

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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Memorandum

*Date:* May 2, 2013  
*From:* Norma Griffin, Regulatory Health Project Manager DOP2/OHOP  
*Subject:* NDA 202806: Biostatistics Secondary/Tertiary Reviews

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Drs. Kun He and Thomas Gwise signed off on Dr. Weishi Yuan's April 10, 2013, review as a complete review.



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**BLA Serial Number:** 202806/ 00  
**Drug Name:** Tafinlar® / Dabrafenib  
**Indication(s):** unresectable or metastatic melanoma with BRAF V600 mutation  
**Applicant:** GlaxoSmithKline (GSK)  
Receipt Date 07/30/2012  
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**Review Priority:** Standard

**Biometrics Division:** V  
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**Keywords:** Log-rank Test, Pike Estimator, Progression Free Survival (PFS), Overall Survival (OS), Melanoma

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## 1. EXECUTIVE SUMMARY

The applicant submitted data and final study reports of a pivotal study to support approval for dabrafenib indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test. This is the first indication dabrafenib is seeking.

This application was based on a single randomized trial, Study BRF113683 (Study 113683), titled “A Phase III randomized, open-label study comparing dabrafenib to dacarbazine (DTIC) in previously untreated patients with BRAF mutation positive metastatic melanoma.” The primary endpoint was progression free survival (PFS). Secondary endpoints included overall survival (OS) and overall response rate (ORR). A total of 250 patients were randomized in a 3:1 allocation with 187 in the dabrafenib arm and 63 in the DTIC arm.

The data and analyses from current submission showed that dabrafenib prolonged PFS compared with dacarbazine (DTIC). Based on investigator’s assessment, the median PFS was 5.1 months in the dabrafenib arm compared with 2.7 months in the dacarbazine arm. The estimated hazard ratio (HR), based on a stratified Pike estimator, was 0.33 with 95% confidence interval (CI) (0.20, 0.55). The p-value from the stratified log-rank test was less than 0.001. The results of independent radiologist assessed PFS and independent radiologist and oncologist assessed PFS were similar.

There was no difference in OS between dabrafenib and DTIC. With a total of 30 deaths, the median survivals in the two study arms were not estimable. The estimated hazard ratio (HR) was 0.69 with 95% CI (0.32, 1.51). The p-value from the stratified log-rank test was 0.35. Bigger ORR was observed in the dabrafenib arm when compared with the DTIC arm.

Based on the data and analyses, the study results showed that dabrafenib showed a statistically significant improvement in PFS compared with dacarbazine. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

The quality of the original data submission was not adequate to evaluate and review the submission. Problems included poor data organization and management, missing data variables, data sets and documents, un-executable SAS programs, and lack of documentation throughout the whole data submission. More than 10 formal data quality related information requests were sent to the applicant to request additional data, documentations, and programs. The reviewers had multiple face-to-face meetings, telephone-conferences and email communications with the applicant. As a result, the applicant withdrew the priority review request voluntarily and a standard review was conducted. The final analysis data used in this review were derived by the reviewer from raw data.

## 2. INTRODUCTION

The applicant submitted data and final study reports of a pivotal study to seek a regular approval for a new indication for dabrafenib. This application was based on Study BRF113683 (Study 113683), a Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated patients with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma. This is the first indication dabrafenib is seeking.

### 2.1 Overview

#### 2.1.1. Class and Indication

Dabrafenib was reported to be a potent and selective RAF kinase inhibitor of human wild type BRAF and CRAF enzymes as well as the mutation positive forms BRAF V600E, BRAF V600K and BRAF V600D. The indication sought was the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test. This is the first indication dabrafenib is seeking.

#### 2.1.2. Regulatory History

Dabrafenib was studied under IND 105032, which was submitted in June 2009, the applicant met with FDA to discuss their development plan for dabrafenib in July 2010 and June 2011.

In the July 2010 meeting, the applicant proposed Study 113683 as the Phase III study to support the proposed indication, with PFS and OS as co-primary endpoints in 600 patients. On October 7, 2010, FDA held a Type A meeting with GSK to discuss the revised clinical plan. FDA stated that an improvement in PFS of sufficient magnitude may be an appropriate endpoint for the Study BRF113683 provided that an improvement in OS is not demonstrated in a prior approval of another drug in the proposed population. On October, 22, 2010, (b) (4)

The orphan drug exclusivity was granted on January 12, 2011 and fast track was granted on February 11, 2011. The Pre-NDA meeting was held on May 9, 2012.

#### 2.1.3. Study Reviewed

Study 113683 was a randomized, open-label, dacarbazine (DTIC) controlled, multicenter Phase III study of dabrafenib on prolonging PFS in previously untreated patients with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma

Patients were randomized in a 3:1 ratio to receive either oral dabrafenib 150 mg twice daily or intravenous DTIC 1000 mg/m<sup>2</sup> every 3 weeks. Randomization was stratified

based on disease staging at study entry (unresectable III+IVM1a+IVb vs. IVM1c). Study treatment continued until disease progression, unacceptable toxicity, death, or withdrawal from the study. The study also included an optional crossover arm to transition patients from DTIC to dabrafenib.

The primary objective of this study was to compare the treatment effect of dabrafenib with DTIC on prolonging progression-free survival (PFS) in patients with advanced or metastatic (unresectable stage III or Stage IV) BRAF V600 mutation-positive melanoma. However only BRAF V600E mutation-positive patients were supposed to be included in this trial according the inclusion criteria The secondary objectives were to compare the treatment effect of dabrafenib with DTIC on overall survival (OS), objective response rate (ORR), duration of response (DoR) and to assess the safety and tolerability of dabrafenib compared with DTIC.

## 2.2 Data Sources

Due to the data quality issue discovered during the review process, Data from multiple submissions were used for review is from the electronic submission received from July 30, 2012 to April 5, 2013. The network paths for these submissions are:

- \\Cdsesub1\evsprod\NDA202806\0003;
- \\Cdsesub1\evsprod\NDA204114\0014;
- \\Cdsesub1\evsprod\NDA204114\0023;
- \\Cdsesub1\evsprod\NDA204114\0042;
- \\Cdsesub1\evsprod\NDA204114\0050; and
- \\Cdsesub1\evsprod\NDA204114\0054.

### 3. STATISTICAL EVALUATION

#### 3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted as well as the related SAS programs for analysis.

The quality of the original data submission was not optimal.

Data quality related issues were identified throughout the review process. Problems included poor data organization and management, missing data variables, data sets and documents, un-executable SAS programs, and lack of documentation throughout the whole data submission. During the review, more than 10 formal data quality related information requests were sent to the applicant to request additional data, documentations, and programs. In addition, face to face meetings, telephone-conferences, and emails were used to discuss solutions on ways to conduct a thorough review due to the limitation of the data in the original submission and amendments.

In the original data submission:

1. The applicant did not submit the meeting minutes and reports of the independent data monitoring committee (IDMC).
2. The applicant did not provide functional hyperlinks in the annotated electronic case report form (e-CRF).
3. A few datasets were missing. The data set *ronccom* was on purposely not submitted because ‘it had very few records’.
4. The applicant manipulated the data. For example, one sort key was deleted in the analysis data set because ‘the values of this variable were all equal to 1’.
5. Issues related to the datasets include:
  - a. The raw/derived data sets were not submitted as separated data files. The raw data were embedded within the derived datasets. Some of the raw and derived variable/data set used the same variable/data name.
  - b. The primary efficacy data was in the long format, which needed extra data manipulation to conduct efficacy analysis.
  - c. Some raw datasets were not in SAS transport file format.
  - d. A lot of missing values were captured in the submission without adequate explanation. Many variables were coded as ‘Yes’ or missing, without any information on what the missing meant.
  - e. The applicant did not provide a separate data with complete demographic, baseline characteristics and screening information at subject level. The reviewer had to derive key demographic characteristics variables based on the limited reviewer guide and define file.
  - f. Data format was not consistent. Multiple variables were coded by a mix of numerical values and character values.

- g. In the efficacy analysis datasets for some observations, date of event used imputed date without adequate documentation in the submission.
6. Issues related to the documentation include:
    - a. Overview/user guide for the contents of each data set was not provided.
    - b. Many bookmarks/hyperlinks were incorrect for the contents of data files, derivations of the variables, coding of the variables.
    - c. The columns of comment and label were empty in the key efficacy analysis datasets.
    - d. Some of the data derivations in the comment column were incorrect.
    - e. For some variables, classification did not match what was shown in the code column.
  7. Issues related to the SAS programs include:

The SAS programs provided by the applicant did not have sufficient details and were not executable SAS programs to verify the derivation of the analysis dataset from raw dataset, and the analyses associated with the results presented in the proposed package insert.

The applicant's responses to the information requests were disappointing. In many cases the responses were inadequate, and the timelines for submission were not met. For example, the applicant once responded an information request with only a cover letter stating that the required information will be submitted. The information request sent in September was not completely responded until late November and finally the reviewers still found the November submission did not correct the data as requested and discussed in face-to-face meetings.

After all the information requests and meetings, with multiple rounds of resubmissions of data, some problems remain unsolved and unaddressed.

1. Raw datasets still contained derived data and IRC external data. The applicant stated that the external data were provided by IRC. All of the response data sets contained derived data and external data. The applicant can not provide sufficient documentation to support the external data.
2. Multiple variables were still coded by a mix of numerical values and character values. The datasets submitted on Nov, 2012 were not useful.
3. Documentation for data was still inadequate. In the response to FDA's information request dated 11/02/2012, the applicant stated that "GSK has conducted a full quality check of the Define Files in the NDA as well as updated the by-patient datasets to include the additional requested variables. We have identified a small number of minor errors in the Define files (mostly resulting from transcription). While GSK regrets the existence of errors in the Define files, these do not impact the programs, the datasets used by the programs and the analyses." However, throughout the whole database many variables lacked of comments and explanation. For example, dataset RRESP2E1 contained best overall response per independent oncologist assessments and most of its variables were simply coded as 'EXTERNAL DATA' without any explanation on the meaning of the variables. Similar cases were captured in many other datasets.

**Figure 1. Snapshot of the GSK define file**

Study brf113683 - rresp2e1(IRC Best overall response)				
Variable	Type	Label	Codes	Comments
STUDYID	Char	Unique identifier for the study		EXTERNAL DATA: Data provided by external vendor
USUBJID	Char	Unique subject ID		DERIVED DATA: STUDYID '.' SUBJID
SUBJID	Num	Subject ID		EXTERNAL DATA: Data provided by external vendor <a href="#">blankorf, Page 6</a>
ACQUAL	Char	Clinical, radiologic data quality acpt?	N=No U=Unknown X=Not applicable Y=Yes Z=Not done	EXTERNAL DATA: Data provided by external vendor
CLIMPACT	Char	Clinical info impact the radiologic asmt	N=No U=Unknown X=Not applicable Y=Yes Z=Not done	EXTERNAL DATA: Data provided by external vendor
RDTYPECD	Char	Read type code	11=1st production read 12=2nd production read	EXTERNAL DATA: Data provided by external vendor
REVID	Char	Reviewer ID		EXTERNAL DATA: Data provided by external vendor
VISIT	Char	Visit description		EXTERNAL DATA: Data provided by external vendor
VISITNUM	Num	Visit sequence number		EXTERNAL DATA: Data provided by external vendor
ONSRCCD	Char	Oncology assessment source code	1=Investigator 2=Independent radiologist 3=Independent Oncologist	EXTERNAL DATA: Data provided by external vendor
ONTYPECD	Char	Oncology criteria type code	11=RECIST 1.1	EXTERNAL DATA: Data provided by external vendor
PROGDT	Date	Date of progression		EXTERNAL DATA: Data provided by external vendor
ONVENDCD	Char	Oncology independent review vendor code	3=Perceptive	EXTERNAL DATA: Data provided by external vendor

4. Some of information requests were never addressed.
  - a. For example, a full list of decoding for visit numbers was not submitted as FDA requested. The reviewer had to do one to one tabulation to understand the meaning of visit number, which was time consuming and labor intensive.
  - b. Similar situations were observed for many other variables throughout this submission.
  - c. Most of the missing values remain missing. According to the applicant, the CRF was not designed to capture any information other than “yes” for many categorical data variables. The missing can be “no”, “not-evaluable”, “unknown” or true missing.
5. Most SAS programs submitted were not usable. For example, in the tumor assessment derivation program, more than 10 SAS macros were called in loops. None of the macros contained documentation/comments to help understanding the logic and algorithms involved.

These problems caused inefficient review of this NDA. Significant amount of time was wasted waiting for responses from the applicant, manually cleaning the data and searching for documentation in the submission. With insufficient documentations and poor data quality, this reviewer could not duplicate data derivations and analysis. The applicant withdrew the priority review request voluntarily. The review clock had to be extended from 6 months to 10 months.

The key efficacy data and analysis had to be re-derived from raw data. The applicant agreed to use FDA reviewer’s algorithm to derive the primary analysis data based on RECIST 1.1

criteria based on raw-lesion data. In addition, the last set of required data was submitted on April. 4, 2013, which resulted in review completion later than the due date according to the PDUFA calendar.

## **3.2 Evaluation of Efficacy**

### **3.2.1. Study Design and Endpoints**

Study 113683 was a randomized, open-label, DTIC controlled, multicenter Phase III study of dabrafenib on prolonging PFS in previously untreated patients with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma.

Patients were randomized in a 3:1 ratio to receive either oral dabrafenib 150 mg twice daily or intravenous DTIC 1000 mg/m<sup>2</sup> every 3 weeks. Randomization was stratified based on disease staging at study entry (unresectable III+IVM1a+IVb vs. IVM1c). Study treatment continued until disease progression, unacceptable toxicity, death, or withdrawal from the study. Patients randomized to DTIC may elect to cross over to treatment with dabrafenib after progression; these patients will have a crossover treatment period and receive dabrafenib until disease progression or unacceptable toxicity.

The primary objective of this study was to compare the treatment effect of dabrafenib with DTIC on prolonging progression-free survival (PFS) in patients with advanced or metastatic (unresectable stage III or Stage IV) BRAF V600 mutation-positive melanoma. However only BRAF V600E mutation-positive patients were included in the trial according the inclusion criteria The secondary objectives were to compare the treatment effect of dabrafenib with DTIC on overall survival (OS), objective response rate (ORR), duration of response (DoR) and to assess the safety and tolerability of dabrafenib compared with DTIC.

No interim efficacy analyses are planned for this study. An independent data monitoring committee (IDMC) conducted routine reviews of safety data.

#### **Reviewer's Comments:**

In Section 8.2.1 of the statistical analysis plan it was stated that “Subjects will be stratified according to the actual data recorded in the e-CRF if this differs for the classification reported at the time of randomization.” This reviewer conducted analyses based on stratum in the e-CRF and on stratum at randomization.

### **3.2.2. Efficacy Measures**

In the applicant's analysis plan the primary endpoint was investigator assessed PFS defined as the time from randomization until the first date of either objective disease progression or death due to any cause. Post-baseline response evaluations were made at Week 6, Week 12, Week 21, Week 30, Week 39, Week 48, and every 12 weeks thereafter.

In general the applicant’s analysis plan followed the FDA’s Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

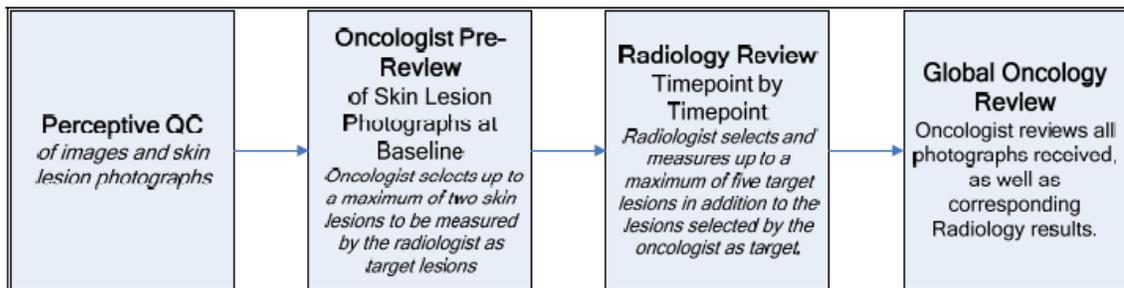
The applicant’s data analysis plan included imputation of data for patients who received subsequent anti-cancer therapy. Specifically, if the start date of the anti-cancer therapy is partial (i.e. either missing the day but has the month and year available),

- If partial date falls in the same month as the last dose of study treatment (either randomized therapy or crossover therapy as appropriate), then assign to earlier of (date of last dose of study treatment+1, last day of month).
- If partial date falls in the same month as the subject’s last assessment and the subject’s last assessment is progressive disease (PD), then assign to earlier of (date of PD+1, last day of month).
- If both rules above apply, then assign to latest of the 2 dates.
- Otherwise, impute missing day to the first of the month.

PFS was also assessed by an independent review committee (IRC). According to the IRC Charter, The independent review will be composed of two sequential stages of review: 1.) the Independent Radiology Review, a central blinded assessment of medical imaging data by one qualified radiologist; and 2.) the Independent Oncology Review, in which one independent qualified oncologist will assess the skin lesion photographs in addition to the independent radiology findings to make a final determination for the case, if applicable.

For the independent review, the primary radiologist will assess study imaging to determine overall radiographic tumor response at each time point using modified RECIST 1.1. If applicable, the radiologist will include target skin lesions in the time point assessments. The oncologist will assess any additional skin lesions and determine relevant endpoints based on a combined assessment of radiologic and skin lesions. The following figure summarizes the review procedure.

**Figure 2. IRC Paradigm**



Source: Section 7.1 of IRC charter for BRF113683 (P18 of 50)

For the secondary endpoints, OS was defined as the time from randomization to death by any cause. For patients who had not died, duration of survival was censored at the date the patient was last known to be alive. The OS included all deaths, including those following crossover. Survival follow-up will continue until 70% of the total number of

randomized patients have died or otherwise been lost to follow-up. The OS included all deaths including those who crossed over to dabrafenib.

Overall response rate (ORR) is defined as the percentage of patients achieving either a CR or PR per RECIST 1.1. The ORR will be calculated from both the investigator's and the IR's assessment of response and will be based on confirmed and unconfirmed responses.

DoR was defined as the time from first documented evidence of CR or PR until first documented disease progression or death due to any cause.

Reviewer's Comments:

1. This reviewer does not agree that the investigator assessed PFS stratified by the stratum recorded on the CRF should be considered as the primary endpoint of the study. Instead, in this review, PFS stratified by the stratum at randomization is considered as the primary endpoint. Analyses based on PFS assessed by IRC independent radiologist (IR), and by IRC independent radiologist (IR) plus independent oncologist (IO) are also performed. The IO assessments included additional information concerning skin lesions that the IR did not have—i.e., non-target disease of the skin, measurements from subcutaneous disease. However the data quality of the IO assessments was not optimal.
2. In the applicant's analysis plan an adequate assessment was defined as an assessment at which the investigator-determined response is CR, PR, or SD. Therefore, PFS would be censored at the last adequate assessment prior to IRC determined PD, death, new anti-cancer therapy, or two consecutive missing tumor assessments; and the non-measurable lesion assessments were excluded from the analyses.
3. The date of new anti-cancer therapy impacts the results of the primary analysis. It was not acceptable to impute data related to primary analysis. The date of new anti-cancer therapy was submitted under derived dataset RESP2 (best overall response per INV assessment). Due to inadequate documentation of the program and data files, it is not clear if the imputation was implemented according to the analysis plan. However, only one patient used imputed date. Thus the results should be not drastically shifted due to imputation and the dates of anti-cancer therapy as the imputed date were used in the FDA's analysis.
4. Similar to PFS, in this review ORR and DoR assessed by the IRC are reported.

### **3.2.3. Sample Size Consideration**

A total of 200 patients were planned for this study. Assuming the hazard ratio of dabrafenib versus DTIC is 0.33, a median PFS of 2 months for the DTIC arm and 6 months for the dabrafenib arm, 102 events will provide approximately 99.7% power at a significance level of 0.02 using a 1-sided log-rank test.

No interim efficacy analyses are planned for this study.

A total of 250 patients were centrally randomized with 187 in the dabrafenib arm and 63 in the DTIC arm.

Reviewer's Comments:

Despite the over powered design for PFS on the ITT population, this study enrolled 50 more patients than the pre-specified number of patients and had more PFS events than the required number of events.

### **3.2.4. Statistical Methodologies**

The Intent-to-Treat (ITT) population was used for the efficacy analysis. The ITT population comprises all randomized patients regardless of whether or not treatment was administered.

Both PFS and OS were summarized using the Kaplan-Meier estimates and the difference between the two treatment arms was tested using a stratified log-rank test, stratifying for disease stage at screening (unresectable III+IVM1a+IVM1b vs. IVM1c). The hazard ratio (HR) was estimated by the Pike estimator.

ORR was tested between the two treatment arms using a Fisher's exact test. Exact 95% confidence intervals (CIs) for ORR in each arm and the difference between the two arms were calculated. The applicant's analysis plan also stated that, if sample size permits, the median duration of response will be calculated from the Kaplan-Meier estimates.

For the secondary endpoints, a statistical procedure to adjust multiple endpoints was not proposed.

Reviewer's Comments:

1. Since SAP does not propose a multiplicity adjustment, the secondary endpoints and subgroup analyses were considered as exploratory.
2. The DOR analysis is limited to responders. Therefore regardless of the sample size no comparison can be made to the responder analysis.

### **3.2.5. Patient Disposition, Demographic and Baseline Characteristics**

A total of 250 patients were randomized to one of two treatment arms using a 3:1 randomization ratio with 187 patients in the dabrafenib arm and 63 patients in the DTIC arm. A total of 70 study centers enrolled patients in 12 countries across Europe (184 [73.6%] patients; 9 countries), North America (50 [20%] patients; 2 countries), and Australia (16 [6.4%] patients).

The study was initiated on February 2, 2011 and primary analysis data cut-off date was December 19, 2011. The median (range) time on study was 5.06 (0.0, 9.9) and 4.83 (0.0, 9.3) months for the dabrafenib and DTIC groups, respectively.

As of the primary analysis cut-off date, 43% and 73% of patients in the dabrafenib and DTIC arms, respectively, had discontinued investigational product. Twenty-eight patients randomized to DTIC received dabrafenib in the crossover phase, and 21 patients (75%) were continuing study treatment. The patient disposition is summarized in Table 1.

**Table 1. Patient Disposition**

	<b>Dabrafenib</b>	<b>DTIC</b>
	N (%)	N (%)
<b>Randomized</b>	187 (100)	63 (100)
<b>Ongoing randomized treatment</b>	106 (57)	14 (22)
<b>Discontinued randomized treatment</b>	80 (43)	46 (73)
<b>Disease Progression</b>	66 (35)	43 (68)
<b>Adverse Events</b>	5 (3)	0
<b>Investigator Discretion</b>	4 (2)	2 (3)
<b>Decision by subject or proxy</b>	5 (3)	1 (2)
<b>Never received randomized treatment</b>	1 (0.5)	3 (5)
<b>Death</b>	21 (11)	9 (14)
<b>In Follow-up</b>	54 (29)	14 (22)
<b>Withdrawn from study</b>	6 (3)	5 (8)
<b>Lost to follow-up</b>	2 (1)	1 (2)
<b>Investigator Discretion</b>	2 (1)	1 (2)
<b>Withdrew consent</b>	2 (1)	3 (5)
<b>Crossover</b>	NA	21 (33)

Demographic characteristics at baseline are summarized in Table 2.

**Table 2 Demographics at Baseline**

	<b>Dabrafenib</b>	<b>DTIC</b>
	N (%)	N (%)
<b>Randomized</b>	187 (100)	63 (100)
<b>Gender</b>		
<b>Male</b>	112 (60)	37 (59)
<b>Female</b>	75 (40)	26 (41)
<b>Race</b>		
<b>Caucasian</b>	184 (98)	63 (100)
<b>Non-Caucasian</b>	3 (2)	0
<b>Age</b>		
<b>&lt; 65</b>	146 (78)	51 (81)
<b>≥ 65</b>	41 (22)	12 (19)
<b>Region</b>		
<b>Europe</b>	140 (75)	44 (70)
<b>North American</b>	36 (19)	14 (22)
<b>Australia</b>	11 (6)	5 (8)

Disease characteristics at baseline are summarized in Table 3.

**Table 3. Disease characteristics at baseline**

	<b>Dabrafenib</b>	<b>DTIC</b>
	N (%)	N (%)
<b>Randomized</b>	187 (100)	63 (100)
<b>ECOG Status at Baseline</b>		
<b>0</b>	124 (66)	44 (70)
<b>1</b>	62 (33)	16 (25)
<b>Missing</b>	1 (0.5)	3 (5)
<b>Stratum at Randomization: Disease Staging</b>		
<b>Unresectable III+IVM1a+IVb</b>	63 (34)	21 (33)
<b>IVM1c</b>	124 (66)	42 (67)
<b>Stratum per e-CRF: Disease Staging</b>		
<b>Unresectable III+IVM1a+IVb</b>	63 (34)	23 (37)
<b>IVM1c</b>	124 (66)	40 (63)
<b>Baseline LDH</b>		
<b>Above ULN</b>	66 (35)	17 (27)
<b>Equal to or below ULN</b>	116 (62)	40 (63)
<b>Missing</b>	5 (3)	6 (10)
<b>Visceral disease</b>		
<b>Visceral</b>	22 (12)	8 (13)
<b>Non-visceral</b>	50 (27)	20 (32)
<b>Visceral and non-visceral</b>	115 (61)	35 (56)
<b>Number of disease sites</b>		
<b>&lt; 3</b>	94 (50)	35 (56)
<b>≥ 3</b>	93 (50)	28 (44)
<b>Tumor classification at Initial Diagnosis</b>		
<b>Cutaneous</b>	165 (88)	56 (89)
<b>Non-cutaneous</b>	6 (3)	2 (3)
<b>Other</b>	3 (2)	0
<b>Unknown</b>	13 (7)	5 (8)
<b>Prior radiotherapy</b>		
<b>Yes</b>	37 (20)	10 (16)
<b>Missing</b>	150 (80)	53 (84)
<b>Prior chemotherapy</b>		
<b>Yes</b>	55 (29)	19 (30)
<b>Missing</b>	132 (71)	44 (70)
<b>Prior cancer related surgery</b>		
<b>Yes</b>	179 (96)	61 (97)
<b>Missing</b>	8 (4)	2 (3)

The inclusion criteria indicated that only patients with BRF600E mutation were supposed to be enrolled in this study. However there were 2 patients with BRF600K mutation, with 1 in each arm, were present in the ITT population.

Reviewer’s comments:

1. The demographic and baseline characteristics of the ITT population are generally balanced over the two arms.
2. The variables “prior radiotherapy”, “prior chemotherapy”, and “prior cancer related surgery” did not contain information of patients who did not have prior therapies. These are due to the missing data problem of the data submission.
3. There are total of 40 (16%) patients have mismatched stratum, disease staging, between the randomization and e-CRF.

	<b>Unresectable III+IVM1a+IVb per e-CRF</b>	<b>IVM1c per e-CRF</b>
<b>Unresectable III+IVM1a+IVb at randomization</b>	65	19
<b>IVM1c at randomization</b>	21	145

4. The 2 patients with BRF V600K mutation were considered to protocol violations.

**3.2.6. Results and Conclusions**

**Primary Endpoint Analysis: PFS**

There were a total of 119 patients who progressed or died at time of the primary analysis, of which 78 were in the dabrafenib arm and 41 in the DTIC arm. Of these events, 76 (97% of 78) in the dabrafenib arm and 41 (100% of 41) in the DTIC arm were progressive diseases; 2 (3% of 78) in the dabrafenib arm and none in the DTIC arm were deaths.

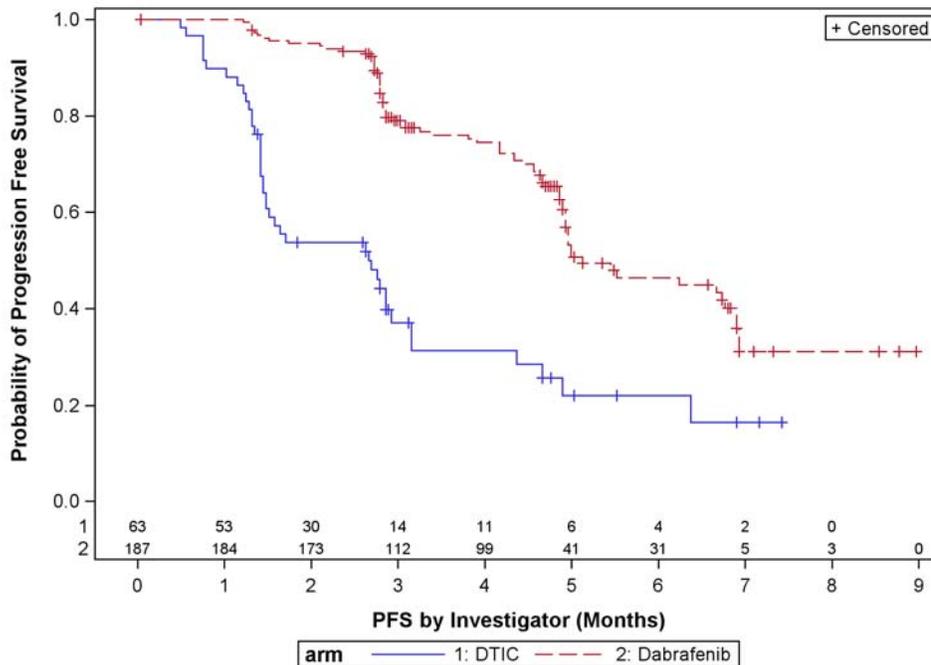
Table 4 summarizes the main efficacy analysis results for PFS assess by investigator. PFS in the dabrafenib arm was longer than that of the DTIC arm with p-value <0.001 (1-sided). The median PFS was 5.1 months for the dabrafenib arm and 2.7 months for the DTIC arm. The estimated HR was 0.33 with 95% CI (0.20, 0.55) based on a Pike estimator stratified by disease staging at randomization.

**Table 4. Results of PFS analysis by investigator**

	<b>Dabrafenib</b>	<b>DTIC</b>
	N = 187	N = 63
<b>Number of Events (%)</b>	78 (42)	41 (65)
<b>PD</b>	76	41
<b>Death</b>	2	0
<b>Median PFS (95% CI)</b>	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
<b>p-value (unstratified log-rank)</b>	< 0.001	
<b>HR (95% CI)</b>		
<b>by Cox unstratified</b>	0.31 (0.21, 0.46)	
<b>by Pike unstratified</b>	0.32 (0.19, 0.53)	
<b>by Cox per stratum at randomization</b>	0.32 (0.22, 0.47)	
<b>by Pike per stratum at randomization</b>	0.33 (0.20, 0.55)	
<b>by Cox per stratum on e-CRF</b>	0.30 (0.20, 0.44)	
<b>by Pike per stratum on e-CRF</b>	0.31 (0.18, 0.52)	

Figure 3 shows the estimated Kaplan-Meier curves for the distribution of PFS assessed by investigator.

**Figure 3. K-M Curves of PFS by investigator**



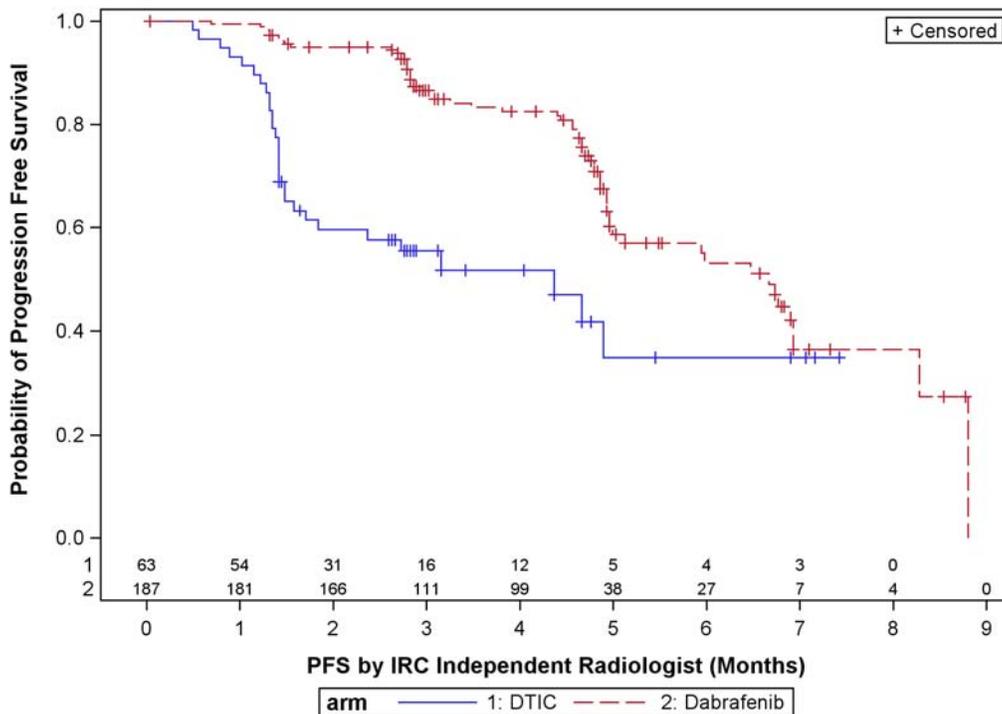
Results of PFS analyses reported by IRC IR are summarized in Table 5.

**Table 5. Results of PFS analysis by IRC IR**

	<b>Dabrafenib</b>	<b>DTIC</b>
	N = 187	N = 63
<b>Number of Events (%)</b>	61 (33)	29 (46)
<b>PD</b>	56	29
<b>Death</b>	5	0
<b>Median PFS (95% CI)</b>	6.7 (5.0, 6.9)	4.4 (1.6, NE)
<b>p-value (unstratified log-rank)</b>	< 0.001	
<b>HR (95% CI)</b>		
<b>by Cox unstratified</b>	0.35 (0.22, 0.55)	
<b>by Pike unstratified</b>	0.36 (0.20, 0.65)	
<b>by Cox per stratum at randomization</b>	0.35 (0.22, 0.54)	
<b>by Pike per stratum at randomization</b>	0.36 (0.20, 0.65)	
<b>by Cox per stratum on e-CRF</b>	0.32 (0.20, 0.51)	
<b>by Pike per stratum on e-CRF</b>	0.34 (0.19, 0.62)	

Figure 4 shows the estimated Kaplan-Meier curves for the distribution of PFS assessed by IRC IR.

**Figure 4. K-M Curves of PFS by IRC IR**



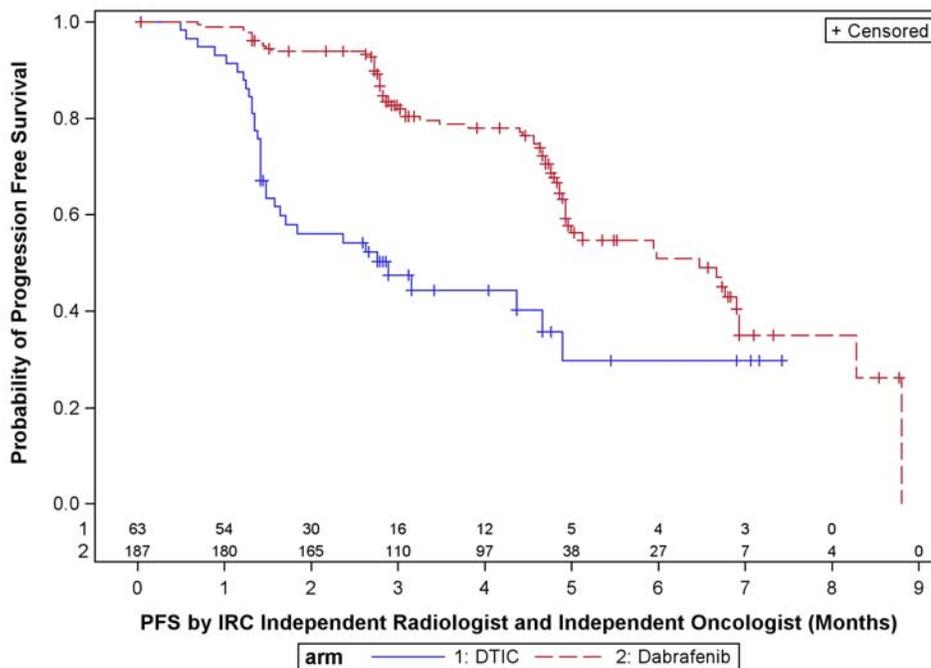
Results of PFS analyses based on IRC independent radiologist (IR) and independent oncologist (IO) are summarized in Table 6.

**Table 6. Results of PFS analysis by IRC IR and IO**

	<b>Dabrafenib</b>	<b>DTIC</b>
	N = 187	N = 63
<b>Number of Events (%)</b>	68 (36)	33 (52)
<b>PD</b>	63	33
<b>Death</b>	5	0
<b>Median PFS (95% CI)</b>	6.5 (4.9, 6.9)	2.9 (1.5, 4.9)
<b>p-value (unstratified log-rank)</b>	< 0.001	
<b>HR (95% CI)</b>		
<b>by Cox unstratified</b>	0.35 (0.23, 0.53)	
<b>by Pike unstratified</b>	0.36 (0.21, 0.62)	
<b>by Cox per stratum at randomization</b>	0.35 (0.23, 0.53)	
<b>by Pike per stratum at randomization</b>	0.36 (0.21, 0.62)	
<b>by Cox per stratum on e-CRF</b>	0.32 (0.21, 0.50)	
<b>by Pike per stratum on e-CRF</b>	0.34 (0.19, 0.59)	

Figure 5 shows the estimated Kaplan-Meier curves for the distribution of PFS assessed by IRC IR and IO.

**Figure 5. K-M Curves of PFS by IRC IR and IO**



Reviewer's comments:

1. As discussed in Section 3.2.5, sixteen percent of the stratum information was misclassified. In the applicant's analysis plan the primary and secondary efficacy analyses were based on stratum information per e-CRF. The magnitude of the discrepancies between the stratum information captured at randomization and on e-CRF made the reliability of the data for the stratification factor, disease staging, questionable. This reviewer recommends the analysis based on stratum information at randomization analysis be considered as primary and secondary efficacy analyses. The unstratified analyses were also conducted to check the robustness of the results.
2. The analyses results reported in this review differ from those in the CSR submitted. In the original submission, PFS analysis data was derived based on response data. The applicant did not provide sufficient documentation and executable SAS program to validate the derivation of the response data from raw lesion data. Therefore this reviewer proposed and re-derived PFS data based on raw lesion data according to RECIST criteria 1.1. The applicant agreed with this proposal and the algorithm developed by this reviewer. The results reported above are calculated from the PFS data derived from raw lesion data.
3. Similar to the analysis data of PFS by investigator, in the original submission the analysis data for PFS by IRC was derived based on response dates and assessments provided by IRC. These data were marked as external data in the raw database and did not have sufficient documentation for justification and validation. Two versions of analysis data for PFS by IRC were re-derived based on raw lesion data by IRC, with one based on IR assessment only and the other based on IR and IO assessments.
4. The difference between the IRC IR and IO was briefly discussed in Section 3.2.2. For more details please refer to the clinical review of this NDA. The IO evaluated PD were recorded in dataset RRESP2E1 without documentation (see Appendix 1). The applicant could not provide documentations on the meaning of variables and values in this dataset. In this reviewer's opinion, the IO assessment could be unreliable due to the uncertainties caused by the data quality.
5. The estimated HR from the three sets of PFS data, based on assessments of IRC IR, IRC IR and IO, and investigators were similar. The medians of PFS differed among the three sets of data.
6. The reviewer conducted various sensitivity analyses to check the robustness of the primary analysis results. The results are consistent with the primary analysis results.
7. Additional sensitivity analyses were also performed on certain subgroups. Please refer to Section 4.2 for results of the subgroup analyses.
8. Sensitivity analyses of PFS using different censoring rules ( $p\text{-value} < 0.0001$ ) were similar to the results reported above.
9. Patterns of time to IRC IR tumor assessment were examined. The data did not show statistically significant difference in the time to scheduled visits between treatment arms.

## **Secondary Endpoints Analyses: OS, ORR and DoR**

### **OS Analysis**

The analysis for OS included data throughout the study including the randomized phase and crossover phase.

There were a total of 30 patients who had died at time of the primary analysis, of which 21 were in the dabrafenib arm and 9 in the DTIC arm.

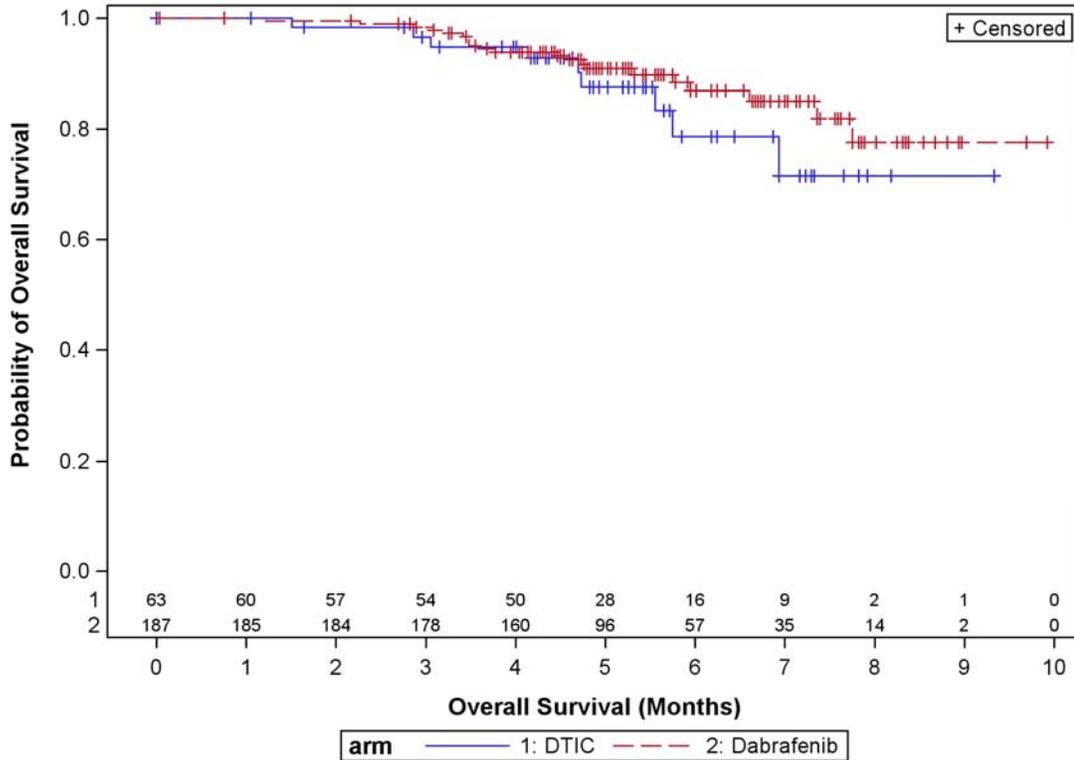
Table 7 summarizes the main efficacy analysis results for OS. OS in the dabrafenib arm was similar to that of the DTIC arm with p-value 0.31 (2-sided). The median OS was not estimable due to small number of deaths observed in neither dabrafenib arm nor DTIC arm. The estimated HR was 0.67 with 95% CI (0.28, 1.58) by the unstratified Pike estimator.

**Table 7. Results of OS analysis**

	<b>Dabrafenib</b>	<b>DTIC</b>
	N = 187	N = 63
<b>Number of Deaths (%)</b>	21 (11)	9 (14)
<b>Median OS (95% CI)</b>	NE (6.9, NE)	NE (NE, NE)
<b>p-value (unstratified log-rank)</b>		0.31
<b>HR (95% CI)</b>		
<b>by Cox unstratified</b>		0.67 (0.31, 1.46)
<b>by Pike unstratified</b>		0.67 (0.28, 1.58)
<b>by Cox per stratum at randomization</b>		0.69 (0.32, 1.51)
<b>by Pike per stratum at randomization</b>		0.69 (0.29, 1.62)
<b>by Cox per stratum on e-CRF</b>		0.61 (0.28, 1.34)
<b>by Pike per stratum on e-CRF</b>		0.61 (0.25, 1.47)

Figure 6 shows the estimated Kaplan-Meier curves for the distribution of OS.

**Figure 6. K-M Curves of OS**



Reviewer's comments:

The results from the OS analysis were not statistically significant due to the small number of deaths.

## ORR and DoR Analysis

Table 8 summarizes the results of the ORR and DoR analyses.

**Table 8. Results of ORR and DoR analyses**

	Investigator		IRC IR		IRC IR and IO	
	Dabrafenib N = 187	DTIC N =63	Dabrafenib N = 187	DTIC N =63	Dabrafenib N = 187	DTIC N =63
<b>ORR</b>	97 (52%)	11 (17%)	92 (49%)	5 (8%)	91 (49%)	5 (8%)
<b>95% CI</b>	(45%, 59%)	(9%, 29%)	(42%, 57%)	(3%, 18%)	(41%, 56%)	(3%, 18%)
<b>CR (%)</b>	6 (3%)	0	6 (3%)	2 (3%)	6 (3%)	2 (3%)
<b>PR (%)</b>	91 (49%)	11 (17%)	86 (46%)	3 (5%)	85 (45%)	3 (5%)
<b>ORR Diff.</b>	34%		41%		41%	
<b>95% CI</b>	(20%, 48%)		(28%, 55%)		(27%, 54%)	
<b>Median DoR (95%CI)</b>	5.6 (5.4, NE)	NE (5.0, NE)	5.6 (5.0, 6.9)	NE	5.6 (5.0, 6.9)	NE

### Reviewer's comments:

1. The ORR and DoR results are considered exploratory.
2. The analyses results reported in this review differ from those in the CSR submitted. Similar to PFS, the analysis data sets for ORR and DoR were re-derived based on raw lesion data according to RECIST criteria 1.1.

### **3.3 Evaluation of Safety**

Please refer to the clinical review of this application for details of the safety evaluation. The following results are adapted from the clinical review of this application by Dr. Marc Theoret.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

As discussed in Section 3, there were discrepancies between the stratum information captured at randomization and on e-CRF. For all the subgroup analyses reported in this section, the stratified analyses are based on the stratum information at randomization.

Since 98% of the patients in the dabrafenib arm and 100% of the patients in the DTIC arm were Caucasians, the subgroup analysis on race is not performed.

Table 9 summarizes the subgroup analysis of PFS by investigator assessments.

**Table 9. Subgroup analysis of PFS by investigator**

Subgroups	events/n		median		HR by Pike	HR by Cox
	Dabrafenib	DTIC	Dabrafenib	DTIC		
<b>Male</b>	53/112	25/37	5.1	2.8	0.31 (0.16 , 0.60 )	0.28 (0.17, 0.47)
<b>Female</b>	25/75	16/ 26	5	2.6	0.34 (0.15 , 0.76 )	0.33 (0.17, 0.63)
<b>Age&lt;65</b>	67/146	34/51	5	2.6	0.32 (0.18 , 0.57 )	0.31 (0.20, 0.47)
<b>Age ≥ 65</b>	11/41	7/12	NE	4.9	0.50 (0.17 , 1.47 )	0.40 (0.14, 1.16)
<b>Europe</b>	62/140	29/44	5	2.7	0.35 (0.19 , 0.63 )	0.34 (0.22, 0.53)
<b>N America</b>	11/36	8/14	6.8	3.2	0.31 (0.10 , 0.99 )	0.28 (0.11, 0.74)
<b>Australia</b>	5/11	4/5	6.9	1.1	0.21 (0.03 , 1.36 )	0.15 (0.03, 0.72)

Table 10 summarizes the subgroup analysis of PFS by IRC IR assessments.

**Table 10. Subgroup analysis of PFS by IRC IR**

Subgroups	events/n		median		HR by Pike	HR by Cox
	Dabrafenib	DTIC	Dabrafenib	DTIC		
<b>Male</b>	39/112	16/37	6.8	4.4	0.33 (0.15 , 0.75 )	0.30 (0.16, 0.56)
<b>Female</b>	22/75	13/26	6.5	1.8	0.38 (0.16 , 0.90 )	0.36 (0.18, 0.73)
<b>Age&lt;65</b>	51/146	23/51	6.5	4.4	0.35 (0.18 , 0.67 )	0.32 (0.19, 0.54)
<b>Age ≥ 65</b>	10/41	6/12	NE	4.9	0.37 (0.11 , 1.33 )	0.35 (0.12, 1.01)
<b>Europe</b>	49/140	18/44	6	4.4	0.41 (0.20 , 0.84 )	0.40 (0.23, 0.70)
<b>N America</b>	8/36	7/14	NE	3.2	0.29 (0.08 , 1.01 )	0.26 (0.09, 0.75)
<b>Australia</b>	4/11	4/5	6.9	1.2	0.16 (0.02 , 1.20 )	0.06 (0.01, 0.57)

Table 11 summarizes the subgroup analysis of PFS by IRC IR and IO assessments.

**Table 11. Subgroup analysis of PFS by IRC IR and IO**

Subgroups	events/n		median		HR by Pike	HR by Cox
	Dabrafenib	DTIC	Dabrafenib	DTIC		
<b>Male</b>	43/112	17/37	6.7	4.4	0.36 (0.17 , 0.78 )	0.33 (0.18, 0.60)
<b>Female</b>	25/75	16/26	6.5	1.8	0.35 (0.16 , 0.77 )	0.33 (0.17, 0.63)
<b>Age&lt;65</b>	56/146	27/51	6	2.8	0.33 (0.18 , 0.62 )	0.31 (0.19, 0.50)
<b>Age ≥ 65</b>	12/41	6/12	6.9	4.9	0.43 (0.13 , 1.45 )	0.41 (0.15, 1.13)
<b>Europe</b>	55/140	21/44	5.1	2.9	0.41 (0.22 , 0.80 )	0.40 (0.24, 0.67)
<b>N America</b>	9/36	8/14	NE	3.2	0.29 (0.09 , 0.93 )	0.26 (0.10, 0.71)
<b>Australia</b>	4/11	4/5	6.9	1.2	0.16 (0.02 , 1.20 )	0.06 (0.01, 0.57)

*Reviewer's comments:*

The analyses showed that the analysis results for subgroups of PFS were consistent with the primary analysis defined in the protocol. Overall, female patients performed worse in the control arm, younger patients performed better than older ones, and patients from North America and Australia performed better than patients from Europe. These analyses are exploratory.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The major statistical issues of this application are related to the data quality problem of the original submission. The problem resulted in multiple rounds of submission for amendments of the data and analyses results, and the final efficacy analyses were completely different in terms of data derivation and testing procedure. In the original submission, the analysis data were derived based on response data, and the efficacy analysis were based on investigator assessments using stratified test and models to compute p-value and estimates for HRs. The stratum information used in the analysis was based on e-CRF instead of stratum information captured at randomization. In this review, and agreed by the applicant, the analysis data were derived based on raw lesion data according to RECIST criteria 1.1, and the efficacy analysis were based on stratification factor captured at randomization.

The original submission contained datasets that are mixture of raw and derived data, inadequate documentation, missing datasets and variables, un-executable SAS programs. Enormous amount of time were spent to sort through problems, data cleaning, communicating with the applicant, searching for necessary documents, and re-write the complete data derivation SAS program.

Based on the current data and analysis results, dabrafenib prolonged PFS compared with dacarbazine (DTIC). Based on the investigator assessments, the median PFS was 5.1 months in the dabrafenib arm compared with 2.7 months in the dacarbazine arm. The estimated hazard ratio (HR) by a stratified Pike estimator was 0.33 with 95% confidence interval (CI) (0.20, 0.55). The p-value from the stratified log-rank test was less than 0.001. The results of PFS assessed by IRC IR and IRC IR and IO were similar.

There is no difference in OS between dabrafenib and dacarbazine. With a total of 30 deaths, the median survivals in the two study arms were not estimable. The estimated hazard ratio (HR) was 0.69 with 95% CI (0.32, 1.51). The p-value from the stratified log-rank test was 0.35. The OS data was not mature and further follow-up is needed to collect more information on OS.

Dabrafenib also showed bigger ORR (52.0%) compared with DTIC (17%) per INV assessments. The ORR difference between the treatment arms was 34% with 95% CI (20%, 48%).

The median DoR was 5.6 months in the dabrafenib arm and was not estimable in the DTIC arm. Further follow up is needed to collect more information on DoR.

### 5.2 Conclusions and Recommendations

Based on the data and analyses, the study results showed that dabrafenib showed a statistically significant improvement in PFS, and bigger ORR, compared with dacarbazine.

Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

### **5.3 Labeling Recommendations**

1. The primary analysis set for the efficacy results are the ITT population.
2. The primary analysis of PFS should use results reported in this review, i.e. analysis using data derived from raw lesion data. The primary analysis for HR should use either stratified analysis based on stratum captured at randomization.
3. The OS results at the final PFS analysis were immature with only 30 (12%) death events. It is recommended not include these preliminary OS results or if reported should be only descriptive.
4. The results of ORR per INV assessments may be included in the label to provide further information on the efficacy of dabrafenib.
5. Because small number of responders had disease progression, DoR cannot be estimated reliably.

## 6. APPENDICESUMMARY AND CONCLUSIONS

### 6.1 Appendix: Summary of Raw Lesion Data and Raw Response Data

The following table summarizes the raw lesion datasets and response datasets submitted. These datasets contain the key data variables for the derivation of the efficacy analysis including PFS and ORR. As discussed in the review, the applicant’s analysis datasets were derived based on the raw response data, while this review used the raw lesion data for the derivation of the analysis datasets. This review does not consider the submitted response data as raw data but external data that lack of necessary documentations.

Dataset Name	Assessment	Definition	Included Information	Comments
Rlesion	INV	lesion	date, longest diameter, lesion location, organ name, scan type	A total of 4752 records for 250 patients.
Rlesioe1	IRC	lesion	date, longest diameter, location, organ name, scan type	A total of 4515 records for 247 patients.
Rresp1	INV	visit response	non-target lesion response, target lesion response type, response assessment type, response index code, all lymph node short axis < 10 mm, sum of lesion diameters, sum of lesion diameter at nadir % change from baseline, % change from nadir, abs change from nadir, new lesion (equivocal: Y/N)	A total of 677 records for 243 patients. This is not a raw data set and it lacks information for derivation of the key variables. Missing documentation on: <ul style="list-style-type: none"> <li>• meaning of nadir</li> <li>• % change from baseline</li> <li>• % change from nadir,</li> <li>• response index code</li> <li>• how to define new lesion based on external data</li> <li>• sum of lesion diameters at nadir</li> </ul>
Rresp1e1	IR	IRC visit response	Non-target lesion response, Target lesion response type, response assessment type, response index code (best vs. other),  Sum of lesion diameters, Sum of lesion diameter at baseline % change from baseline, % change from nadir,  New lesion (equivocal: Y/N)	A total of 961 records for 249 patients. This is not a raw data set and it lacks information for derivation of the key variables. Missing documentation on: <ul style="list-style-type: none"> <li>• meaning of nadir</li> <li>• abs change from nadir</li> <li>• lymph node short axis &lt;10mm</li> <li>• % change from baseline</li> <li>• % change from nadir,</li> <li>• response index code</li> <li>• how to derive PD without abs change</li> </ul>
Rresp2e1	IR and IO	IRC best Overall Response	“read type”, “Clinical info impact the radio. Assessment?”, “response index code, “clinical radiologic data quality acceptable?”, date of progression	A total of 259 records for 247 patients. All variables except subject id were labeled as external data. Missing documentation on every variable except subject id.

## **6.2 Appendix: Data Issue Related Information Requests to the Applicant**

All the data related issues also exists in another NDA 204114 that GSK submitted. The information requests were sent to the applicant for both NDAs. Some of the information requests were listed under one of the NDAs but the requests applied to both NDAs throughout the review process.

16 Pages of information request of the NDA has been removed, a duplicate of these information requests can be found in the Administrative section of the NDA.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 202806**

**Applicant: GSK**

**Stamp Date: 07/30/2012**

**Drug Name:** (b) (4)

**NDA/BLA Type: Original NDA**

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES**

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

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

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