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Title:	Reporting and Analysis Plan – Evaluation of Secondary Malignancies in Patients Treated with Dabrafenib in Randomized, Controlled Trials

Compound Number:	GSK2118436
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Description: This document details the analyses to support an FDA-proposed Clinical Post-Marketing Requirement (PMR) dated May 29, 2013 requesting cumulative safety analyses of new malignancies, including cutaneous squamous cell carcinoma, in all ongoing and subsequently initiated randomized controlled clinical trials through 2020 that use Tafinlar (dabrafenib) capsules alone or in combination with other anti-cancer drugs. There are currently four ongoing randomized, comparative trials that will eventually contribute to these analyses: BRF113683, MEK115306; MEK116513; and BRF115532. The results of BRF113683 were reported in the clinical study report titled 'A Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma' (dated June 2012). The other 3 trials have not reached their primary endpoint analysis as of June 2013. The first Interim Report will contain data from only BRF113683 and be submitted in October 2013; subsequent reports will include data from other included studies.

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ABBREVIATIONS

DSUR	Developmental Safety Update Report
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
IDSL	Integrated Data Standards Library
PMR	Post Marketing Requirement
RAP	Reporting and Analysis Plan

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1. INTRODUCTION

This reporting and analysis plan details the analyses that support an FDA post-marketing requirement (PMR) to further characterize secondary malignancies in subjects treated with dabrafenib, either as monotherapy or in combination with other anti-cancer therapies on randomized controlled clinical trials.

Interim reports will be generated within 6 months of the approval of the new drug application (NDA) and every year thereafter until 2020. The first interim report will be submitted in October 2013 and will only include data from BRF113683. Following the first interim report, analyses will include integrated data from randomized studies of dabrafenib as monotherapy or in combination with other anti-cancer therapies which have reached the study specific primary analysis reporting criteria.

Data from the following phase III randomized studies will be integrated:

- BRF113683, a Phase III study that evaluated efficacy and safety of dabrafenib compared to chemotherapy (dacarbazine/DTIC) in subjects with advanced or metastatic (unresectable stage III or Stage IV) BRAF V600E mutation-positive melanoma, is the first of 4 studies for which results will be analysed and interpreted. The first interim report will include data as of 4 March 2012, the date the last DTIC subject was dosed. Subsequent reports will either include the final study data, if the criteria for study closure (i.e. 70% of subject die or are otherwise lost to follow-up) has been met, or data from the data cut off date for the Developmental Safety Update Report (DSUR).

Beginning in 2014, analyses of cumulative data of studies of dabrafenib in combination with trametinib will be conducted including results from:

- MEK115306 (COMBI-D) in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation positive cutaneous melanoma; double-blinded placebo-controlled; randomized; phase III; trametinib (2mg QD) plus dabrafenib (150 mg BID) vs. Placebo plus dabrafenib (150 mg BID). The data available at the time of the primary analysis will be used for purposes of data integration for the second interim reporting in 2014. Thereafter, data used for the Development Safety Update Report (DSUR) will be included each year until study closure, at which time the final data will be included.
- MEK116513 (COMBI-V) in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation positive cutaneous melanoma; open label; randomized; phase III; trametinib (2mg QD) plus dabrafenib (150 mg BID) versus vemurafenib. Data will not be included in any integration until the study has reached database freeze for the primary endpoint (anticipated for second quarter 2014). At database freeze these data will be integrated. Thereafter, data used for the Development Safety Update Report (DSUR) will be included each year until study closure, at which time the final data will be included.
- BRF115532 (COMBI-AD) in the adjuvant treatment of high risk BRAF V600 mutation-positive melanoma after surgical resection; double-blinded; randomized; phase III; trametinib (2mg QD) plus dabrafenib (150 mg BID) versus two placebos.

Data will not be included in any integration until the study has reached database freeze for the primary endpoint (anticipated for fourth quarter 2015). At database freeze these data will be integrated. Thereafter, data used for the Development Safety Update Report (DSUR) will be included each year until study closure, at which time the final data will be included.

Note: MEK116513 and BRF115532 are event-driven studies, so the timing of database freeze for each is only projected based on the study design and current event rates. If database freeze is achieved prior to the DSUR data cut off date for a given interim and final reporting year, the study will be included in that year's report. The rationale for requiring database freeze prior to the DSUR data cut off date is to allow the time necessary to integrate the data.

Any additional GSK sponsored randomized study of dabrafenib either as monotherapy or in combination with other anti-cancer agents which reaches the primary analysis endpoint during the reporting time period for each interim and final report will also be integrated. The addition of other trials does not require amendments to this RAP unless additional analyses not specified here are required based on study specific data collection or modification in data collection based on evolving experience on currently ongoing studies.

The addition of studies, as specified above, will not require amendments to this RAP unless additional analyses not specified here are required based on study specific data collection or modification in data collection based on evolving experience on currently ongoing studies. All studies included in data integration and analyses will be detailed in the interim and final reports.

2. ANALYSIS OBJECTIVE

The objective of this analysis is to describe more fully the secondary malignancy data from subjects treated with dabrafenib. Cumulative results for each study will be reported separately according to the requested schedule. Data using the DSUR cut-off date for each study will be used.

Interim Report Submission: October 2013 (Will only include analyses of BRF113683 results)
Interim Report Submission: October 2014
Interim Report Submission: October 2015
Interim Report Submission: October 2016
Interim Report Submission: October 2017
Interim Report Submission: October 2018
Interim Report Submission: October 2019
Final Report Submission: October 2020

3. ANALYSIS POPULATION

All analyses will use the Safety population (SAFETY) for each study, which comprises all randomized subjects who received at least one dose of study medication and will be based on the actual treatment received if this differed from that to which the subject was randomized.

4. TREATMENT COMPARISONS

All analyses will be presented by actual treatment arm (e.g., dabrafenib monotherapy, dabrafenib plus trametinib, DTIC). Comparisons will be made within each study, since the comparator arms differ in each of the randomized studies.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All programming will be performed using SAS* version 9.1.3 or greater and S-Plus version 7.0 or higher in a UNIX† environment.

All data analyses and tables, listings, and figures will use the formats in the Integrated Data Standards Library (IDSL), unless there is no standard for a particular analysis. Any non-standard data displays will follow the general format of the IDSL and Therapeutic Standards Team (TST) data displays to the extent possible.

Unless otherwise stated, continuous variables will be summarized with the descriptive statistics mean, median, standard deviation, minimum and maximum, and categorical variables will be summarized with frequency counts and percentages.

Data from all assessments will be included in listings. Summaries of safety data will include data from unscheduled visits only in sections labelled “worst case on-therapy”.

If multiple measurements or evaluations are reported at the same assessment, the worst case rules will apply with the exception of laboratory data reported from both central and local laboratories for a given assessment. In this case, the central laboratory data will be used.

6. DATA HANDLING CONVENTIONS

6.1. Derived and Transformed Data

The following sections describe the derived and transformed variables that will be used to analyze the data. Separate dataset definition tables will provide full details on all data derivations and transformations including descriptions of standard integrated data standards library (IDSL) algorithms and standard Oncology algorithms.

6.2. Common Variables

The following common variables will be added to all analysis and reporting datasets: INVID, CENTREID, USUBJID, AGE, RACE, RACECD, and SEX.

In addition, each dataset will contain variables for the randomized treatment group, the actual treatment group, and the treatment periods (where applicable).

6.3. Actual Treatment

Actual treatment as derived in the primary analysis for each study will be used. For example the rules that were used to derived actual treatment for BRF113683 are:

- If a subject's actual treatment was the same as randomized treatment, then actual treatment is the randomized treatment.
- If a subject received a study treatment that was different from the randomized treatment for the entire time of treatment in the randomized phase, then actual treatment is the different non-randomized treatment.

Similar rules are used in the Phase III combination studies (COMBI-D, COMBI-V, and COMBI-AD).

6.4. Reference Dates

There are two reference dates:

- Because age is an eligibility requirement, the reference date for age is the date of screening.
- The safety reference date is the treatment start date (in the randomized phase for BRF113683), and will be used to calculate study day.

6.5. Study Day for Safety Measures

Study day for safety measures is calculated and stored on the datasets. If the date of interest occurs on or after the safety reference date then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs prior to the safety reference date then the safety study day will be calculated as (date of interest – safety reference date). There will be no safety study day 0. Note: It is possible that the safety study day 1 can be after the randomization day.

6.6. Treatment Periods

For BRF113683:

Pre-therapy is defined for the randomized phase as before the date of the first dose. Measurements from clinical tests or assessments on Day 1 are pre-therapy.

On-therapy for the randomized phase is defined as the date of the first dose until the earliest of 28 days after the last dose of randomized treatment, date of first dose of dabrafenib (*only for subjects randomized to DTIC who received dabrafenib after initial progression*), last contact, or death. If an event occurs on the same date as first dose, then the event will be considered as occurring during the randomized phase.

Post-therapy for the randomized phase is defined as any time beyond the minimum of 28 days post last dose of study treatment until last contact or death for subjects randomized to dabrafenib and subjects randomized to DTIC who do not cross over to treatment with dabrafenib after progression. For subjects randomized to DTIC who crossed over to treatment with dabrafenib after progression, post-therapy for the randomized phase is defined as any time beyond 28 days post last dose of DTIC and prior to the first dose of dabrafenib.

For MEK115306, MEK116513, and BRF115532:

Pre-therapy is defined as before the date of the first dose. Measurements from clinical tests or assessments on Day 1 are pre-therapy.

On-therapy is defined as the date of the first dose until the earliest of 30 days after the last dose of randomized treatment, last contact, or death. If an event occurs on the same date as the first dose, then the event will be considered as on-therapy.

Post-therapy as any time beyond the minimum of 30 days post last dose of study treatment until last contact or death.

6.7. Treatment Arms

As the trials are reported, the treatment arms to be used in analyses are as follows:

- Dabrafenib monotherapy (BREAK-3 + COMBI-D);
- MEK + Dabrafenib (COMBI-D+COMBI-V+COMBI-AD);
- DTIC (BREAK-3);
- Vemurafenib (COMBI-V); and
- Placebo (COMBI-AD).

7. STUDY POPULATION

7.1. Disposition of Subjects

For each study, a summary of the number and percentage of subjects in the Safety population by study treatment status, including reaching the study endpoint or discontinuing study treatment, will be provided. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. Each summary will also include study treatment status (i.e., on study treatment or discontinued).

Subject status and the reasons for withdrawing from the study prematurely will be summarized for each study using the number and percentage of subjects in the Safety population by status. The primary reasons for withdrawal will also be summarized for those subjects who have withdrawn prematurely from the trial.

7.2. Demographic and Baseline Characteristics

Age and sex will be summarized for each trial using the Safety population for the total Safety population and for those with secondary malignancies. Age will be summarized both as a continuous variable and categorized as < 65 and ≥ 65 years.

For each study, disease characteristics at screening (e.g., time since initial diagnosis in months, stage, LDH relative to normal limit) will be summarized for the total Safety population and for those with secondary malignancies.

8. SAFETY ANALYSES

All analyses will be by treatment arm and will use the SAFETY Population. Summaries will include data from unscheduled visits only in sections labeled "worst case on-therapy".

8.1. Secondary Malignancies

For each study, summaries to aid in identification and characterization of the risk of new malignancies, including cutaneous squamous cell carcinoma, will be produced. Tumor type categories are:

- cutaneous squamous cell carcinoma including keratoacanthomas,
- basal cell carcinoma,
- new primary melanoma, and
- other secondary malignancies.

If additional categorization is supported by study data, then the other secondary malignancies category will be further divided as appropriate for the data. Preferred terms for the secondary malignancies to report will be provided by GSK Oncology Clinical Development. GSK Oncology Clinical Development will also provide any clinicopathological data (including pertinent molecular characteristics) that are not in a GSK Oncology Clinical Statistics and Programming dataset.

Prognostic factors for secondary malignancies will include any prior malignancy with characterization of RAS mutation. Other prognostic factors will be included as appropriate.

Summaries of the onset of the first occurrence of secondary malignancies will include times from first and last dose of study treatment classified as 1-<6 weeks, 6-<12 weeks, 12-<18 weeks, 18-<24 weeks, 24-<30 weeks, 30-<36 weeks, 36-<42 weeks, 42-<48, 48-<54, 54-<60, 60-<66 weeks, and ≥66 weeks. These classifications will be adjusted if necessary based on study results.

Summaries of all occurrences, with the number of secondary malignancies (0,1,2,3,4,5,6,7+) and the tumor type category of first, second, and all subsequent malignancies, will be produced.

Summaries of the following will be provided:

- Exposure for each study treatment administered by secondary malignancies tumor type categories and overall;

- Incidence of secondary malignancies, overall and by tumor type categories, for each arm of each trial;

- Characteristics of secondary malignancies adverse events, overall and by tumor type categories, for each arm of each trial, including outcomes and action taken;

- Onset of the first occurrence of secondary malignancies, including timing from the first and last dose of Tafinlar (dabrafenib) overall and by tumor type categories, for each arm of each trial; and

- Prognostic features relevant to each tumor type (e.g., clinicopathologicalfeatures, including pertinent molecular characteristics).

If supported by the data, exploratory analyses of results may be done using appropriate statistical models (e.g., logistic and Cox regression models).

9. REFERENCES

GlaxoSmithKline Document Number UM2010/00166/03: BRF113683, A Phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma. (November 3, 2010).

10. APPENDIX A: TABLES AND LISTINGS FOR EACH STUDY

Table Number	Table
6.1101	Summary of Subject Status and Reason for Study Withdrawal
6.1201	Summary of Study Treatment Status
6.2001	Summary of Demographic Characteristics
6.2101	Summary of Disease Characteristics at Screening
8.9001	Summary of Exposure to Tafinlar (Dabrafenib) by Tumor Type Category
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8.9003	Summary of Secondary Malignancy Incidence by Treatment Arm
8.9004	Summary of Secondary Malignancy Incidence by Treatment Arm and Tumor Type Category
8.9005	Summary of Secondary Malignancies by Occurrence
8.9006	Summary of Characteristics of Secondary Malignancies
8.9007	Summary of Onset of the First Occurrence of Secondary Malignancies
8.9008	Summary of Characteristics of Cutaneous Squamous Cell Carcinoma Including Keratoacanthomas
8.9009	Summary of Onset of the First Occurrence of Cutaneous Squamous Cell Carcinoma Including Keratoacanthomas
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8.9011	Summary of Onset of the First Occurrence of Basal Cell Carcinoma
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8.9013	Summary of Onset of the First Occurrence of New Primary Melanoma
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8.9015	Summary of Onset of the First Occurrence of Other Secondary Malignancies
8.9016	Summary of Prognostic Factors for Secondary Malignancies by Treatment Arm and Tumor Type

Listing Number	Listing
28.9001	Listing of Secondary Malignancies by Treatment Arm
28.9002	Listing of Secondary Malignancies by Treatment Arm and Tumor Type Category
28.9003	Listing of Medical Conditions
28.9005	Listing of Prior Anti-Cancer Therapy