brain Metastases in BRAF V600E Mutation Positive Melanoma. [4] The response rates for intracranial disease in the primary BRAF V600E mutation-positive melanoma population were 39% for Cohort A (treatment naïve) and 31% for Cohort B (prior local therapy); the magnitude and durability of this response has not been reported previously with systemic therapy. The median OS for subjects with brain metastases treated with dabrafenib was >7 months, which is longer than that observed in other studies. The PFS for dabrafenib in BREAK-MB was shorter than in BREAK-3 and BREAK-2 due to the poor prognosis associated with brain metastases.

Efficacy in Subjects with BRAF V600K Mutation Positive Melanoma.[4] In BREAK-2, subjects with BRAF V600K mutation demonstrated a response rate of 13% with a median duration of response of 5.3 months, and a median PFS of 4.5 months. The median OS of subjects with BRAF V600K mutation-positive melanoma (12.9 months) was similar to that observed in subjects with BRAF V600E mutation-positive melanoma (13.1 months).

In BREAK-MB, the intracranial and overall efficacy of dabrafenib was lower in subjects with BRAF V600K mutation-positive melanoma compared to the efficacy of subjects with the BRAF V600E mutation. Nevertheless, when compared with results observed with the use of systemic chemotherapy, the longer PFS and OS achieved with dabrafenib are clinically significant.

3.2 KEY SAFETY FINDINGS

3.2.1 Safety Findings Reported by the Sponsor

Safety findings observed in the integrated safety population were generally consistent with findings from BREAK-3. There were no deaths attributed to treatment with dabrafenib. The most common AEs (≥20% of subjects) observed in the integrated dabrafenib safety population were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, and skin papilloma; these AEs were

[4] Dabrafenib, Clinical Overview, GlaxoSmithKline, 2012, page 35-37.

primarily Grade 1 or Grade 2 in severity. The most frequent AEs occurring at Grade 3 or higher included pyrexia, SCC, hypophosphatemia, and lymphopenia.

The sponsor considered the following risks and proposed managing these with routine pharmacovigilance and labeling (including a patient labeling) (b) (4)

- **Cutaneous squamous cell carcinoma** (cuSCC) – 9% of dabrafenib-treated subjects; this finding is consistent with dabrafenib's mechanism of action.
- **Serious non-infectious febrile events** – 1% of dabrafenib-treated subjects; generally Grade 2 in severity; onset was typically within the first month of therapy; symptoms generally resolved following dose interruption (86%) and/or dose reduction (43%). The sponsor will conduct exploratory research (pre-clinical and clinical) on the mechanism of action for serious non-infectious febrile events.
- **Renal failure** – <1% (4 cases), with no occurrences in the Phase III, BREAK-3 pivotal trial; events of renal failure or acute renal failure can range from mild renal impairment to fatal; of the 4 cases reported, 2 were considered serious (1 of which as study drug-related), 2 were Grade 1, 1 was Grade 2 and 1 was Grade 4.
- **Hypersensitivity** – no confirmed cases of hypersensitivity were identified in the integrated safety dataset; 1 case of Grade 2 hypersensitivity (blister) was identified in Study BRF113928 in a subject with non-small cell lung cancer on dabrafenib 150 mg BID.
- **Pancreatitis** – <1%; 5 cases of pancreatitis (2 included in the integrated safety population and 3 subjects receiving 150 mg BID dabrafenib which were not part of the integrated safety population); all 5 were serious adverse events which resolved; 4 events of pancreatitis were Grade 3 and 1 case was Grade 2.
- **Uveitis** – <1%; 5 dabrafenib-treated subjects in the integrated safety population had uveitis or iritis; all cases were Grade 2 or below in severity and the majority (80%) were attributed to study treatment by the investigator.
- **Palmar-plantar erythrodysesthesia** (PPES) – 13% of dabrafenib-treated subjects experienced PPES and most cases of PPES (95%) were considered related to dabrafenib and none were SAEs; approximately 1/3 of PPES cases resolved.
- **New primary melanoma** – <1% (5 subjects) had a new primary melanoma; of the 5 cases, 1 case was Grade 1, 1 case was Grade 2, 3 cases were Grade 3 and 4 cases (2 considered study drug related).
- **Non-cutaneous malignancies** – 3 subjects treated with dabrafenib were reported with non-cutaneous malignancies (mycosis fungoides (Grade 1, associated to dabrafenib by investigator), acute myeloid leukemia (AML), and myelodysplastic syndrome [MDS]); no cases of non-cutaneous SCC associated to dabrafenib were identified in the drug development program
- **Pregnancy** – no human pregnancy exposure data available; animal studies have shown maternal and developmental reproductive toxicity; the efficacy of hormonal contraceptives may be decreased from CYP3A4 induction from dabrafenib, thus, hormonal contraceptives would not considered adequate protection and an alternate method of contraception, such as barrier methods, should be considered for these women.

- **Testicular toxicity** – studies in animals have demonstrated testicular toxicity; there may be considerable risk of impaired spermatogenesis in human males, which is potentially irreversible.

The following safety issues identified for BRAF inhibitors were not a cause of concern with dabrafenib because these were not present, occurred infrequently, or were low in severity: liver laboratory abnormalities, photosensitivity, severe dermatologic reactions, and QTc prolongation.

3.2.2 Division of Oncology Products 2 Main Safety Concerns[5]

The Division of Oncology Products 2 (DOP 2) determined that dabrafenib has a favorable benefit-risk profile for treatment of patients with BRAF V600E mutation-positive unresectable or metastatic melanoma when compared to available treatments. The most concerning risks associated with dabrafenib therapy include the occurrence of new primary cutaneous malignancies (i.e., cutaneous squamous cell carcinoma/keratoacanthoma (cuSCC) and new primary melanomas) and serious febrile drug reactions (fever complicated by hypotension, dehydration, severe rigors/chills, or renal failure in the absence of another identifiable etiology).[6]

Uveitis, an important risk associated with the use of vemurafenib, was also observed in patients treated with dabrafenib. Uveitis was reported in about 1% of patients treated with dabrafenib. [5]

Reproductive and developmental toxicities identified in embryo-fetal studies in rats exposed to dabrafenib included: cardiac malformations in developing fetuses (cardiac ventricular septal defects); visceral and skeletal malformations (misshapen or split thymuses and decreased skeletal ossification); decrease in the number of corpora lutea, implantations and live fetuses; increase in pre- and post-implantation loss; and a reduction in fetal body weights.[7]

A signal for cardiac valve toxicity was identified in dabrafenib's clinical development program. The data submitted in support of this application are insufficient to conclude that dabrafenib causes valvular toxicities, thus, collection of additional safety data postmarketing is required.[5]

4 DISCUSSION

The dabrafenib clinical development program demonstrated its efficacy for the treatment of BRAFV600 mutation-positive metastatic or unresectable melanoma, regardless of site of metastases, subject's prognosis, or whether previously treated with chemotherapy.

The risk:benefit assessment of dabrafenib by DOP2 has not identified any confirmed or potential risks that would require the implementation of a REMS to assure the benefits of its use outweigh its risks. The main safety concerns identified with dabrafenib include: new primary cutaneous malignancies and serious non-infectious febrile events. Additional safety concerns include the risk of uveitis, a potential for embryo-fetal toxicity, and a signal for cardiac valve toxicity.

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[5] Marc Theoret MD, Medical Officer, Division of Oncology Products 2, Clinical Review draft, April 25, 2013.

[6] Ibid. Recommendations/Risk Benefit Assessment section: *"The rate of cuSCC was 11% across clinical trials of dabrafenib and, in the BRF113683 trial, was 7.5% in dabrafenib-treated patients and nil in DTIC-treated patients. In addition, new primary melanoma lesions occurred in three (1.6%) dabrafenib-treated patients and in none of the DTIC-treated patients. Cutaneous malignancies appear to be manageable with excision and do not require dose modification of dabrafenib."*

[7] Alexander H. Putman, Ph.D., Division of Hematology Oncology Toxicology, Pharmacology/Toxicology NDA Review and Evaluation, April 11, 2013.

As shown in Table 6 in the Appendix, vemurafenib presents similar safety findings which are all managed through labeling. DRISK concurs with DOP 2 that a REMS is not necessary to ensure that its benefits outweigh the risks and that professional labeling, a Medication Guide, pharmacovigilance, and postmarketing requirements (to obtain additional safety data) is sufficient to address the risks identified in clinical development program with dabrafenib.

5 CONCLUSION AND RECOMMENDATIONS

DRISK recommends managing identified safety risks associated with treatment with dabrafenib through labeling, including a Medication Guide as part of labeling and not a REMS. The need for a REMS can be re-evaluated if new safety data becomes available that warrants more extensive risk mitigation.

APPENDIX

Table 1. Development Program for Dabrafenib as Monotherapy in Metastatic Melanoma as of the Clinical Cut-off Dates for Each Study

Study Identifier	Protocol Name	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	BRAF Mutation Status at Enrollment [b]	Total No. of Subjects by Group Entered/ Completed
BREAK-3 (BRF113683)	A Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated subjects with BRAF mutation positive metastatic melanoma	Dabrafenib (HPMC) 150 mg BID (dose may be reduced); oral; DTIC 1000 mg/m^2 every 3 weeks; continued treatment until disease progression, death or unacceptable adverse event	V600E: 249 V600K: 1[a]	Dabrafenib 187 enrolled 80 completed DTIC 63 enrolled 46 completed
BREAK-MB (BRF113929)	A Phase II open-label, two-cohort, multicenter study of dabrafenib as a single agent in treatment naïve and previously treated subjects with BRAF mutation-positive metastatic melanoma to the brain	Dabrafenib (HPMC) 150 mg BID (dose may be reduced); oral; continued treatment until disease progression, death or unacceptable adverse event	V600E: 139 (Cohort A: 74; Cohort B: 65) V600K: 33 (Cohort A: 15; Cohort B: 18)	172 Enrolled Cohort A: 89 enrolled 63 completed Cohort B: 83 enrolled 56 completed
BREAK-2 (BRF113710)	A Phase II single-arm, open-label study of dabrafenib in BRAF mutant metastatic melanoma	Dabrafenib (Gelatin) 150 mg BID (dose may be reduced); oral; continued treatment until disease progression, death or unacceptable adverse event	V600E: 76 V600K: 16	92 enrolled/ 59 completed

BID: twice daily; DTIC: dacarbazine, HPMC: hydroxypropyl methyl cellulose

a. Randomized in error and did not receive treatment; included in ITT population but not the Safety Population (see BRF113683 CSR Section 5.2 and Section 5.3)

b. An allele-specific real-time PCR assay was utilized to specifically detect the BRAF V600E vs. V600K mutation (see Section 1.6).

Source: Dabrafenib, Clinical Overview, 2012, Table 3, page 12.

Table 2. Description of Dabrafenib Studies in the Integrated Safety Analysis with Cut-off Dates and Subjects included in Safety Population

GlaxoSmithKline (GSK) Study and Design	Data Cut-off Date	Subjects Included in Integrated Analysis (N)	
BREAK-3 (BRF113683)[a] Phase III, randomized, open-label, two-arm, active-controlled study of dabrafenib as compared with dacarbazine (DTIC) in subjects with unresectable or metastatic BRAF V600E mutation-positive melanoma	19 December 2011	Randomized to dabrafenib Crossover to dabrafenib following disease progression on DTIC Total	187 28 215
BREAK-MB (BRF113929) Phase II, two-cohort, open-label study in subjects with BRAF V600 E/K mutation-positive melanoma metastatic to brain	28 November 2011		172
BREAK-2 (BRF113710)[b] Phase II, single-arm, open-label study in subjects with BRAF V600 E/K mutation-positive metastatic melanoma	07 July 2011		92
BRF113220 Phase I/II, multi-part, open-label, dose-escalation study of dabrafenib in combination with trametinib in subjects with BRAF mutant metastatic melanoma	01 September 2011	Part C (monotherapy dabrafenib arm only)	52
BRF112680[c] Phase I, first-time-in-human (FTIH), open-label, dose-escalation study of dabrafenib in subjects with solid tumors	25 March 2011	Part 1 Cohort 7 (V600 mutation-positive melanoma) Part 2 Melanoma Total	17 30 47
Total			578

a. This is the pivotal study for the claim of efficacy
b. According to the summary document analysis plan, data from the BREAK-2 study through a cut-off date of 20 February 2012 was to be included in the integrated safety analysis; instead, the cut-off date for the BREAK-2 clinical study report as indicated above, was used.
c. Includes only subjects who were treated with dabrafenib 150 mg BID in Part 1 or Part 2
Source: Dabrafenib, Risk Management Plan, 2012, Table 1, page 10.

Table 3. Key Efficacy Data from the Pivotal Study BREAK-3

	Intention-to-Treat Population	
Endpoints/ Assessment	**Dabrafenib N=187**	**DTIC N=63**
Progression-free survival		
INV-assessed, median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR (95% CI)	0.30 (0.18, 0.51) p<0.0001	
IRC-assessed, median, months (95% CI)	6.7 (5.0, 6.9)	2.9 (1.7, 4.9)
HR (95% CI)	0.35 (0.20, 0.61)	
Overall survival		
% at 6 months[a] (95% CI)	87 (79.2, 91.9)	79 (59.7, 89.5)
HR (95% CI)	0.61 (0.25, 1.48)	
Overall response[b,c]		
INV-assessed, % (95% CI)	53 (45.5, 60.3)	19 (10.2, 30.9)
CR	3	0
PR	50	19
IRC-assessed, % (95% CI)	50 (42.4, 57.1)	6 (1.8, 15.5)
Overall response duration[c]		
INV-assessed	N=99	N=12
Median, months (95% CI)	5.6 (4.8, NR)	NR (5.0, NR)
IRC-assessed	N=93	N=4
Median, months (95% CI)	5.5 (5.0, 6.7)	NR (NR, NR)

Abbreviations: **CI**: confidence interval; **CR**: complete response; **DTIC**: dacarbazine; **HR**: hazard ratio; **INV**: investigator-assessed; **IRC**: independent review committee; **NR**: not reached; **PR**: partial response.
a. Estimated from Kaplan-Meier estimates at 6 months; overall survival data are not yet mature and median overall survival has not been reached for either arm. **b.** Defined as complete response+partial response. **c.** Confirmed response.
Source: Dabrafenib, Clinical Overview, 2012, Table 4, page 25.

Table 4. Key Efficacy Data from the Key Study BREAK-MB

	All Treated Subjects Population			
	BRAF V600E (Primary)		BRAF V600K	
Endpoints/ Investigator Assessment	**Cohort A N=74**	**Cohort B N=65**	**Cohort A N=15**	**Cohort B N=18**
Overall intracranial response rate[a]				
% (95% CI)	39 (28.0, 51.2)	31 (19.9, 43.4)	7 (0.2, 31.9)	22 (6.4, 47.6)
Overall intracranial response duration,				
Median, months (95% CI)	N=29 4.6 (2.8, NR)	N=20 6.5 (4.6, 6.5)	N=1 2.9	N=4 3.8 (NR, NR)
Overall response[a]				
% (95% CI) PR[b]	38 (26.8, 49.9) 38	31 (19.9, 43.4) 31	0 (0, 21.8) 0	28 (9.7, 53.5) 28
Overall response duration				
Median, months (95% CI)	N=28 5.1 (3.7, NR)	N=20 4.6 (4.6, 6.5)	NA	N=5 3.1 (2.8, NR)
Progression-free survival				
Median, months (95% CI)	3.7 (3.6, 5.0)	3.8 (3.6, 5.5)	1.9 (0.7, 3.7)	3.6 (1.8, 5.2)
Overall survival				
Median, months (95% CI)	7.6 (5.9, NR)	7.2 (5.9, NR)	3.7 (1.6, 5.2)	5.0 (3.5, NR)

Abbreviations: **CI**: confidence interval; **INV**: investigator-assessed; **IRC**: independent review committee; **NA**: not applicable; **NR**: not reached; **PR**: partial response.
a. Confirmed response.
b. There were no complete responses.
Cohort A: subjects with no prior local therapy for brain metastasis.
Cohort B: subjects who received prior local therapy for brain metastasis.
Source: Dabrafenib, Clinical Overview, 2012, Table 5, page 26.

Table 5. Key Efficacy Data from the Supportive Study BREAK-2

	All Treated Subjects Population	
Endpoints/ Investigator Assessment	**BRAF V600E (Primary) N=76**	**BRAF V600K N=16**
Overall response rate[a]		
% (95% CI)	59 (48.2, 70.3)	13 (0, 28.7)
Response duration		
	N=45	N=2
Median, months (95% CI)	5.2 (3.9, NR)	5.3 (3.7, 6.8)
Progression-free survival		
Median, months (95% CI)	6.3 (4.6, 7.7)	4.5 (2.6, 6.2)
Overall survival		
Primary analysis at 6 months follow-up Median, months (95% CI)	9.5 (9.5, NR)	7.9 (5.5, NR)
Updated analyses at 12 months follow-up[b] Median, months (95% CI)	13.1 (10.4, NR)	12.9 (6.9, 17.1)

Abbreviations: **CI**: confidence interval; **NR**-not reached
a. Confirmed response.
b. Updated analyses at 30 April 2012 data cut-off.
Source: Dabrafenib, Clinical Overview, 2012, Table 6, page 26.

Table 6. A side-by-side Comparison of Dabrafenib and Vemurafenib

	DABRAFENIB	VEMURAFENIB
Trade Name:	Tafinlar	Zelboraf
NDA:	202806	202429
Sponsor:	GlaxoSmithKline	Genentech
FDA Approval:	Pending	August 17, 2011
Class:	Kinase inhibitor	Kinase inhibitor
Target:	BRAF V600	BRAF V600
Indication:	For the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA-approved test.	For the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.
Limitations of Use	TAFINLAR is not recommended for use in patients with wild-type BRAF melanoma.	ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma
Risk Management	Labeling (medication guide) and routine pharmacovigilance	Labeling (medication guide) and routine pharmacovigilance
Labeling		
o Box Warning	None	None
o Warning & Precautions	• Cutaneous squamous cell carcinomas (cuSCC) • New primary melanomas • Uveitis and iritis • Potential fetal harm • May decrease effectiveness of hormonal contraceptives • Potential impaired spermatogenesis • Serious non-infectious febrile events • Increased risk of non-cutaneous malignancies • Confirmation of BRAF V600 mutation using an FDA-approved test is required • Not recommended for use in patients with wild-type BRAF melanoma	• Cutaneous squamous cell carcinomas (cuSCC) • New primary malignant melanomas • Serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion • Potential fetal harm • Serious hypersensitivity reactions, including anaphylaxis • Severe dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis • QT prolongation • Liver laboratory abnormalities • Photosensitivity • Confirmation of BRAF V600 mutation using an FDA-approved test is required • The efficacy and safety of ZELBORAF have not been studied in patients with wild-type BRAF melanoma.
o Pregnancy Category	D	D

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/s/

AMARILYS VEGA
04/29/2013

CLAUDIA B MANZO
04/29/2013
concur