

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206192Orig1s000

STATISTICAL REVIEW(S)



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 ADDENDUM

NDA/BLA #: 206192
Serial #: 000
Drug Name: Cobimetinib (GDC-0973)
Indication: Combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation
Applicant: Genentech Inc.
Received Date: October 13, 2015
PDUFA Date: November 11, 2015
Review Type: Priority
Biometrics Division: Division of Biometrics V
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Keywords: stratified log-rank test, Kaplan-Merier method, Cox regression

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This addendum is to Dr. Xiaoping (Janet) Jiang’s statistical review for this new drug application NDA206192N000 (dated May 6, 2015).

On December 11, 2014, the applicant submitted a NDA to seek an approval of cobimetinib for the proposed indication (b) (4)

. In the submission, the applicant provided clinical data and results from Study GO28141 entitled ‘A Phase III, Double-Blind, Placebo-Controlled Study Of Vemurafenib Versus Vemurafenib Plus GDC-0973 In Previously Untreated BRAFV600-Mutation Positive Patients With Unresectable Locally Advanced or Metastatic Melanoma’, and other studies.

In Study GO28141, a total of 495 eligible patients were randomized in a 1:1 ratio to receive cobimetinib (GDC-0973) plus vemurafenib or placebo plus vemurafenib. The randomization was stratified by metastatic classification and geographic region. The primary endpoint was progression-free survival (PFS), determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. The primary analysis was a stratified log-rank test. For details regarding the design, data analyses, and results of the study GO28141, please refer to Dr. Xiaoping (Janet) Jiang’s statistical review (May 6, 2015).

The data provided in the original NDA submission (dated on December 11, 2014) was based on data cut-off date of May 9, 2014. The applicant conducted an updated efficacy analyses based on the data cut-off date of January 16, 2015 for Study GO28141. On October 13, 2015, the applicant submitted the updated data and efficacy results based on the data cut-off date of January 16, 2015. Table 1 summarizes this reviewer’s PFS analyses based on the updated data.

Table 1 Result of Progression-Free Survival Analysis (INV)

| | Placebo + Vemurafenib (n=248) | Cobimetinib + Vemurafenib (n=247) |
|--|--|--|
| Number of Event (%) | 180 (72.6) | 143 (57.9) |
| Progression | 169 | 131 |
| Death | 11 | 12 |
| Number of Censored (%) | 68 (27.4) | 104 (42.1) |
| Median PFS in months (95% CI) | 7.2 (5.6, 7.5) | 12.3 (9.5, 13.4) |
| Strata Recorded from IxRS^a | | |
| Hazard Ratio ^b (95%CI) | 0.56 (0.45, 0.70) | |
| P-value (stratified ^c log-rank) | <0.0001 | |
| Strata Recorded from CRF | | |
| Hazard Ratio ^b (95%CI) | 0.58 (0.46, 0.72) | |
| p-value (stratified ^c log-rank) | <0.0001 | |

^a IxRS= interactive response system; ^b estimated by Cox model stratified by region and metastatic classification; a hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib; ^c stratified by region and metastatic classification

Reviewer’s Comments:

1. Since cobimetinib is a New Molecular Entity (NME), the efficacy results based on updated data may provide more information for physicians and patients. The PFS result submitted in the original NDA showed statistically significant difference in favor of the combination of cobimetinib and vemurafenib, hence conducting an PFS analysis based on the updated data will not inflate type I error rate.

Figure 1 displays this reviewer’s Kaplan-Meier curves of PFS based on data cut-off date of January 16, 2015.

Figure 1 Kaplan-Meier Curves of Progression-Free Survival

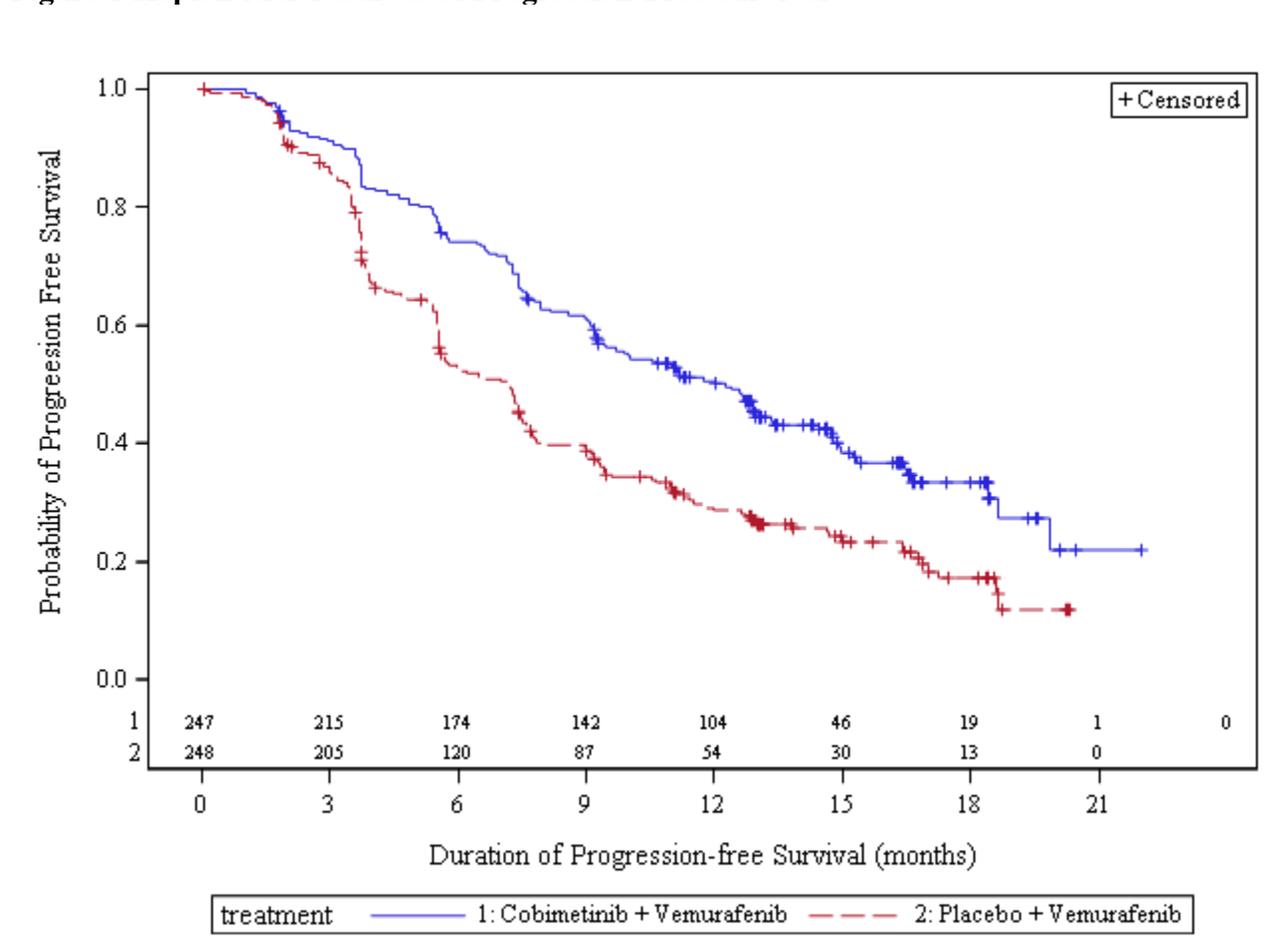


Table 2 summarizes this reviewer’s analysis of objective response rate (ORR) based on data cut-off date of January 16, 2015.

Table 2 Results of Objective Response and Duration of Response

| | Vemurafenib + Placebo (n=248) | Cobimetinib + Vemurafenib (n=247) |
|---|----------------------------------|--------------------------------------|
| Complete Responder (CR) | 26 (10.5%) | 39 (15.8%) |
| Partial Responder (PR) | 98 (39.5%) | 133 (53.8%) |
| Responder (CR+PR) | 124 | 172 |
| Response Rate with 95%CI | 50.0% (43.6%, 56.4%) | 69.6% (63.5%, 75.3%) |
| P-value (χ^2 -test) | | <0.0001 |
| Median of Duration of Response (months) | 9.2 (7.5, 12.8) | 13.0 (11.1, 16.6) |

Overall survival was another secondary endpoint evaluated in Study GO28141. Table 3 summarizes this reviewer's analysis based on data cut-off date of January 16, 2015.

Table 3 Result of Overall Survival

| | Vemurafenib + Placebo (n=248) | Cobimetinib + Vemurafenib (n=247) |
|--|----------------------------------|--|
| Number of Event (%) | 109 (43.9) | 79 (32.0) |
| Number of Censored (%) | 139 (56.1) | 168 (68.0) |
| Median OS in Months (95% CI) | 17.0 (15.0, NR ^a) | NA ^a (20.7, NR ^a) |
| Strata Recorded from CRF | | |
| Hazard Ratio ^c (95%CI) | 0.65 (0.49, 0.87) | |
| P-value (stratified ^d log-rank) | 0.0034 | |
| Strata Recorded from IxRS^b | | |
| Hazard Ratio ^c (95%CI) | 0.63 (0.47, 0.85) | |
| P-value (stratified ^d log-rank) | 0.0019 | |

^aNR= Not reached due to small number of events occurred; ^bIxRS= interactive response system; ^cestimated by Cox model stratified by region and metastatic classification; a hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib; ^dstratified by region and metastatic classification.

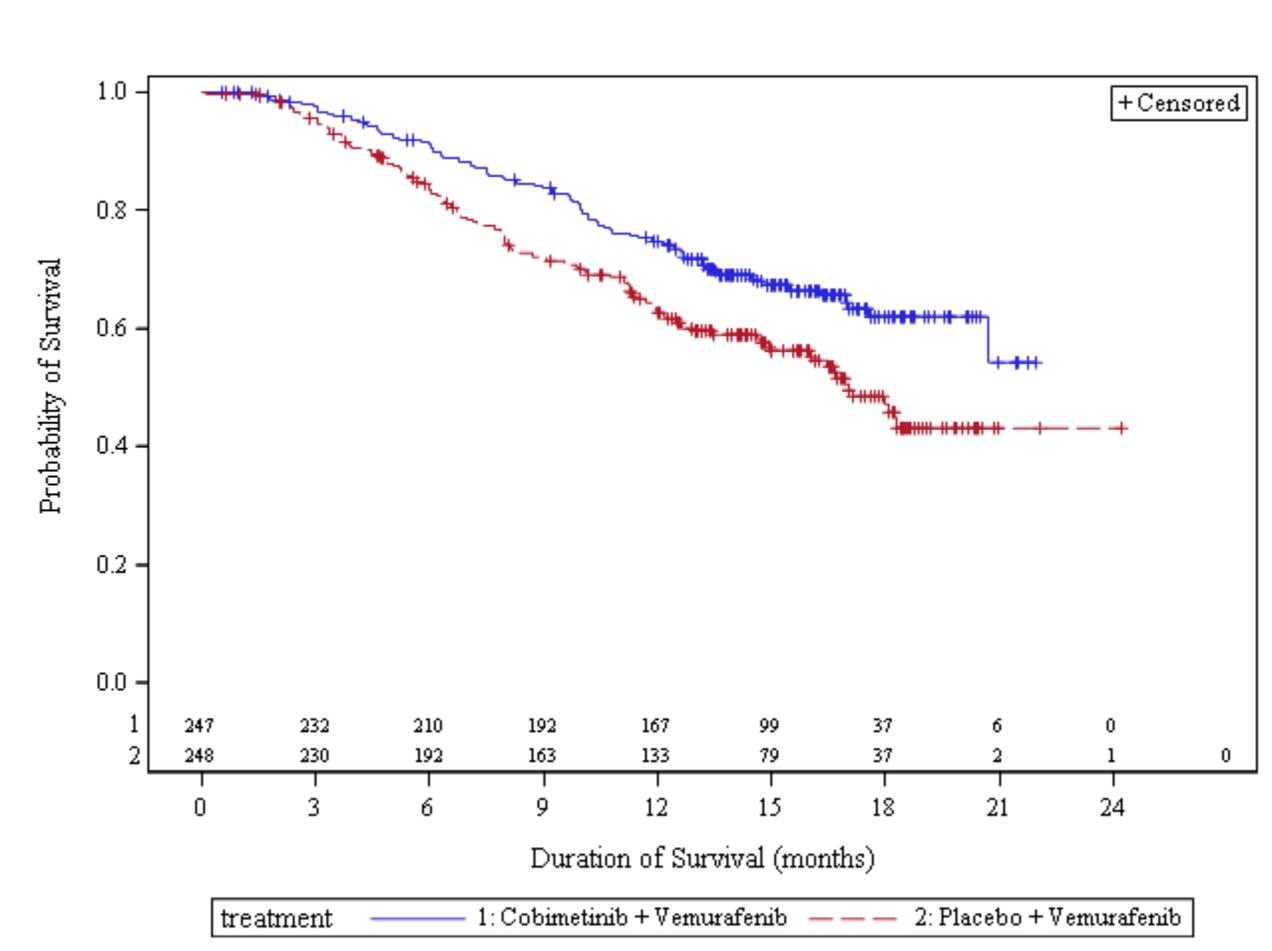
Reviewer's Comments:

2. FDA considers stratified OS analysis using strata recorded from IxRS as the primary analysis and OS analysis using strata recorded from CRFs as a sensitivity analysis.
3. Study GO28141 was originally designed to have three OS analyses with two interim analyses (one was conducted at the final PFS analysis, second interim analysis was planned to be conducted when 256 (67% of the events required for the final OS analysis) events had been observed, and the final OS analysis would be conducted when 385 events had been observed. In February 2015, the protocol was amended (version 5) to reduce the number of the OS interim analyses from 3 to 2 and the final analysis would be conducted when 250 events had been observed. FDA considers this updated OS analysis

as the second interim analysis with 75% (188/250) information available. As shown in the Table 3, the stratified log-rank test p-value is 0.0019 based on strata recorded from interactive response system (IxRS), the result crosses the pre-specified boundary for statistical significance (allocated $\alpha=0.019$) according to the pre-specified OBF method (based on 75% of required number of events have been observed). Hence, this OS interim analysis result demonstrates that patients treated with cobimetinib plus vemurafenib had statistically significant improvement in survival compared to patients treated with placebo plus vemurafenib

Figure 2 displays this reviewer’s Kaplan-Meier curves of OS based on data cut-off date of January 16, 2015.

Figure 2: Kaplan-Meier curves of Overall Survival



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/s/

XIAOPING JIANG
11/02/2015

KUN HE
11/02/2015

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11/02/2015



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

NDA/BLA #: 206192
Serial #: 000
Drug Name: Cobimetinib (GDC-0973)
Indication: Combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation
Applicant: Genentech Inc.
Received Date: December 11, 2014
PDUFA Date: August 11, 2015
Review Type: Priority
Biometrics Division: Division of Biometrics V
Statistical Reviewer: Xiaoping (Janet) Jiang, Ph.D.
Concurring Reviewers: Kun He, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Division Director
Medical Division: Division of Oncology Products 2
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Keywords: stratified log-rank test, Kaplan-Merier method, Cox regression

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1. EXECUTIVE SUMMARY

On December 11, 2014, the applicant submitted a new drug application (NDA) to seek an approval of cobimetinib for the proposed indication (b) (4)

In the submission, the applicant provided clinical data from Study GO28141 entitled 'A Phase III, Double-Blind, Placebo-Controlled Study Of Vemurafenib Versus Vemurafenib Plus GDC-0973 In Previously Untreated BRAFV600-Mutation Positive Patients With Unresectable Locally Advanced or Metastatic Melanoma', and other studies.

In GO28141, a total of 495 eligible patients were randomized in a 1:1 ratio to receive cobimetinib (GDC-0973) plus vemurafenib or placebo plus vemurafenib. The randomization was stratified by metastatic classification and geographic region. The primary endpoint was progression-free survival (PFS), determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria.

The primary analysis was a stratified log-rank test. Based on 207 PFS events determined by investigators, the PFS result demonstrated that patients treated with cobimetinib plus vemurafenib had statistically significant improvement in PFS compared to patients treated with placebo plus vemurafenib (stratified log-rank p-value<0.0001). The estimated median PFS was 9.9 months (95% CI: 9.0, NR (not reached at the time of analysis)) for cobimetinib plus vemurafenib arm and 6.2 months (95% CI: 5.6, 7.4) for the placebo plus vemurafenib arm. The hazards ratio was 0.50 (95% CI: 0.38, 0.67) in favor of the treatment with cobimetinib plus vemurafenib. The result of objective response rate (ORR) showed that the patients treated with cobimetinib plus vemurafenib had statistically significantly higher objective response rate than the patients treated with placebo plus vemurafenib (Chi-Square test p-value <0.0001). The estimated objective response rate for the cobimetinib plus vemurafenib arm was 67.4% (95% CI: 61.4, 73.4) with at least 9.3 months duration of response and 44.8% (95% CI: 38.5, 51.2) for the placebo plus vemurafenib arm. A planned interim analysis of overall survival (OS) was conducted at the time of final analysis of PFS. Compared to the nominal p-value of 0.0000037 according to pre-specified O'Brien-Fleming (OBF) method, the OS interim analysis result showed that there was no statistical difference between the two treatment arms (stratified log-rank p-value= 0.0273) with the estimated hazards ratio of 0.62 (95% CI: 0.40 0.95). The median OS had not yet been reached for either of the treatment arms at the time of the interim analysis. The final OS analysis will be conducted after 385 death events have been observed.

Whether the results from Study GO28141 provide a favorable benefit to risk ratio to support an approval of cobimetinib in combination with vemurafenib for the proposed indication will be determined by the clinical review team.

2. INTRODUCTION

2.1 Overview

Cobimetinib is a potent and highly selective, targeted small molecule inhibitor of mitogen-activated protein kinase (MEK). In this NDA, the applicant submitted the data from study GO28141 and other studies to seek an approval of cobimetinib for a proposed indication in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma.

There were 495 randomized patients in Study GO28141. The primary objective was to evaluate the efficacy of vemurafenib in combination with cobimetinib (GDC-0973), compared with vemurafenib and placebo, in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma, as measured by prolongation of progression-free survival (PFS), as assessed by the study site investigator. GO28141 was conducted at 133 sites in 19 countries. Majority of the countries are European. The first patient entered the study on January 8, 2013 and last patient entered the study on January 31, 2014. The data cutoff for the primary analysis was on May 9, 2014.

The secondary objectives of the study included comparisons of objective response rate (ORR) and overall survival (OS) between the two randomized treatment arms.

2.2 Data Sources

Data used for this review were from the electronic submission received on December 11, 2014. The link was "[\\CDSESUB1\evsprod\NDA206192\206192.enx](#)"

3. STATISTICAL EVALUATION

This section focuses on efficacy evaluation for Study GO28141.

3.1 Data and Analysis Quality

The quality of submitted data allowed this reviewer to verify the applicant's major efficacy results and conduct the reviewer's own analyses. The protocol including its amendments and statistical analysis plan (SAP) were provided in the NDA submission.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

GO28141 was a randomized, double-blind, placebo controlled phase III study. The study inclusion criteria included 1) Patients with histologically confirmed melanoma, either unresectable Stage IIIc or Stage IV metastatic melanoma, as defined by the American Joint Committee on Cancer 7th edition. Unresectability of Stage IIIc disease needed confirmation from a surgical oncologist; 2) Patients must have been naïve to treatment for locally advanced unresectable or metastatic disease (i.e., no prior systemic anti-cancer therapy for advanced disease; Stage IIIc and IV). Prior adjuvant therapy (including immunotherapy, e.g., ipilimumab) was allowed. Eligible patients were randomized with a ratio of 1:1 to one of the following two arms through an interactive response system (IxRS).

- Arm A (control arm): vemurafenib 960 mg by mouth (PO) twice daily (BID) on Days 1–28 and placebo PO once daily (QD) on Days 1–21 of each 28-day treatment cycle
- Arm B (investigational arm): vemurafenib 960 mg PO BID on Days 1–28 and cobimetinib (GDC-0973) 60 mg PO QD on Days 1–21 of each 28-day treatment cycle

The randomization was stratified by geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; or M1c). Treatment was continued until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurred earliest. Patients on the vemurafenib and placebo treatment arm were not eligible to cross over to the vemurafenib and cobimetinib (GDC-0973) treatment arm at disease progression and were followed up for survival.

Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Response was assessed by the investigators at 8-week intervals.

Per the protocol and the SAP, the primary endpoint PFS was defined as the time from randomization to the first occurrence of disease progression, as determined by the investigators using RECIST v1.1, or death from any cause, whichever came first. PFS for patients who did not have disease progression or death were censored at the last tumor assessment date. PFS for patients with no post-baseline tumor assessment were censored at the randomization date

The secondary endpoints in the study included OS, and ORR. OS was defined as the time from randomization to death from any cause. ORR for patients with measurable disease at baseline was defined as complete or partial response as assessed by investigator according to RECIST v1.1.

3.2.2 Statistical Methodologies

Per the protocol and SAP, the primary analysis of PFS was a log-rank test stratified by two randomized stratified factors: geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c) at two-sided significance level of 0.05. The primary analysis was based on the intent-to-treat (ITT) population, defined as all randomized patients. The Kaplan-Meier method was used to estimate the median PFS and 95% confidence intervals (CIs) for each treatment arm. Hazard ratio and its 95% confidence intervals were estimated using the Cox proportional hazards model stratified by region and metastatic classification.

Sample size calculation was based on the assumptions that the true PFS hazard ratio was 0.55 corresponding to median PFS of 6 months in the vemurafenib plus placebo arm and 11 months in the vemurafenib plus cobimetinib arm. A total of 206 events were needed to detect a hazard ratio of 0.55 with 95% power at a 2-sided alpha level of 0.05. Taking consideration of enrollment rate of 65 patients per month and 5% dropout rate, approximately 500 patients were planned to be randomized.

The secondary endpoint OS was analyzed using Kaplan-Meier product-limit estimates and compared between two treatment arms using a stratified log-rank test. The stratified OS analyses

would use the same stratification factors as for the primary PFS analysis. The final analysis will be conducted after 385 events have been observed (at approximately 46 months after the first patient was randomized). Another secondary endpoint ORR was tested by using χ^2 test at two-sided alpha of 0.05. A hierarchical order to control the overall family-wise error rate at level $\alpha = 0.05$ for the secondary endpoints ORR and OS was pre-specified in the protocol and SAP: the ORR would be tested first at the 0.05 level after the primary analysis of PFS showing statistical significance. Only if it was significant, OS would then be tested at the 0.05 level.

There were two planned interim OS analyses. The first OS interim analysis was conducted at the time of the final PFS; second one would be when 256 (67%) OS events have been observed (it was estimated that the timing would be at approximately 27 months after the first patient was randomized.) The Lan-DeMets implementation of the O'Brien and Fleming spending function was used to control the overall Type I error rate at a significance level of 0.05 (2-sided) for all OS comparisons.

Patients report outcomes (PRO)s measured by EORTC QLQ-C30, were evaluated for patients with a baseline assessment and at least one post-baseline QLQ-C30 assessment that generate a score. Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of absolute scores of the QLQ-C30 and their changes from baseline were summarized at each assessment timepoint for the two treatment arms.

Reviewer’s Comments:

1. *The applicant did not pre-specify whether strata derived from case report form (CRF) or from randomization system IxRS would be used in the primary PFS and OS analyses. FDA considers the stratified analysis using strata recorded from IxRS as the primary analysis because it is consistent with the intend-to-treat (ITT) principle. FDA considers the stratified analysis using strata recorded from CRFs as a supportive analysis.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were 495 patients randomized in GO28141. By May 09, 2014, the date of data cut-off for the final PFS analysis, the median duration of follow-up was 7.0 months for patients in placebo plus vemurafenib arm versus 7.4 months for patients in cobimetinib plus vemurafenib arm. Table 3.1 summarizes the patient disposition of ITT population.

Table 3.1 Patient Disposition

| | Placebo + Vemurafenib (n=248) (%) | Cobimetinib + Vemurafenib (n=247) (%) |
|-----------------------|--------------------------------------|--|
| Randomized | 248 (100) | 247 (100) |
| Treated | 247 (96) | 246 (96) |
| Withdrawal from study | 67 (27.0) | 48 (19.4) |
| Death | 51 (20.6) | 34 (13.8) |
| Withdrew by subject | 13 (5.2) | 10 (4) |
| Physician’s decision | 0 | 3 (1.2) |
| Lost to follow-up | 3 (1.2) | 1 (0.4) |

[Source: Clinical Study Report Figure 3]

Table 3.2 summarizes the demographics of ITT population.

Table 3.2 Summary of Demographics

| | Placebo + Vemurafenib (n=248) (%) | Cobimetinib + Vemurafenib (n=247) (%) |
|------------------------------|--------------------------------------|--|
| Age (year) | | |
| Median (Min-Max) | 55 (25-85) | 56(23-88) |
| Age group, n (%) | | |
| <65 | 179 (72.2) | 183 (74.1) |
| >=65 | 69 (27.8) | 64 (25.9) |
| Sex, n (%) | | |
| Male | 140 (56.5) | 146 (59.1) |
| Female | 108 (43.5) | 101 (40.9) |
| Region, n (%) | | |
| Europe | 184 (74.2) | 182 (73.7) |
| North America | 26 (10.5) | 25 (10.1) |
| Australia/New Zealand/Others | 38 (15.3) | 40 (16.2) |
| Race, n (%) | | |
| White | 235 (94.8) | 227(91.9) |
| Non-White | 13(5.2) | 20 (8.1) |

Reviewer's Comments:

- The demographics appear balanced between the two treatment arms.*

Table 3.3 summarizes the major baseline characteristics for ITT population.

Table 3.3 Summary of Major Baseline Characteristics

| | Placebo + Vemurafenib (n=248) (%) | Cobimetinib + Vemurafenib (n=247) (%) |
|--|---|---|
| Screening Serum Lactate Dehydrogenase, n (%) | | |
| LDH Normal | 138 (57.0) | 130 (53.7) |
| LDH Elevated | 104 (43.0) | 112 (46.3) |
| Time from melanoma first diagnosed (Months) | | |
| Median (Min-Max) | 25.13 (0.1 - 337.5) | 28.11 (0.4 - 420.8) |
| Prior adjuvant therapy, n (%) | | |
| No | 224 (90.3) | 223 (90.3) |
| Yes | 24 (9.7) | 24 (9.7) |
| ECOG performance status, n (%) | | |
| 0 | 164 (67.2) | 184 (75.7) |
| 1 | 80 (32.8) | 58 (23.9) |
| 2 | 0 | 1 (0.4) |
| Stage of melanoma at time of study randomization, n (%) | | |
| IIIc | 13 (5.2) | 21 (8.5) |
| M1a | 40 (16.1) | 40 (16.2) |
| M1b | 42 (16.9) | 40 (16.2) |
| M1c | 153 (61.7) | 146 (59.1) |

[Source: Clinical Study Report Table 12 and a Table on page 329]

Reviewer’s Comments:

3. *The major baseline characteristics appear balanced between the two treatment arms.*

3.2.4 Results and Conclusions

3.2.4.1 Results of Primary Endpoint

Table 3.4 summarizes the primary analysis of PFS.

Table 3.4 Result of Progression-Free Survival Analysis (INV)

| | Placebo + Vemurafenib (n=248) | Cobimetinib + Vemurafenib (n=247) |
|----------------------------------|----------------------------------|--------------------------------------|
| Number of Event (%) | 128 (51.6) | 79 (32.0) |
| Progression | 125 | 74 |
| Death | 3 | 5 |
| Number of Censored (%) | 120 (48.4) | 168 (68.0) |
| Median PFS in months (95% CI) | 6.21 (5.55, 7.39) | 9.89 (9.00, NR*) |
| Strata Recorded from IxRS | | |
| Hazard ratio** (95%CI) | | 0.50 (0.38, 0.67) |
| p-value (stratified*** log-rank) | | <0.0001 |
| Strata Recorded from CRF | | |
| Hazard ratio** (95%CI) | | 0.51 (0.39, 0.68) |
| p-value (stratified*** log-rank) | | <0.0001 |

*NR=not reached due to small number of events occurred; **a hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib; ***stratified by region and metastatic classification

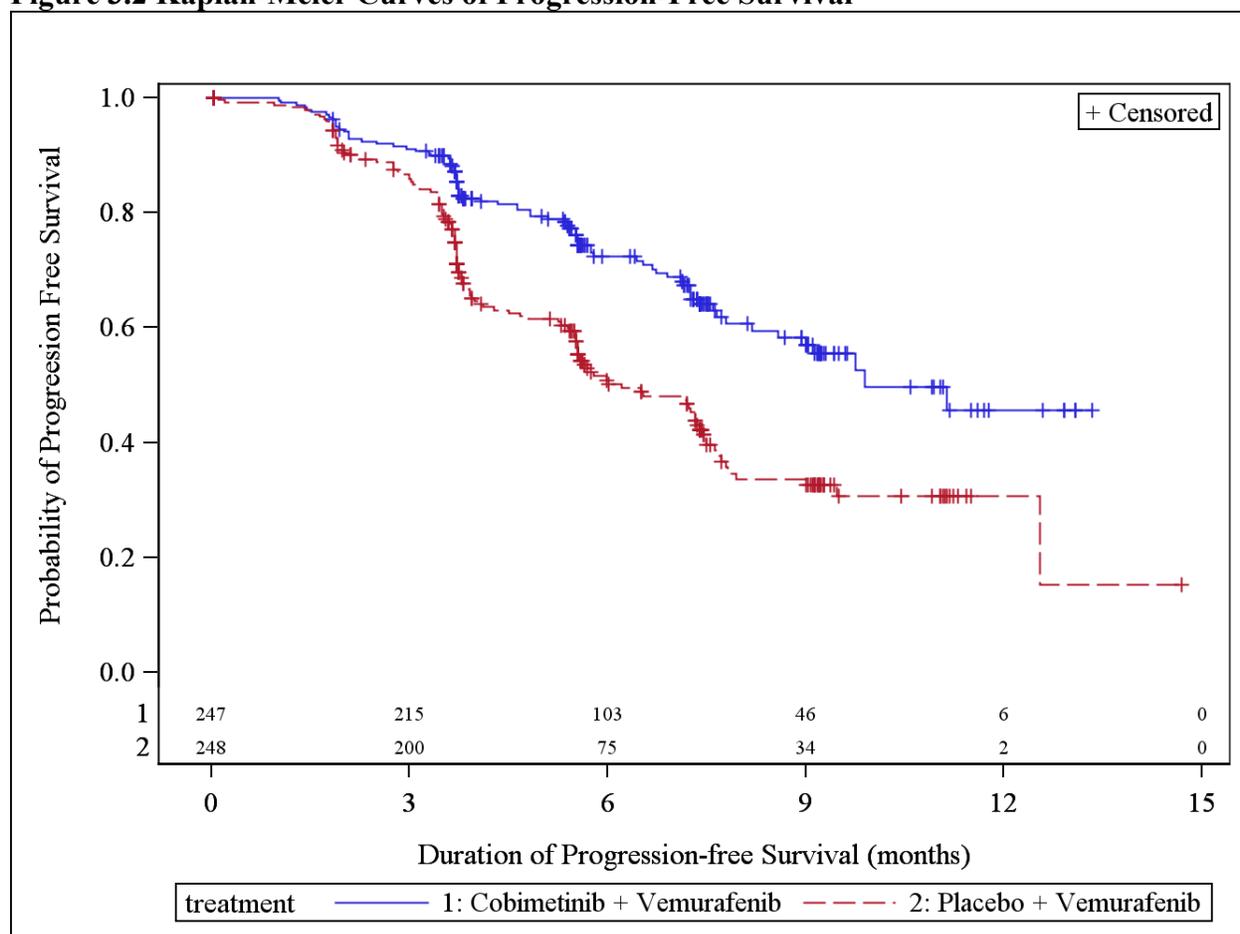
Reviewer’s Comments:

4. *FDA does not agree with the applicant’s stratified analysis using strata derived from CRF data, because it is not consistent with the ITT principle. FDA considers the stratified PFS analysis using strata recorded from IxRS as the primary analysis and the PFS analysis using strata recorded from CRFs as a supportive analysis. As you can see from Table 3.4, both analyses are consistent. The same principle will be applied to the stratified analyses of OS.*

5. *The primary PFS analysis results shown in Table 3.4 demonstrated that treatment with combination of cobimetinib and vemurafenib statistically significantly prolonged PFS compared to treatment with combination of placebo and vemurafenib.*

Figure 3.2 displays the reviewer’s Kaplan-Meier curves of PFS.

Figure 3.2 Kaplan-Meier Curves of Progression-Free Survival



Reviewer’s Comments:

6. The primary endpoint PFS was determined by investigator’s assessment and PFS assessed by an Independent Review Facility (IRF) using RECIST v1.1 was one of the secondary endpoints. Table 3.5 summarizes PFS analysis based on IRF assessment.

Table 3.5 Result of Progression-Free Survival Analysis (IRF)

| | Placebo + Vemurafenib (n=248) | Cobimetinib + Vemurafenib (n=247) |
|----------------------------------|----------------------------------|--------------------------------------|
| Number of Event (%) | 117 (47.2) | 82(33.2) |
| Number of Censored (%) | 131(52.8) | 165 (66.8) |
| Median PFS in months (95% CI) | 6.01 (5.55, 7.49) | 11.33 (8.54, NR*) |
| Strata Recorded from IxRS | | |
| Hazard ratio** (95%CI) | | 0.60 (0.45,0.79) |
| p-value (stratified*** log-rank) | | 0.0003 |

*NR=not reached due to small number of events occurred; **a hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib; ***stratified by region and metastatic classification.

7. In order to assess if there was any potential bias in determination of PD between the investigator (INV) and IRF, this reviewer conducted a discordance analysis. Table 3.6 summarizes the reviewer's discordance analysis.

Table 3.6 Concordance of INV and IRF

| INV Assessment, n (%) | IRF Assessment, n (%) | | | |
|-----------------------|----------------------------------|------------|--------------------------------------|------------|
| | Placebo + Vemurafenib (n=248) | | Cobimetinib + Vemurafenib (n=247) | |
| | Event | No Event | Event | No Event |
| Event | 98 (39.5) | 27 (10.9) | 62 (25.1) | 12 (4.9) |
| No Event | 16 (6.5) | 104 (41.9) | 15 (6.1) | 153 (61.9) |

8. As shown in Table 3.6, the concordance rates (concordance of event + concordance of no event (censored)) between investigators and IRF assessments are comparable. The concordance rate between investigators and IRF assessments was 87.0% (=25.1% + 61.9%) for the cobimetinib plus vemurafenib arm and 81.4% (=39.5% + 41.9%) for the placebo plus vemurafenib arm.
9. In order to evaluate the robustness of the observed PFS treatment effect, the applicant and this reviewer conducted several PFS sensitivity analyses. The applicant's sensitivity analyses including unstratified analysis; stratified analysis using the IRF assessment, one of secondary endpoints; analysis by censoring PFS at the date of the last evaluable tumor assessment prior to start of non-protocol anti-cancer therapy. Per the applicant, a planned PFS sensitivity analysis 'PFS censoring accounting for missed visits' was not conducted due to very low number of patients (only one) who had a PFS event after two or more consecutive missed visits for tumor assessments. The reviewer's sensitivity analysis was conducted by using the combination of the INV assessment and IRF assessment. Specifically, a patient was assigned to have a PFS event if one of INV and IRF assessments showing the patient had a PFS event, and the shorter PFS time of PFS times assessed by INV and IRF was assigned to the patient. Table 3.7 summarizes the applicant's and this reviewer's sensitivity analyses.

Table 3.7 Summary of Progression-Free Survival Sensitivity Analyses

| | Number of Events (%) | | HR (95%CI) |
|---|-------------------------------------|--|-------------------|
| | Placebo + Vemurafenib (n=248) | Cobimetinib+ Vemurafenib (n=247) | |
| Applicant's Analyses | | | |
| unstratified analysis | 128 (51.6) | 79 (32.0) | 0.51 (0.39, 0.68) |
| PFS censored for non-protocol anti-cancer therapy | 126 (50.8) | 77 (31.2) | 0.51 (0.38, 0.67) |
| PFS assessed by IRF | 117 (47.2) | 82 (33.2) | 0.60 (0.45, 0.79) |
| Reviewer's Analysis | | | |
| using the INV and IRF assessment | 144 (58.06) | 94 (38.06) | 0.55 (0.42, 0.71) |

As shown in Table 3.7, the results of sensitivity analyses are consistent with the result of the primary analysis.

3.2.4.2 Results of Secondary Endpoints

Objective response rate (ORR) was a secondary endpoint in Study GO28141. Table 3.8 summarizes ORR analysis based on INV assessment.

Table 3.8 Results of Objective Response and Duration of Response

| | Vemurafenib + Placebo (n=248) | Cobimetinib + Vemurafenib (n=247) |
|---|-------------------------------------|---|
| Response (CR+PR), n (%) | 111 (44.8) | 167 (67.6) |
| 95%CI | (38.5, 51.2) | (61.4, 73.4) |
| Complete response, n (%) | 11 (4.5) | 25 (10.1) |
| Partial response, n (%) | 100 (40.3) | 142 (57.5) |
| P-value (χ^2 -test) | | <0.0001 |
| Median of Duration of Response (months) | 7.29 (5.8, NA) | NA (9.3, NA) |

Reviewer's Comments:

10. The Applicant pre-specified a hierarchical test order for the secondary endpoints to adjust multiplicity that the ORR would be tested first at the 0.05 level after the primary analysis of PFS showed statistical significance. As shown in Table 3.8, the result of ORR showed that the patients treated with combination of cobimetinib and vemurafenib had statistically significantly higher objective response rate than patients treated with combination of placebo and vemurafenib.

Overall survival was another secondary endpoint evaluated in Study GO28141. Table 3.9 summarizes the applicant's OS interim analysis conducted at the time of final analysis of PFS.

Table 3.9 Result of Overall Survival

| | Vemurafenib +Placebo (n=248) | Cobimetinib + Vemurafenib (n=247) |
|----------------------------------|---------------------------------|--------------------------------------|
| Number of Event (%) | 51 (20.6) | 34 (13.8) |
| Number of Censored (%) | 197 (79.4) | 213 (86.2) |
| Median OS in Months (95% CI) | NR*(11.9, NR*) | NR*(NR*, NR*) |
| Strata Recorded from CRF | | |
| Hazard ratio ** (95%CI) | 0.65 (0.42, 1.00) | |
| p-value (stratified*** log-rank) | 0.0463 | |
| Strata Recorded from IxRS | | |
| Hazard ratio** (95%CI) | 0.62 (0.40, 0.95) | |
| p-value (stratified*** log-rank) | 0.0273 | |

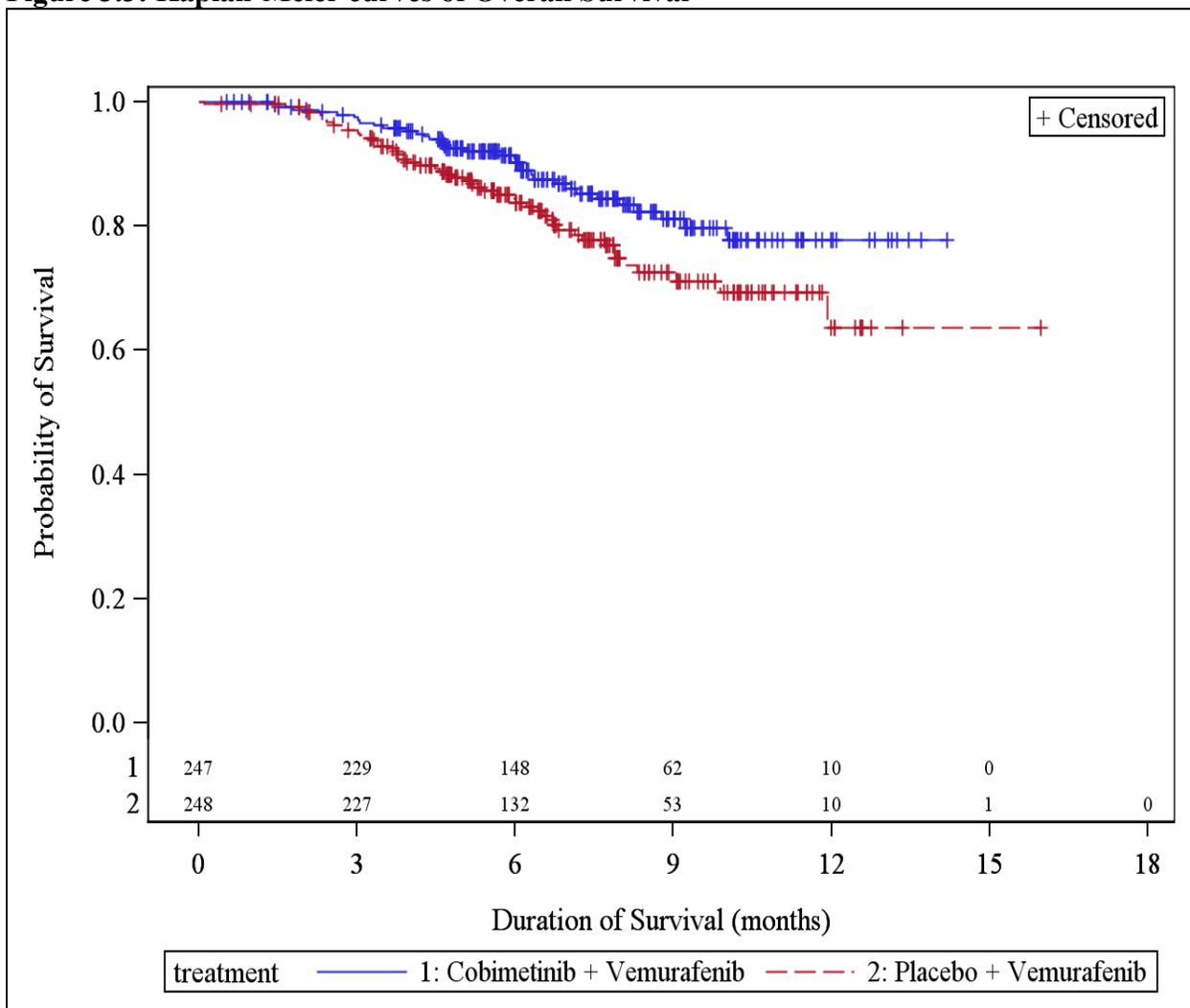
*NR=Not reached due to small number of events occurred; **a hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib; ***stratified by region and metastatic classification.

Reviewer’s Comments:

11. FDA considers stratified OS analysis using strata recorded from IxRS as the primary analysis and OS analysis using strata recorded from CRFs as a sensitivity analysis. As shown in the Table 3.9, based on strata recorded from IxRS, the stratified log-rank test $p= 0.0273$, but the result did not cross the pre-specified boundary for statistical significance ($\alpha=0.0000037$) according to pre-specified OBF method (based on 22% of planned events). Median OS had not yet been reached for either of the treatment arms at this pre-specified interim analysis.

Figure 3.3 displays the reviewer’s Kaplan-Meier curves of OS.

Figure 3.3: Kaplan-Meier curves of Overall Survival



Reviewer's Comments:

12. Based on interim analysis data with 85 deaths, this reviewer created the K-M curves of OS shown in Figure 3. The Kaplan-Merier curves show a trend favoring the combination of cobimetinib and vemurafenib.

Health-related quality of life (HRQL) in patients, measured by EORTC QLQ-C30, was evaluated as a secondary endpoint for patients with a baseline assessment and at least one post-baseline QLQ-C30 assessment that generated a score. The completion rate of the EORTC QLQ-C30 at baseline for both treatment arms was 96.7%. Completion rates were greater than 88% among all cycles for both treatment arms, through the final study visit. The applicant conducted an exploratory analysis, in which patients were considered to have had a clinically meaningful improvement in EORTC QLQ-C30 score if they had at least a 10-point improvement in the score at one or more post-baseline assessments. Table 3.10 summarizes the exploratory analysis across all functioning domains (cognitive, emotional, social, role, and physical), and most symptoms (appetite loss, constipation, nausea and vomiting, dyspnea, pain, fatigue) of the EORTC QLQ-C30.

Table 3.10 Patients with Clinically Significant Improvement in EORTC QLQ-C30

| | Vemurafenib + Placebo (n=209) (95%CI) | Vemurafenib + Cobimetinib (n=211) (95% CI) | Difference in Treatment Clinical Significant proportions (%) (95%CI) |
|-----------------------------|--|---|---|
| Global Health Status | 76 (37.6) 30.92, 44.3 | 74 (36.3) 29.68, 42.9 | -1.35 (-10.74, 8.04) |
| Functioning Scales | | | |
| Physical | 54 (26.7) (20.77, 33.28) | 65 (31.9) (25.53, 38.62) | 5.13 (-3.71, 13.97) |
| Role | 62 (30.7) (24.65, 37.33) | 70 (34.3) (27.83, 41.01) | 3.62 (-5.48, 12.73) |
| Emotional | 104 (51.5) (44.37, 58.56) | 111 (54.4) (47.54, 61.38) | 2.93 (-6.78, 12.63) |
| Cognitive | 60 (29.7) (23.49, 36.14) | 68 (33.3) (27.05, 40.05) | 3.63 (-5.40, 12.66) |
| Social | 66 (32.7) (26.26, 39.50) | 88 (43.1) (36.48, 50.06) | 10.46 (1.08, 19.85) |
| Symptom Scales | | | |
| Fatigue | 90 (44.6) (37.76, 51.65) | 109 (53.4) (46.50, 60.43) | 8.88 (-0.81, 18.56) |
| Nausea and Vomiting | 45 (22.3) (16.94, 28.58) | 57 (27.9) (21.90, 34.35) | 5.66 (-2.75, 14.08) |
| Pain | 90 (44.6) (37.76, 51.65) | 105 (51.5) (44.41, 58.51) | 6.92 (-2.78, 16.61) |
| Dyspnea | 49 (24.3) (18.52, 30.45) | 55 (27.0) (21.16, 33.41) | 2.7 (-5.78, 11.19) |
| Insomnia | 77 (38.1) (31.55, 44.86) | 110 (53.9) (47.02, 60.91) | 15.8 (6.23, 25.38) |
| Appetite Loss | 57 (28.2) (22.13, 34.71) | 69 (33.8) (27.57, 40.53) | 5.61 (-3.38, 14.59) |
| Constipation | 37 (18.3) (13.49, 24.03) | 47 (23.0) (17.45, 29.21) | 4.72 (-3.14, 12.59) |
| Diarrhoea | 26 (12.9) (8.59, 18.07) | 29 (14.2) (9.73, 19.66) | 1.34 (-5.31, 8.00) |

[Source: Clinical Study Report Table 25]

Reviewer's Comments:

13. As shown in Table 3.10, differences of >10% were seen in insomnia and social functioning.

3.3 Evaluation of Safety

Please refer to Dr. Ruthann Giusti’s clinical review for safety evaluation of cobimetinib in combination with vemurafenib.

3.4 Benefit-Risk Assessment

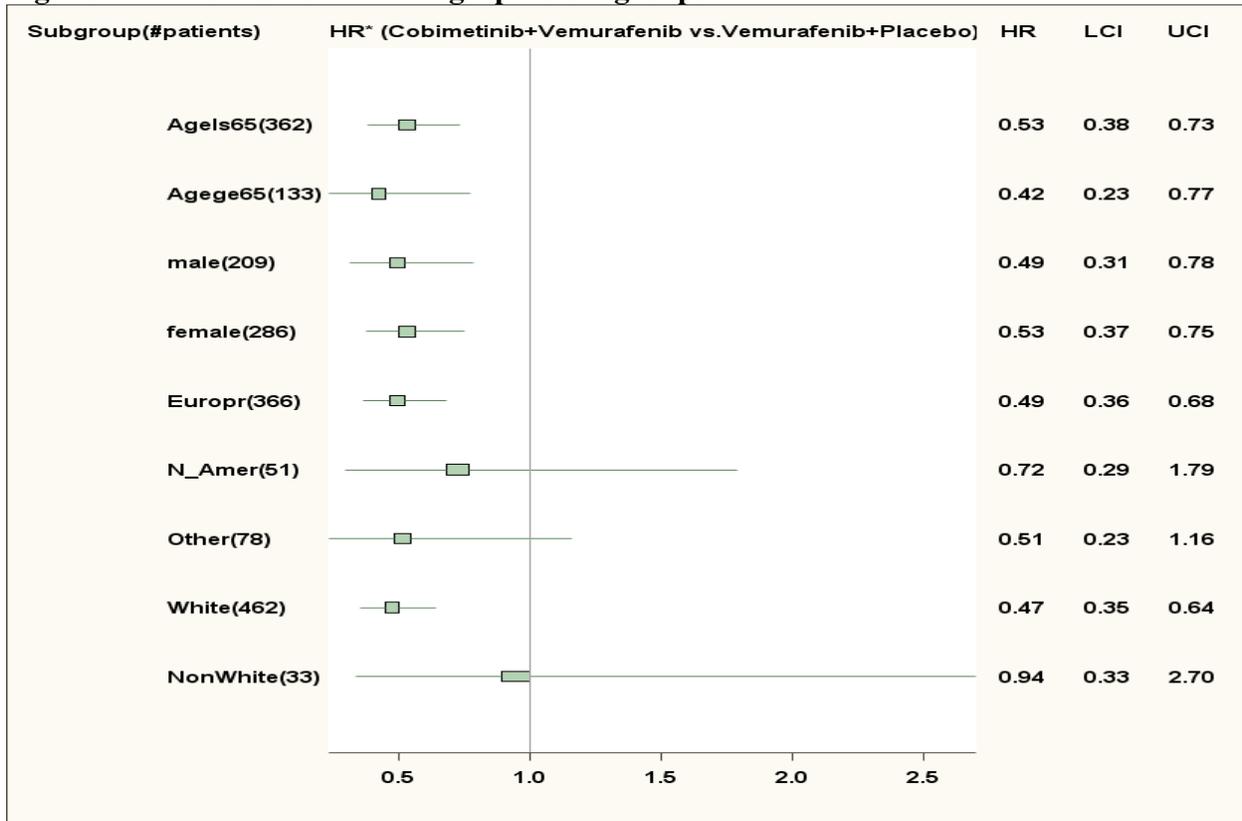
For the previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma, the results of PFS and ORR from Study GO28141 show that treatment with combination of cobimetinib statistically significantly improves PFS and ORR compared to treatment with placebo and vemurafenib. In addition, based on 22% of planned events for final OS analysis, an OS interim analysis shows a trend favoring the combination of cobimetinib and vemurafenib. Whether the results from Study GO28141 provide a favorable benefit to risk ratio to support an approval of cobimetinib for the proposed indication will be deferred to the clinical review team.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race, and Geographic Region

This reviewer conducted PFS analyses in the subgroups defined by age, gender, race, and geographic region. Figure 4.1 displays the forest plot of PFS analyses in the demographic subgroups.

Figure 4.1: PFS Results in Demographic Subgroups



*hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib.

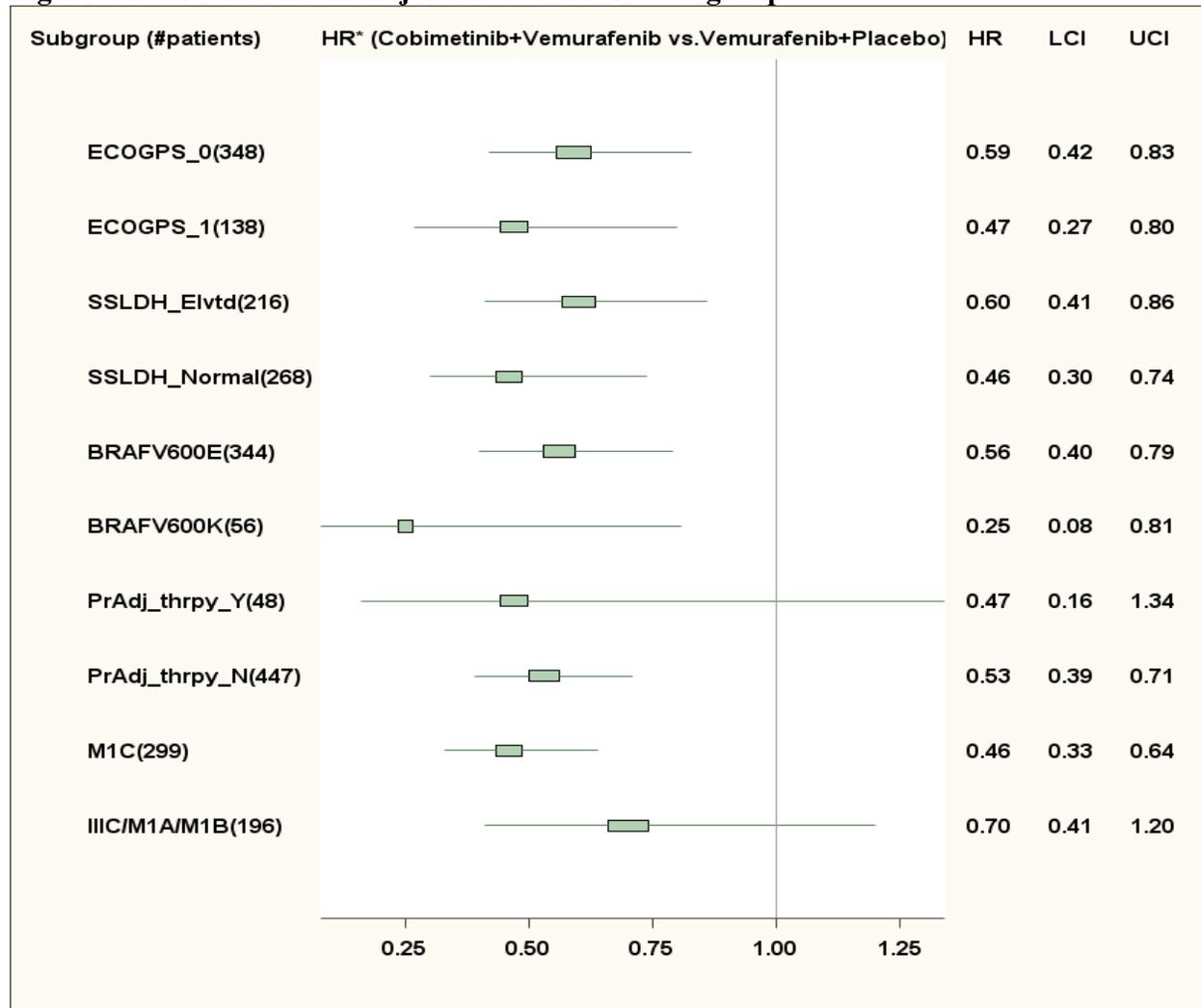
Reviewer’s Comments:

13. The subgroup analyses results are considered exploratory. The subgroup analyses results show no outliers.

4.2 Statistical Issues Other Special/Subgroup Population

This reviewer conducted the PFS analyses in subgroups defined by major baseline disease characteristics. Figure 4.2 displays the forest plot of the PFS analyses in the major characteristic subgroups.

Figure 4.2: PFS Results in major Characteristics Subgroups



* hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib.

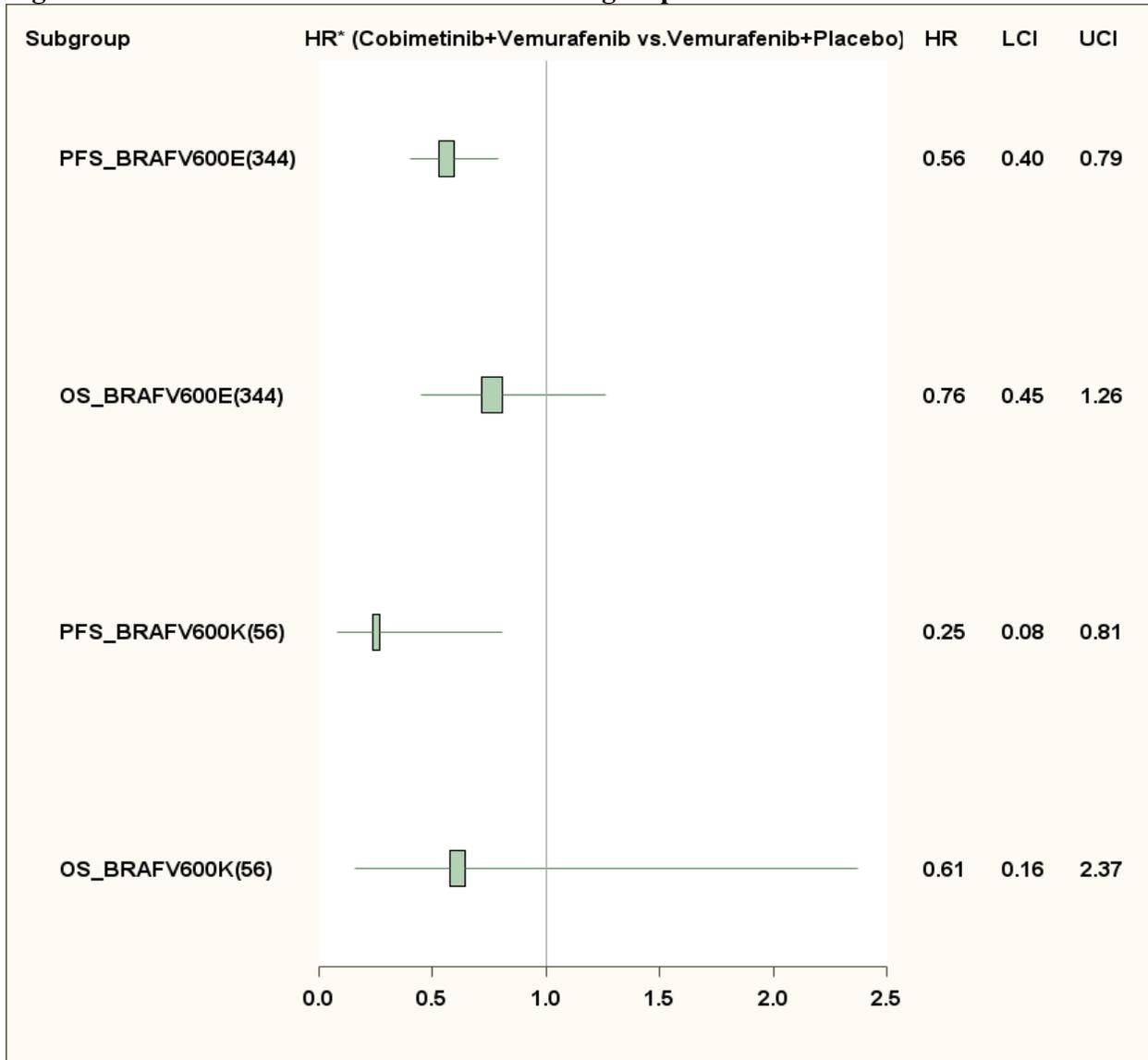
Abbreviations: ECOGPS_0/1= subgroup of patients whose Eastern Cooperative Oncology Group performance status=0/1; SSLDH_Elvtd/Normal=subgroups of patients with elevated/normal screening serum LDH level; BRAFV600E/K = subgroup of patients with BRAF V600 mutation status (V600E, V600K); PrAdj_thrpy_Y/N=subgroup of patients with/without prior adjuvant therapy; M1C= subgroup of patients with disease stage M1C; IIIC/M1A/M1B= subgroup of patients with disease stage IIIC, M1a, M1b.

Reviewer's Comments:

14. The results of the major characteristic subgroup analyses are considered exploratory. No outliers were observed.

This reviewer also conducted exploratory PFS and OS analyses in the subgroups of patients with BRAF V600 mutation status V600E or V600K. Figure 4.3 displays the forest plot of the results of PFS and OS analyses in the subgroups.

Figure 4.3: Frost Plot of PFS/OS Results in Subgroups of BRAF V600 Mutation Status



* hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib.

Abbreviations: PFS_BRAFV600E/K = PFS result in the subgroup of patients with BRAF V600 mutation status (V600E, V600K); OS_BRAFV600E/K = OS result in the subgroup of patients with BRAF V600 mutation status (V600E, V600K).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

This reviewer found no major statistical issue that impacted the primary analysis of PFS and major secondary efficacy analyses.

5.2 Collective Evidence

Based on the data from the Study GO28141, the primary analysis result of PFS demonstrated that patients in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma had statistically significant improvement in PFS when treated with combination of cobimetinib and vemurafenib compared to those treated with placebo and vemurafenib (stratified log-rank p-value <0.0001). The estimated median PFS was 9.9 months (95% CI: 9.0, NR (not reached at the time of analysis)) for combination of cobimetinib and vemurafenib arm and 6.2 months (95% CI: 5.6, 7.4) for placebo and vemurafenib arm. The hazards ratio of PFS was 0.50 (95% CI: 0.38, 0.67) in favor of the treatment with combination of cobimetinib and vemurafenib. The result of secondary endpoint ORR showed that there was statistically significantly higher objective response rate in patients treated with cobimetinib plus vemurafenib compared to those treated with placebo plus vemurafenib. Compared to the significant level of 0.0000037 (according to pre-specified OBF method), an interim OS analysis with 85 death events (22% of planned events for the final OS analysis), conducted at the time of final analysis of PFS, showed that there was no statistical difference between the two treatment arms (stratified log-rank p-value= 0.0273) with an estimated hazards ratio of 0.62 (95% CI: 0.40 0.95).

5.3 Conclusions and Recommendations

This reviewer concludes that Study GO28141 has met its primary objective. The results of Study GO28141 show that patients treated with combination of cobimetinib and vemurafenib have statistically significant improvement in progression free survival and objective response rate compared to those treated with placebo and vemurafenib. The PFS findings are statistically robust and no outlier subgroup was identified. Whether the results from Study GO28141 provide a favorable benefit to risk ratio to support an approval of cobimetinib in combination of vemurafenib for the proposed indication will be determined by the clinical review team.

5.4 Labeling Recommendations

This reviewer recommends use the primary analyses results of PFS, ORR and OS in the label of cobimetinib.

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

/s/

XIAOPING JIANG
05/06/2015

KUN HE
05/07/2015

RAJESHWARI SRIDHARA
05/11/2015

STATISTICS FILING CHECKLIST FOR NDA206192

NDA Number: 206192 Applicant: Genentech, Inc.

Stamp Date: December 11, 2014

Drug Name: Cobimetinib NDA Type: Type 1- New Molecular Entity

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

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

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

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

File name: Statistics Filing Checklist for NDA206192

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/s/

XIAOPING JIANG
01/26/2015

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