CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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

CLINICAL STUDIES

NDA/BLA #:	BLA 125554
Drug Name:	Opdivo (Nivolumab)
Indication(s):	Patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive
Applicant:	Bristol-Myers Squibb
Date(s):	Receipt Date: 07/30/2014
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Review Priority:	Priority
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Keywords: Objective Response Rate, Duration of Response

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1 EXECUTIVE SUMMARY

In this Biologics License Application, the applicant submitted Study CA209037 interim results seeking an accelerated approval for Nivolumab for the treatment of patients with advanced (unresectable or metastatic) melanoma who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor in addition to anti-CTLA-4-therapy.

The study CA 209037 was a randomized, open-label, Phase 3, multicenter, global study designed to evaluate nivolumab monotherapy (3 mg/kg every two weeks [Q2W]) vs. investigator's choice (dacarbazine or carboplatin and paclitaxel) with overall response rate (ORR) and overall survival (OS) as the co-primary endpoints. The key secondary endpoint was progression free survival. Although the study was a randomized study with two treatment arms, in this submission of interim results, a non-comparative analysis of only one of the co-primary endpoints of the study, overall response rate, was performed. The efficacy analysis population for the primary endpoint of response rate was restricted to a total of 120 subjects who were randomized and received at least one dose of the study drug, nivolumab, and had at least 6 months of follow-up.

The primary endpoint of confirmed ORR was assessed by an independent radiology review committee (IRRC) and using RECIST v1.1 criteria and was further characterized by duration of response (DOR). The primary analysis was to provide the point estimates of ORR and the corresponding two-sided 95% exact confidence interval using Clopper-Pearson method. Based on the data from 120 Nivolumab treated patients, the estimated percentage of responders was 31.7% [95% CI=(23.5, 40.8)]. The median DOR among IRRC-assessed responders in nivolumab arm was not reached at the time of data cut-off and the response durations ranged from 1.4+ to 10.0+ months. Approximately 95% of responders maintained their response with 84.2% remained on treatment including 78.9% with ongoing response at the time of analysis.

A preliminary non-comparative descriptive statistics for PFS and OS was provided in this and a subsequent interim CSR submission respectively (see the results in 3.2.4). The adequacy of the study to support an approval and whether the results from Study CA 209037 demonstrate an overall favorable benefit:risk profile is deferred to the clinical review team.

2 INTRODUCTION

Nivolumab is a programmed death-1 (PD-1) immune checkpoint inhibitor indicated for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

In this Biologics License Application (BLA), the applicant submitted Study CA209037 interim results seeking an accelerated approval for Nivolumab for the treatment of patients with advanced (unresectable or metastatic) melanoma who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor in addition to anti-CTLA-4-therapy.

2.1 Overview

Initially this BLA was submitted to IND 115195 on October 17, 2012 under Study CA209037 "A randomized, open-label phase 3 trial of BMS-936558(nivolumab) versus investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 Therapy". The primary objective of the study was to estimate the ORR in nivolumab arm and to compare OS of nivolumab to investigator's choice in subjects with advanced melanoma. The key secondary endpoint was to compare the progression-free survival (PFS) of nivolumab to investigator's choice in subjects with advanced melanoma. The corresponding endpoints were analyzed at different time points (Table 4) based on the analyses plan in the order of ORR, interim analyses for OS and final analyses of OS. PFS will be analyzed at the time of OS final analysis. In this report, the results from the formal analyses of ORR was reported based on a total of 120 subjects who were randomized and received at least one dose of the study drug, nivolumab, and had at least 6 months of follow-up followed by a preliminary non-comparative descriptive statistics for PFS and OS based on the data accrued until the ORR analysis time point.

The study was initiated in the year 2012 with the first subject enrolled on December 21, 2012 and the last patient's last visit for the ORR analysis occurred on March 10, 2014. The study CA209037 was still ongoing at the time of ORR analysis and the clinical database cutoff date occurred when the first 180 randomized subjects had at least 6 months of follow-up and. This was a multi-center and multi-national study with subjects enrolled across 90 institutions located in 14 countries (US, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, and United Kingdom). A brief summary of Study CA209037 is provided in Table 1.

Subjects were randomized 2:1 ratio to receive either of the following therapies:

- Nivolumab: Administered at 3mg/kg intravenously over 60 minutes on Day-1 of each 2 week cycle
- Chemotherapy consisting of the investigator's choice of either
    - Dacarbazine: Administered at 1000 mg/m^2 intravenously over 30 to 60 minutes on Day-1 of every 3 week treatment cycle.
    - Carboplatin and paclitaxel: Paclitaxel administered at 175 mg/m^2 as a 180 minute IV infusion on Day 1 of a every 3 week treatment cycle. Carboplatin administered at a dose of AUC 6 as a 30 minute IV infusion on Day 1 of every 3 week treatment cycle.

Treatment is continued until disease progression (PD) or unacceptable toxicity.

Table 1: List of the studies analyzed in this report

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
CA209037	Phase 3, randomized, Open-label, multi-center, active-controlled A randomized, open-label phase 3 trial of BMS-936558(nivolumab) versus investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 Therapy	*Treatment Cycles: Nivolumab arm : Two weeks Investigator's Choice: Three weeks* *Treatment was continued until PD, discontinuation due to toxicity or other reasons, or discontinuation of study therapy in sibjects receiving nivolumab beyond progression*	*Two follow-up visits (after treatment discontinuation) for safety and PK sample collection. Subjects were followed every 3 months for upto 5 years beyond the analysis of primary endpoint.*	*Treatment arm: 120* *Investigator's Choice: 60*	*Patients of atleast 18 years or older patients with histologically confirmed stage-III or IV (unresectable or metastatic) melanoma who progressed after anti-CTLA-4 therapy, regardless of the BRAF status.*

2.2 Data Sources

The application's data (including raw and analysis datasets) from the original submission for the study CA209037and the SAS programs used to derive the analysis datasets and perform the analysis are located in the following network link:
\\cdsesub1\evsprod\BLA125554\0000\m5\datasets\ca209037

The clinical study report for this study is located in the following link:
\\cdsesub1\evsprod\BLA125554\0000\m5\53-clin-study-rpts\535-rep-effic-safety-stud\melanoma\5351-stud-rep-contr\ca209037

The quality and integrity of the data will be discussed in Section-3.1.

3 STATISTICAL EVALUATION

A detailed review of Study CA209037, summary of the protocol and SAP amendments, data submitted, statistical methodologies and the efficacy results obtained using the methodologies pre-specified are presented in the following sections.

3.1 Data and Analysis Quality

The applicant submitted raw datasets in SDTM (Study Data Tabulation Model) and analysis data sets in ADaM (Analysis Data Model Implementation) formats, the defined files for the study variables and the corresponding SAS programs for the primary ADaM data derivation to document the analysis results. The documentation for the derived variables appears to be easy to follow.

This reviewer was able to replicate the applicant's primary analysis results based on the ADaM and SDTM data and conduct the reviewer's own analyses.

3.2 Evaluation of Efficacy

The study CA 209037 was a randomized, open-label, Phase 3, multicenter, global study designed to evaluate efficacy and safety of nivolumab monotherapy (3 mg/kg every two weeks [Q2W]) compared to the investigator's choice therapy (dacarbazine or carboplatin and paclitaxel) in patients with advanced melanoma who progressed after anti-CTLA-4 therapy, regardless of the BRAF status.

The primary objective for the study was to estimate the objective response rate in the nivolumab treatment arm and to compare the overall survival of nivolumab to investigator's choice in all randomized population. The target population for this study was patients with the following eligibility criteria:

- 18 years or older patients with a histologically confirmed stage-III (unresectable) or Stage IV melanoma
- Classified as PD-L1 positive, negative or indeterminate by a pretreatment recent core or biopsy with no intervening systemic therapy administered between the biopsy and the randomization
- Evidence of disease progression during or after at least 1 or 2 prior anti-CTLA-4 treatment regimens for advanced melanoma completed at least 6 weeks before the study drug administration.

- Prior chemotherapy or immunotherapy must have completed at least 4 weeks before the study drug administration or a prior radiotherapy completed atleast 2 weeks prior to first dose of study drug administration
- Measurable disease by CT or MRI as per RECIST v1.1 criteria and an ECOG performance status of 0 or 1.

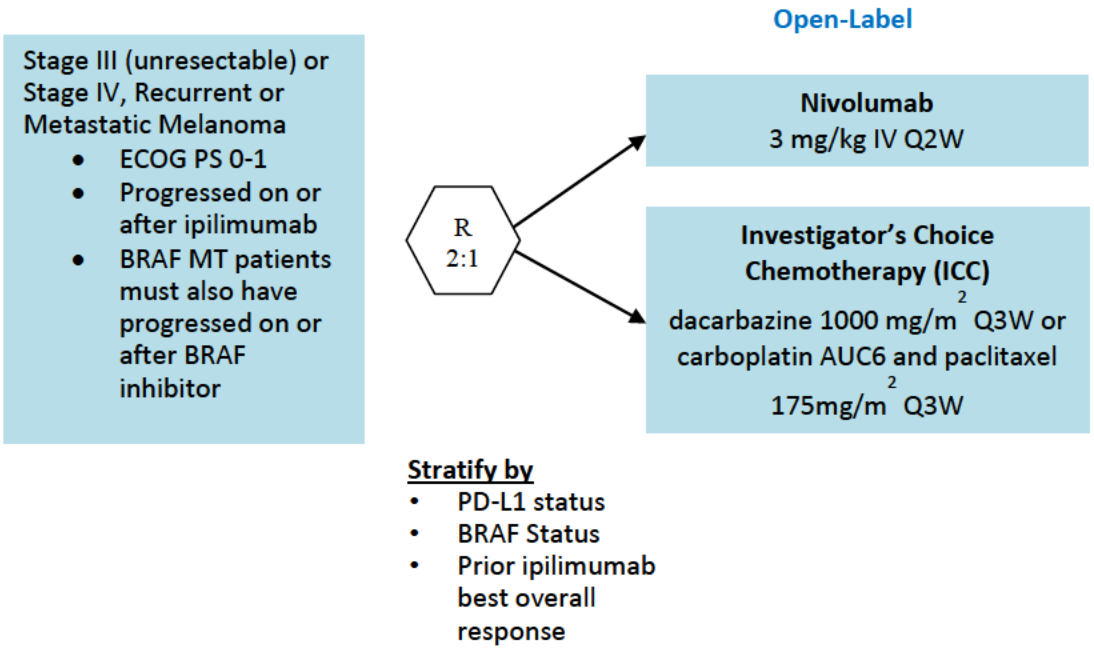
3.2.1 Study Design and Endpoints

Eligible subjects after screening were randomized in a 2:1 ratio to either the treatment arm (Nivolumab) or the control arm (investigator's choice of Dacarbazine or Carboplatin and Paclitaxel) and the randomization was stratified using the following stratification factors:

- PD-L1 status
  - PD-L1 positive vs.
  - PD-L1 negative
- BRAF status
  - Wildtype
  - Mutation positive
- Prior anti-CTLA-4 best response
  - Prior anti-CTLA-4 therapy clinical benefit (Best Overall Response of Stable Disease, Partial Response or Complete Response) vs.
  - No Prior anti-CTLA-4 therapy clinical benefit (Best Overall Response of Progressive Disease)

Figure 1 below presents the schematics of the study design.

Figure 1: Trail design for Study CA209037



Primary Efficacy Endpoint
The co-primary endpoints of the study were:

ORR: Objective response rate is defined as the percentage of subjects whose confirmed best overall response was either a complete response (CR) or partial response (PR) documented by an independent radiologic review committee (IRRC) using the RECIST v1.1 criteria.

OS: Overall survival is defined as the time from randomization to the date of death due to any cause.

Key Secondary Efficacy Endpoints

PFS: Progression-free survival is defined as the time from randomization to the date of the first documented progression as assessed by the IRRC per RECIST v1.1, or death due to any cause whichever occurs first.

In addition to the primary and secondary endpoints, the co-primary endpoint of ORR is further characterized by the duration of response (DOR) and time to response (TTR).

DOR is defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression as determined by the IRRC (per RECIST v1.1), or death due to any cause, whichever occurs first.

TTR is defined as the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by the IRRC.

Analysis Populations:

The following analyses populations were used to conduct the efficacy analyses for ORR, OS and PFS.

Enrolled population: All Subjects who signed an informed consent and were registered into the IVRS.

Randomized population: All enrolled subjects who were randomized to either treatment group in the study.

All Treated Population: All randomized subjects who were treated with at least one dose of study drug.

ORR Population: All Randomized subjects with at least 6 months of follow-up at the time of ORR analysis. This dataset was used for study population and some efficacy analyses of ORR and PFS.

Treated Subjects among ORR population: Subjects in ORR population who received at least one dose of treatment and had at least 6 months of follow-up. This is the primary analysis dataset for ORR analysis restricted to the subjects treated with nivolumab. In addition to the ORR analysis, some safety and exposure analyses were also presented for this population.

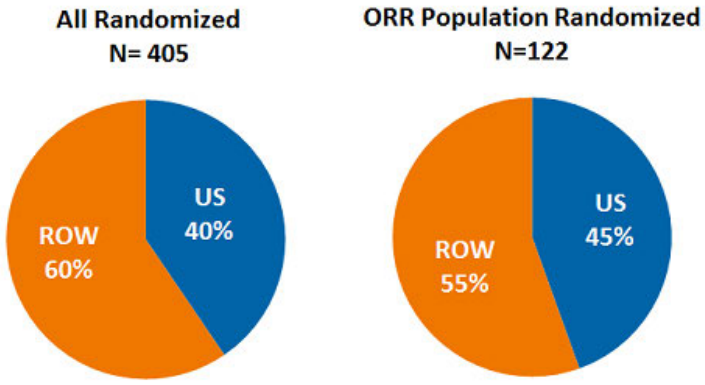
Table 2 defines the total number of subjects enrolled in the study and number of subjects in each of the analyses population defined above.

Table 2: Analyses populations

Analyses Population	Nivolumab	Investigator's Choice	Total
Enrolled: All eligible subjects who enrolled into the study			631
All Randomized: -All enrolled subjects who were randomized to either treatment group	272	133	405
All Treated Population - All subjects treated with at least one dose of study drug	268	102	370
ORR Population - All Randomized subjects with at least 6 months of follow-up at the time of ORR analysis	122	60	182
Treated Subjects among ORR population - ORR Subjects who received at least one dose of treatment	120	47	167

A total of 631 patients were enrolled in the study from 90 sites across 14 countries. Figure 2 presents the percentage of patients recruited in US vs other countries among the all randomized and the nivolumab treated ORR populations.

Figure 2: Randomization by Region



ROW: Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, United Kingdom

In this report the primary analysis of ORR was restricted to the nivolumab treated subjects among ORR population group (120 subjects) and a preliminary non-comparative descriptive statistics for PFS and OS was provided for the same population. The analysis schedule for the co-primary endpoints is defined in Table 3.

Sample Size Calculations

A total of approximately 390 subjects were planned to be randomized to the two treatment armsin a 2:1 ratio to account for the co-primary efficacy endpoints of ORR and OS with an alpha allocation of 0.1% and 4.9%, respectively. Formal analyses of ORR and OS will be conducted at different time points as defined in Table 3 with ORR being analyzed first followed by interim and final OS analyses.

ORR: Approximately 120 subjects randomized to nivolumab treatment arm (180 subjects in total: 120 in nivolumab treatment arm and 60 in investigator's choice treatment arm) having a minimum follow-up of 6 months were considered to perform the ORR formal analysis. A total of 120 subjects were considered to achieve a maximum width of 17.1% for the exact two-sided 95% confidence interval (CI) when the ORR is expected to be in the 5% to 30% range as summarized in Table 3 . A sample size of 120 patients was chosen such that the lower-limit of the exact 95% confidence interval excludes a response rate of 15% or less.

Table 3: Observed ORR with exact 95 % CI

Observed ORR	95% Exact CI
5%	(1.9%-10.6%)
10%	(5.3%-16.8%)
15%	(9.1%-22.7%)
20%	(13.3%-28.3%)
25%	(17.5%-33.7%)
30%	(22%-39%)

OS: The formal analysis of OS was performed using the all randomized analysis population. Among the 390 randomized subjects at least 260 deaths are required to achieve a 90% power to detect a hazard ratio of 0.65 corresponding to a 4.3 months improvement in median OS from 8 months in the investigator's choice arm to 12.3 months in the nivolumab arm. A planned accrual period of 17 months and a minimum follow-up period of 11 months for survival were assumed.

Interim Analyses

One formal interim analysis of OS was planned to assess the evidence of clinical benefit conducted after 65% (169 deaths) of the expected total number of 260 OS events (deaths) had occurred. Stopping the study for substantial evidence of nivolumab benefit will be considered if the OS is significantly better in the nivolumab treatment arm compared to the investigator's choice arm. The stopping boundaries for the interim analysis was derived based on the Lan-DeMets alpha spending function with O'Brien-Fleming boundaries; significance level for the interim OS analysis is 0.0105 and 0.0457 for the final OS analysis.

The projection of the timings of the analysis is given in Table 4.

Protocol amendments related to Statistical analysis:

The original protocol was finalized on September 19, 2012 and has undergone 11 amendments later on. The sample size calculations were based on some of these amendments. The major amendments related to the statistical analysis and the corresponding protocol amendment number is listed in Table 5.

Table 4: Timing and the analyses population

Endpoint	Criteria	Projected timing	Formal Analysis	Primary Population
Formal ORR analysis (1st analysis)	First approximately 180 randomized subjects with at least 6 months of follow-up	16 months from start of accrual.	ORR (95%CI)	Subjects treated with nivolumab and with at least 6 months of follow-up
Formal IA OS comparison (2nd analysis)	At least 169 deaths	19 months from start of accrual	OS (O'Brien-Fleming 4.9% two-sided) PFS (4.9% two-sided, hierarchy on OS)	All randomized subjects
Formal final OS comparison (3rd analysis)	At least 260 deaths	28 months from start of accrual	OS (O'Brien-Fleming 4.9% two-sided)	All randomized subjects

PFS (4.9% two-sided hierarchy on OS)

Table 5: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Revised Protocol 1 (Amendment-6)	13 April 2013	Update to Summary of Safety Section to include new preliminary reproductive toxicology data that was distributed as a Non-clinical Expedited Safety Report and to include change to the guidance on contraception.
Revised Protocol 2 (Amendment-8)	29 April 2013	Modified to expand the number of prior therapies allowed in the eligibility criteria. Confirmation of objective response now required and clarification that subjects receiving palliative radiotherapy would be classified as having unequivocal progression for the purpose of guiding treatment. Multiple other modifications.
Revised Protocol 3 (Amendment-9)	24 October 2013	Updated the study design to allow an adequately powered statistical comparison of the co-primary endpoint of ORR at an earlier timepoint while maintaining the power for statistical comparison of the other co-primary endpoint of OS. Formal analyses of ORR and OS will be conducted at different timepoints with ORR being analyzed first followed by interim and final OS analyses.

Revised Protocol 4 (Amendment-10)	28-Mar-2014	Study design is modified to allow non comparative estimation of ORR on nivolumab arm. OS co-primary endpoint comparison significance level increased from 2.5% to 4.9%.

There were consequently two versions of the statistical analysis plan incorporating the above amendments.

3.2.2 Statistical Methodologies

There was no formal hypothesis test of ORR planned for this interim report of Study CA209037 and the formal analysis of OS will be included in a separate CSR to be submitted later. The key patient population for the evaluation of ORR was the all treated ORR population (See Table 2) and all randomized population was considered for the OS interim and final analysis.

Analysis methods for ORR

The planned analysis of ORR was originally designed to compare the nivolumab treatment to the investigator's choice arm; however, due to protocol amendment-10, the study design was modified to allow non-comparative estimation of ORR on nivolumab arm. The point estimates of the confirmed IRRC assessed ORR and its corresponding 95% exact two-sided confidence intervals using the Clopper-Pearson method were calculated. In addition, for the subgroup analysis unweighted differences in ORR between the two treatment arms and the corresponding 95% CI using the Newcomb method were calculated.

Analysis methods for OS and PFS

Only descriptive analysis of the co-primary endpoint OS and the key secondary endpoint of PFS were presented in this report using the all treated ORR population and the ORR population. The median OS and median PFS were estimated using the Kaplan-Meier method and the corresponding 95% CI were reported. The hazard ratio for OS and PFS and the corresponding 95% CI were calculated using the cox-proportional hazards model, with treatment arm as a single covariate. The KM plots for OS and PFS were also presented.

Multiplicity adjustment

Multiplicity adjustments were incorporated within the co-primary endpoints and between the primary and secondary endpoints.

The alpha allocation for the co-primary efficacy endpoints of ORR and OS was 0.1% and 4.9%, respectively.

The efficacy analysis for the key secondary endpoint of PFS will conducted only at the time of final OS analysis. The co-primary endpoint OS analysis will serve as the gatekeeper for the PFS analyses, i.e., the primary efficacy hypothesis of OS must be rejected at the 2-sided 0.049 significance level before the efficacy hypotheses for the secondary efficacy endpoints of PFS can be evaluated.

Analysis method for DOR and TTR

Median response duration and the time to response calculated using the Kaplan-Meier method and the corresponding two-sided 95% CI, and range were reported for each treatment arm for subjects with a confirmed BOR of CR or PR. For subjects who neither progress nor die, the duration of objective response will be censored at the same time they will be censored for the primary definition of PFS.

Sensitivity analysis for ORR

Sensitivity analysis was performed to support the primary analysis of ORR using the following:

1. Investigator's assessed ORR analysis using the all treated ORR analysis population.
2. IRRC assessed ORR using the ORR analysis population.

Reviewer's Comment:

1. *Concordance rate between the IRRC and investigator assessed ORR was computed to check for discrepancies in the assessments.*
2. *This reviewer has performed an additional descriptive analysis OS and PFS using the all treated ORR population in addition to the sponsor's analysis of OS and PFS using the ORR population.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

The first subject was enrolled on December 21, 2012 and the last patient's last visit for the ORR analysis occurred on March 10, 2014. The study CA209037 was still ongoing at the time of ORR analysis and the database cutoff date for the ORR analysis occurred on April 30, 2014. Table 6 presents the patient disposition status as of the data cutoff date of ORR analysis.

Among the 405 subjects who were randomized to either treatment arm, 182 subjects had a minimum 6 months of follow-up by the data cutoff date for ORR analysis which occurred on April 30, 2014. Similarly, among the 370 subjects who were randomized and treated with at least one-dose of study drug, 167 subjects had a minimum follow-up of 6 months by the cutoff date.

Table 6: Disposition of Subjects

	Nivolumab	Investigator's Choice	
Subjects Enrolled			631
Subjects Randomized	272	133	405
Subjects not randomized:			226
Reason for Screen failure:			
Did not meet inclusion Criteria			198
Withdrew Consent			17
Died before randomization			3
Adverse Event			1
Lost to follow-up			1
Poor/Non-compliance			1
Other			5
Subjects Treated	268	102	370
Subjects not treated	4	31	35
Reason for not being treated:			
Discontinue study treatment	0	5	5
Withdrew consent	1	22	23
Poor/non-compliance	1	0	1
Did not meet study criteria any longer	2	2	4
Other	0	2	2
Randomized subjects with 6 months follow-up	122	60	182
Treated subjects with 6 months follow-up	120	47	167

Demographic Characteristics

Table 7 and Table 8 present the patient demographic characteristics for the all randomized and the treated subjects among ORR analysis populations respectively. In general, the distribution of demographic characteristics for both the analyses populations appears to be balanced between treatment arms.

Table 7: Demographic Characteristics for All Randomized Subjects

	Nivolumab N=272	Investigator's Choice N=133	Total N=405
Age			
N	272	133	405
Mean(std dev)	58.7 (14.1)	60.3 (12.4)	59.2 (13.6)
Median	59	62	60
Min,Max	23,88	29,85	23,88

Age Categorization			
< 65	177 (65.1%)	80 (60.2%)	257 (63.5%)
>= 65 AND < 75	55 (20.2%)	37 (27.8%)	92 (22.7%)
>= 75	40 (14.7%)	16 (12.0%)	56 (13.8%)
Gender			
Female	96 (35.3%)	48 (36.1%)	144 (35.6%)
Male	176 (64.7%)	85 (63.9%)	261 (64.4%)
Race			
Asian	2 (0.7%)	0 (0.0%)	2 (0.5%)
Black or African American	1 (0.4%)	2 (1.5%)	3 (0.7%)
Other	0 (0.0%)	2 (1.5%)	2 (0.5%)
White	269 (98.9%)	129 (97.0%)	398 (98.3%)
Region			
US	106 (39.0%)	58 (43.6%)	164 (40.5%)
Non-US	166 (61.0%)	75 (56.4%)	241 (59.5%)
Smoking			
Yes	109 (40.1%)	60 (45.1%)	169 (41.7%)
No	148 (54.4%)	65 (48.9%)	213 (52.6%)
Unknown	15 (5.5%)	8 (6.0%)	23 (5.7%)
Baseline LDH Category			
<= ULN	129 (47.4%)	77 (57.9%)	206 (50.9%)
> ULN	139 (51.1%)	46 (34.6%)	185 (45.7%)
Not Reported	4 (1.5%)	10 (7.5%)	14 (3.5%)
ECOG Performance Score			
0	162 (59.6%)	84 (63.2%)	246 (60.7%)
1	110 (40.4%)	48 (36.1%)	158 (39.0%)
2	0 (0.0%)	1 (0.8%)	1 (0.2%)

Reviewer's Comment:
Age was derived based on the birth date and the informed consent date.

Table 8: Demographic Characteristics for Treated subjects among ORR population

	Nivolumab N=120	Investigator's Choice N=47	Total N=167
Age			
N	120	47	167
Mean (std dev)	58 (13.8)	61.6 (13.2)	59 (13.7)
Median	58	64	60
Min,Max	25,88	29,84	25,88
Age Categorization			
< 65	82 (68.3%)	25 (53.2%)	107 (64.1%)
>= 65 AND < 75	24 (20.0%)	15 (31.9%)	39 (23.4%)
>= 75	14 (11.7%)	7 (14.9%)	21 (12.6%)
Gender			
Female	42 (35.0%)	17 (36.2%)	59 (35.3%)
Male	78 (65.0%)	30 (63.8%)	108 (64.7%)
Race			
Asian	2 (1.7%)	0 (0.0%)	2 (1.2%)
Black Or African American	0 (0.0%)	1 (2.1%)	1 (0.6%)
Other	0 (0.0%)	1 (2.1%)	1 (0.6%)
White	118 (98.3%)	45 (95.7%)	163 (97.6%)
Region			
US	52 (43.3%)	22 (46.8%)	74 (44.3%)
Non-US	68 (56.7%)	25 (53.2%)	93 (55.7%)
Smoking			
No	63 (52.5%)	25 (53.2%)	88 (52.7%)
Unknown	4 (3.3%)	0 (0.0%)	4 (2.4%)
Yes	53 (44.2%)	22 (46.8%)	75 (44.9%)
Baseline LDH Category			
<= ULN	53 (44.2%)	27 (57.4%)	80 (47.9%)
> ULN	67 (55.8%)	20 (42.6%)	87 (52.1%)
ECOG Performance Score			
0	70 (58.3%)	26 (55.3%)	96 (57.5%)
1	50 (41.7%)	20 (42.6%)	70 (41.9%)
2	0 (0.0%)	1 (2.1%)	

Baseline Disease Characteristics

Table 9 and Table 10 below summarize the baseline disease characteristics for the all randomized and the treated subjects among ORR analysis populations respectively. In general, the distribution of baseline characteristics for both the analyses populations also appears to be balanced between treatment arms.

Table 9: Baseline Disease Characteristics for All Randomized Subjects

	Nivolumab N=272	Investigator's Choice N=133	Total N=405
M Stage at study entry			
M0	10 (3.7%)	2 (1.5%)	12 (3.0%)
M1A	15 (5.5%)	11 (8.3%)	26 (6.4%)
M1B	44 (16.2%)	18 (13.5%)	62 (15.3%)
M1C	203 (74.6%)	102 (76.7%)	305 (75.3%)
AJCC Stage at Study entry			
STAGE III	11 (4.0%)	2 (1.5%)	13 (3.2%)
STAGE IV	261 (96.0%)	131 (98.5%)	392 (96.8%)
Brain Metastases			
NO	219 (80.5%)	115 (86.5%)	334 (82.5%)
YES	53 (19.5%)	18 (13.5%)	71 (17.5%)

Table 10: Baseline Disease Characteristics for Treated subjects among ORR population

	Nivolumab N=120	Investigator's Choice N=47	Total N=167
M Stage at study entry			
M0	5 (4.2%)	0 (0.0%)	5 (3.0%)
M1A	8 (6.7%)	2 (4.3%)	10 (6.0%)
M1B	16 (13.3%)	10 (21.3%)	26 (15.6%)
M1C	91 (75.8%)	35 (74.5%)	126 (75.4%)
AJCC Stage at Study entry			
STAGE III	5 (4.2%)	0 (0.0%)	5 (3.0%)
STAGE IV	115 (95.8%)	47 (100.0%)	162 (97.0%)
Brain Metastases			
NO	99 (82.5%)	40 (85.1%)	139 (83.2%)
YES	21 (17.5%)	7 (14.9%)	28 (16.8%)

Stratification factors Characteristics

Table 11 and Table 12 below summarize the stratification factors of PD-L1 status, BRAF status and prior anti-CTLA-4 best response for the all randomized and the treated subjects among ORR analysis populations respectively.

Table 11: Stratification factors for All Randomized Subjects

	Nivolumab N=272	Investigator's Choice N=133	Total N=405
PD-L1 Status			
Negative/Indeterminate	138 (50.7%)	66 (49.6%)	204 (50.4%)
Positive	134 (49.3%)	67 (50.4%)	201 (49.6%)
BRAF Status			
Mutant	60 (22.1%)	29 (21.8%)	89 (22.0%)
Wild Type	212 (77.9%)	104 (78.2%)	316 (78.0%)
Prior Anti-CTLA-4 Best Response			
No Prior Therapy Benefit (BOR Of PD)	173 (63.6%)	86 (64.7%)	259 (64.0%)
Prior Therapy Clinical Benefit (BOR Of CR, PR Or SD)	99 (36.4%)	47 (35.3%)	146 (36.0%)

Table 12: Stratification factors for Treated subjects among ORR population

	Nivolumab N=120	Investigator's Choice N=47	Total N=167
PD-L1 Status			
Negative/Indeterminate	65 (54.2%)	25 (53.2%)	90 (53.9%)
Positive	55 (45.8%)	22 (46.8%)	77 (46.1%)
BRAF Status			
Mutant	26 (21.7%)	11 (23.4%)	37 (22.2%)
Wild Type	94 (78.3%)	36 (76.6%)	130 (77.8%)
Prior Anti-CTLA-4 Benefit			
No Prior Therapy Benefit (BOR Of PD)	76 (63.3%)	31 (66.0%)	107 (64.1%)
Prior Therapy Clinical Benefit (BOR Of CR, PR Or SD)	44 (36.7%)	16 (34.0%)	60 (35.9%)

3.2.4 Results and Conclusions

In this section, the non-comparative primary efficacy results for the co-primary endpoint of ORR based on the treated subjects among ORR population is presented. The analysis results are restricted to the nivolumab-treated arm; however, the results from the Investigator's choice arm are also presented for reference and no formal hypothesis tests were performed. In addition, using the same patient population and the ORR population, a preliminary non-comparative analysis of the co-primary endpoint of OS and the key secondary endpoint of PFS were also presented.

The best overall response based on the IRRC assessed confirmed response for the treated subjects among ORR population is summarized by response category for each treatment arm in Table 13.

Table 13: Best Overall Response for the treated subjects among ORR population

Best Overall Response	Nivolumab N=120	Investigator's Choice N=47
Complete Response	4 (3.3%)	0 (0.0%)
Partial Response	34 (28.3%)	5 (10.6%)
Stable Disease	28 (23.3%)	16 (34.0%)
Progressive Disease	42 (35.0%)	15 (31.9%)
Not Evaluable	12 (10.0%)	11 (23.4%)

Primary Efficacy Analysis of ORR:

Table 14 presents the efficacy analysis results for confirmed ORR characterized by the median duration of response calculated based on the responders whose best overall response of either CR or PR. The ORR was 31.7% [95% CI= (23.5, 40.8)] in the nivolumab arm. Although the median response duration was not reached in the nivolumab arm, the range of the response duration was 1.4+ to 10+ months with 95% of the ongoing response at the time of data cutoff for ORR formal analysis.

Among the 38 responders, 1 patient dies, 1 had PD, 3 patients among the 36 remaining responders were censored. Among the 36 patients who were censored: 3 patients were censored due to initiation of subsequent therapy, 3 patients were progression free during the follow-up and the remaining 30 were still on treatment. Hence, the number of ongoing responders were 87% (33/36) in the nivolumab arm.

Table 14: ORR results for the treated subjects among ORR population

	Nivolumab (N=120)	Investigator's choice (N=47)
ORR n (%) CR PR	38 (31.7%) 4 34	5 (10.6%) 0 5
95% CI of response rate	(23.5,40.8)	(3.5,23.1)
Median Response Duration in months (range) [a]	Not reached (1.4+, 10+)	3.6 (1.3+, 3.5)
Median Time to response in months (range)	2.1 (1.6, 7.4)	3.5 (2.1, 6.1)
Response ongoing[b]	87%	40%

CR: Complete Response PR: Partial Response

[a]: DOR for the subjects who were censored at the last tumor assessment date is denoted by a + symbol

[b]: see the reviewer's comment below for the calculation of ongoing responders

Reviewer's comment:
According to the response to the information request, dated Dec 2, 2014, the Applicant stated that the percentage of ongoing responders was 89% (previously stated as 95% in the CSR) which was computed by considering the patients who had not had a PD-defining event or were not censored for receiving further treatment at the data cutoff date (30/38), who were progression free during the follow-up (3/38) and also included one additional patient who was censored by the IRRC due to initiation of subsequent therapy (surgical resection of lesion in small bowel that was biopsy-proven melanoma) but was not assessed to have a PD by the IRRC as they did not evaluate this lesion. The Applicant considered this particular patient as an ongoing responder since the IRRC was not following this lesion and did not assess the patient to have PD. However, this reviewer does not consider the patient censored due to initiation of subsequent therapy by the investigator after declaring PD on a new biopsy-proven lesion and hence limits the percentage of ongoing responses to those who had not had a PD-defining event or were not censored for receiving further treatment by the data cutoff date (30/38) and those who were progression free during follow-up (3/38).

Table 15 presents the Kaplan-Meier estimates of the response duration, calculated as the time between the first confirmed best response of either CR or PR until disease progression, for the 38 responders in the nivolumab-treated arm.

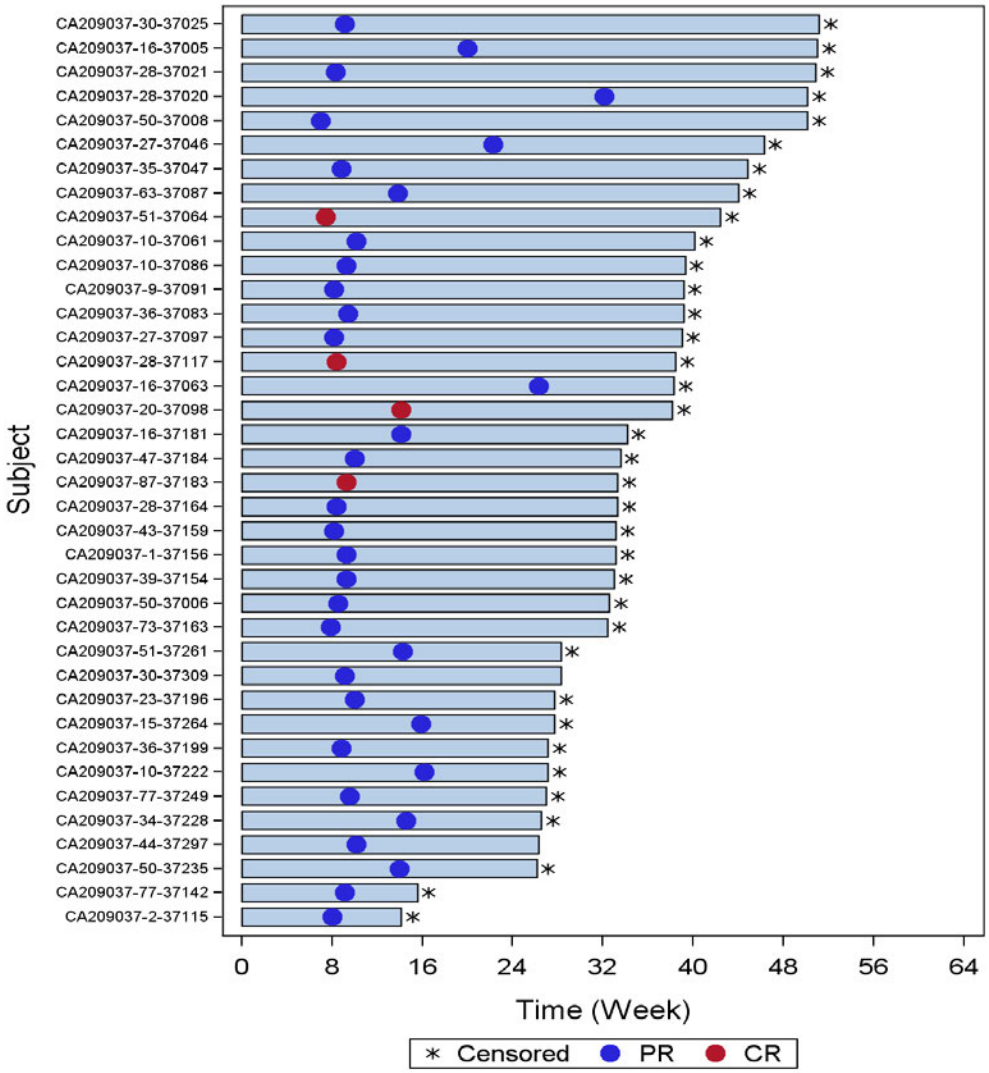
Table 15: Response Duration in months for the responders in the Nivolumab arm

Patient ID	Nivolumab Responders N=38
CA209037-2-37115	1.45*
CA209037-77-37142	1.51*
CA209037-10-37222	2.56*
CA209037-15-37264	2.76*
CA209037-16-37063	2.79*
CA209037-34-37228	2.79*
CA209037-50-37235	2.83*
CA209037-51-37261	3.25*
CA209037-44-37297	3.75
CA209037-77-37249	4.04*
CA209037-23-37196	4.11*
CA209037-28-37020	4.17*
CA209037-36-37199	4.24*
CA209037-30-37309	4.44
CA209037-16-37181	4.63*
CA209037-47-37184	5.45*
CA209037-39-37154	5.49*
CA209037-1-37156	5.52 *
CA209037-20-37098	5.55*
CA209037-27-37046	5.55*
CA209037-50-37006	5.55*
CA209037-87-37183	5.55*
CA209037-73-37163	5.68*
CA209037-28-37164	5.75*
CA209037-43-37159	5.78*
CA209037-36-37083	6.87*
CA209037-10-37061	6.93*
CA209037-10-37086	6.93*
CA209037-28-37117	6.93*
CA209037-63-37087	6.97*
CA209037-27-37097	7.13*
CA209037-16-37005	7.16*
CA209037-9-37091	7.16*
CA209037-51-37064	8.08*
CA209037-35-37047	8.31*
CA209037-30-37025	9.69*
CA209037-28-37021	9.82*
CA209037-50-37008	9.95*

* Patient is either still on treatment as of the cutoff date, received subsequent therapy, off study or progression free in follow-up

Figure 3 presents the graphical display of the response duration analysis for the nivolumab-treated responders.

Figure 3: Plot of response duration for the nivolumab responders



Sensitivity Analysis of ORR

A sensitivity analysis was performed to assess the robustness of the primary ORR results based on:

1. Investigator assessed ORR using the same analysis population as the primary analysis of ORR
2. IRRC assessed ORR using the ORR analysis population.

Table 16: Sensitivity analysis of ORR

	Sensitivity Analysis-1		Sensitivity Analysis-2	
	Nivolumab (N=120)	Investigator's choice (N=47)	Nivolumab (N=122)	Investigator's choice (N=60)
ORR CR PR	31 (25.83%) 2 29	5 (10.6%) 0 5	38 (31.1%) 4 34	5 (8.3%) 0 5
95% CI	(18.3,34.6)	(3.6,23.1)	(23.1,40.2)	(2.8,18.4)
Median Response Duration in months (range) [a]	Unavailable*	Unavailable*	Not reached (1.4+, 10+)	3.6 (1.3+, 3.5)

*The data corresponding to the investigator assessed DOR was not available

There was 75.4% concordance between the IRRC and the Investigator assessments for the responders vs. non-responders in the nivolumab treatment arm and 81.7% in the investigator's choice arm.

Preliminary Efficacy Analysis of the co-primary endpoint OS:

A non-comparative preliminary analysis of the OS endpoint based on the data cutoff for the ORR formal analysis and the all randomized population is presented in Table 16. The corresponding Kaplan-Meier plots for the survival probabilities are given in Figure 4 and Figure 5. No conclusions can be drawn from the interim results since the data is immature and there is a high percentage of censoring due to the early cutoff date.

Table 17: OS efficacy results for Treated subjects among ORR population

	ORR Treated subjects		**All Randomized Subjects**	
	Nivolumab n=120	**Investigator's choice n=47**	**Nivolumab n=272**	**Investigator's choice n=133**
No of events	33 (28.33%)	14 (29.79%)	69 (25.37%)	25 (18.8%)
Median(95% CI)	NR(11.47,NR)	11.76(7.79,NR)	NR(11.47,NR)	11.76(7.786,NR)
HR	0.78(0.42, 1.47)		1.02(0.64, 1.61)	
Nominal p-val (Unstratified logrank test)	0.446		0.9472	

Figure 4: KM plot for OS based on Treated subjects among ORR population

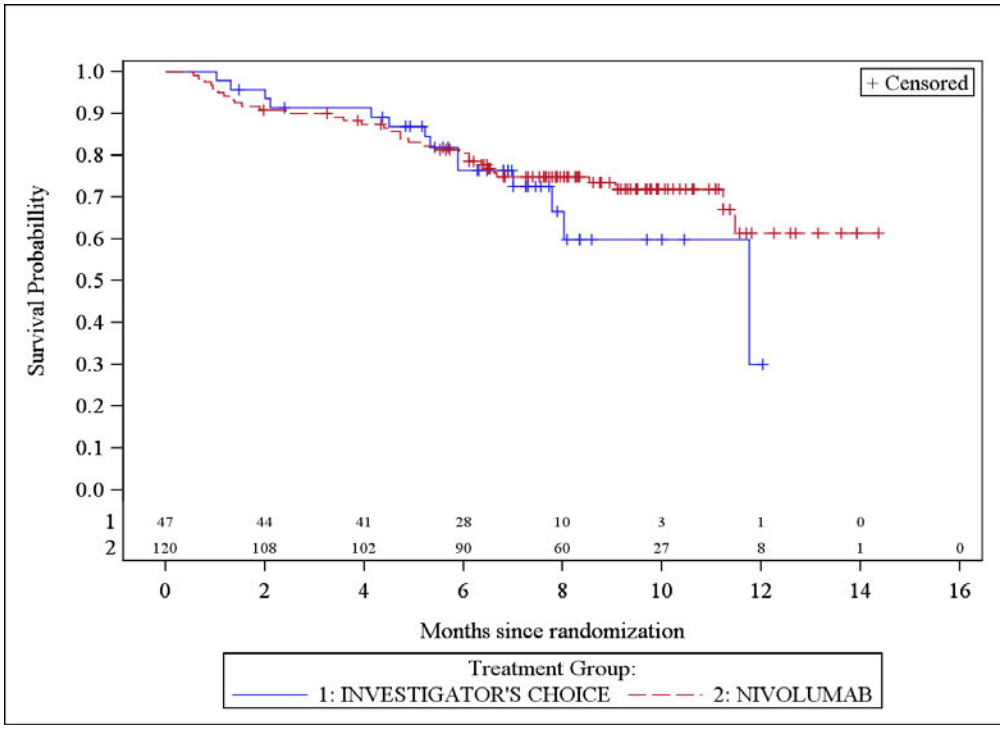
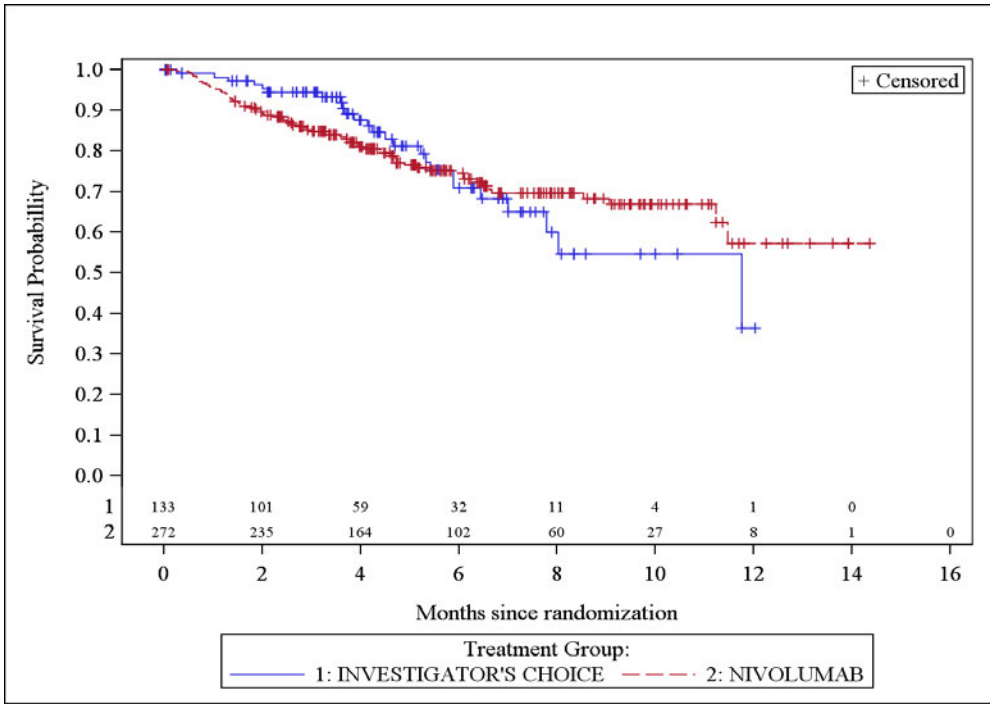


Figure 5: KM plot for OS based on Treated subjects among ORR population



Preliminary Efficacy Analysis of the key secondary endpoint of PFS

Table 17 presents the efficacy results for PFS as assessed by the Investigator and the IRRC based on the ORR treated analysis data. The corresponding KM curves of PFS in Figure 6 and Figure 7 graphically shows the difference in the assessments.

Table 18: INV and IRC assessed PFS efficacy results for the ORR treated population

	PFS by INV		**PFS by IRC**	
	Nivolumab n=120	**Investigator's choice n=47**	**Nivolumab n=120**	**Investigator's choice n=47**
No of events, n (%)	71 (59.17%)	33 (70.21%)	70 (58.33%)	26 (55.32%)
Median (95% CI)	3.58 (2.33,6.54)	2.17 (2.1,4.21)	4.67 (2.33,6.51)	4.24 (2.14,6.34)
Unadjusted HR	0.62 (0.41,0.94)		0.73 (0.46, 1.16)	
Nominal p-val (Unstratified logrank test)	0.0212		0.1773	

Figure 6: KM Plot for PFS assessed by Investigator

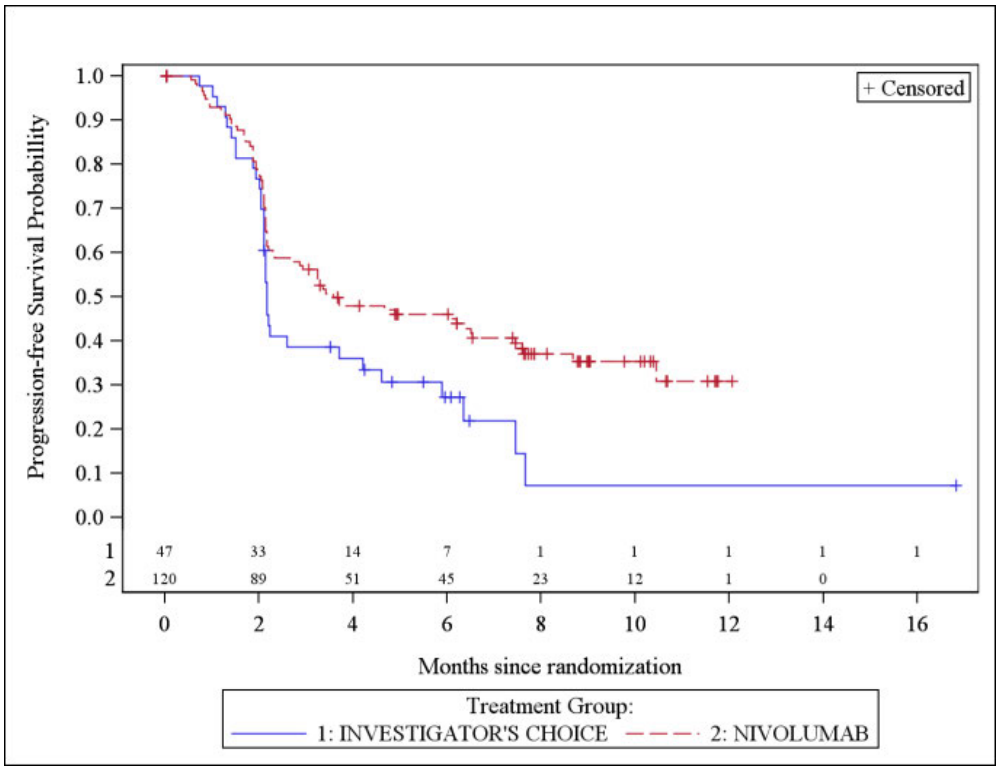
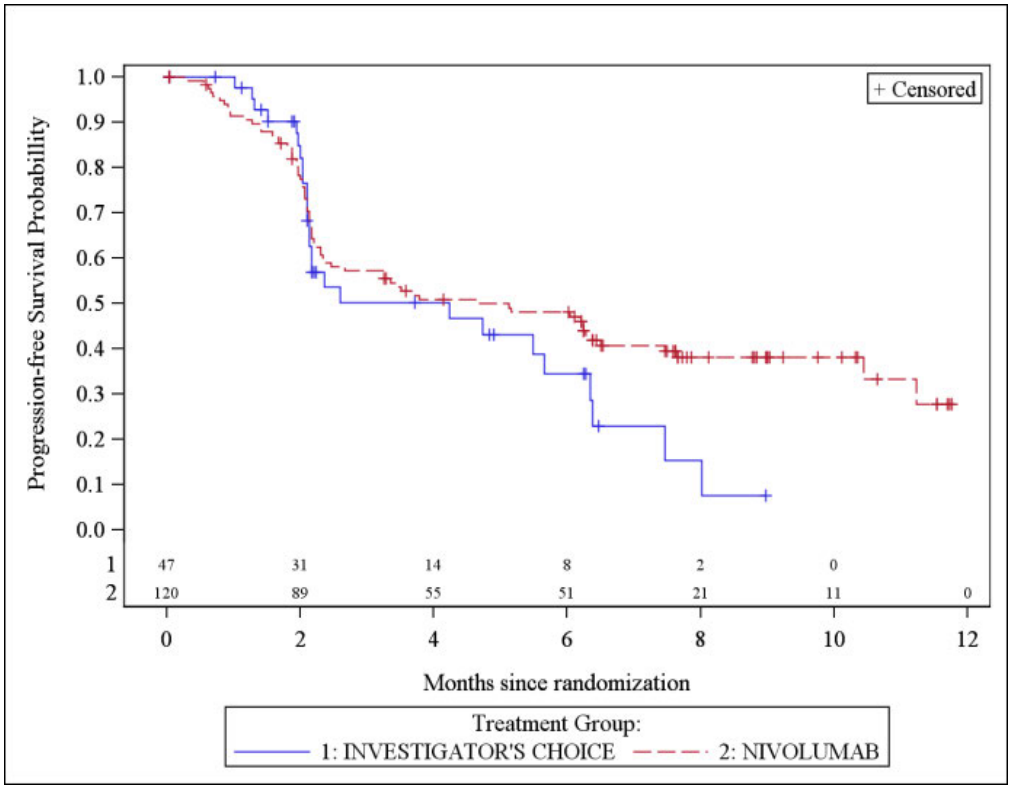


Figure 7: KM Plot for PFS assessed by IRC



3.3 Evaluation of Safety

The safety assessments were deferred to the clinical judgment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis results based on the following factors were examined for the ORR co-primary endpoint using the treated subjects among ORR analysis population.

- BRAF Status (wild vs. positive)
- PD-L1 status (≥ 5% vs. < 5% cutoff)
- Prior anti-CTLA-4 benefit (yes/no)
- M Stage at study entry (M0/M1a/M1b and M1c)
- Age (< 65, ≥ 65 to <75, and ≥75 years)
- Gender (male and female)
- Race (White, Black, Asian, and Other)
- Region (US vs. Non-US)
- Baseline ECOG Performance Status (0 and 1)
- History of Brain Metastases (yes/no)

- Smoking Status (yes/no)
- Baseline LDH (≤ULN, > ULN)
- AJCC Stage (III and IV)

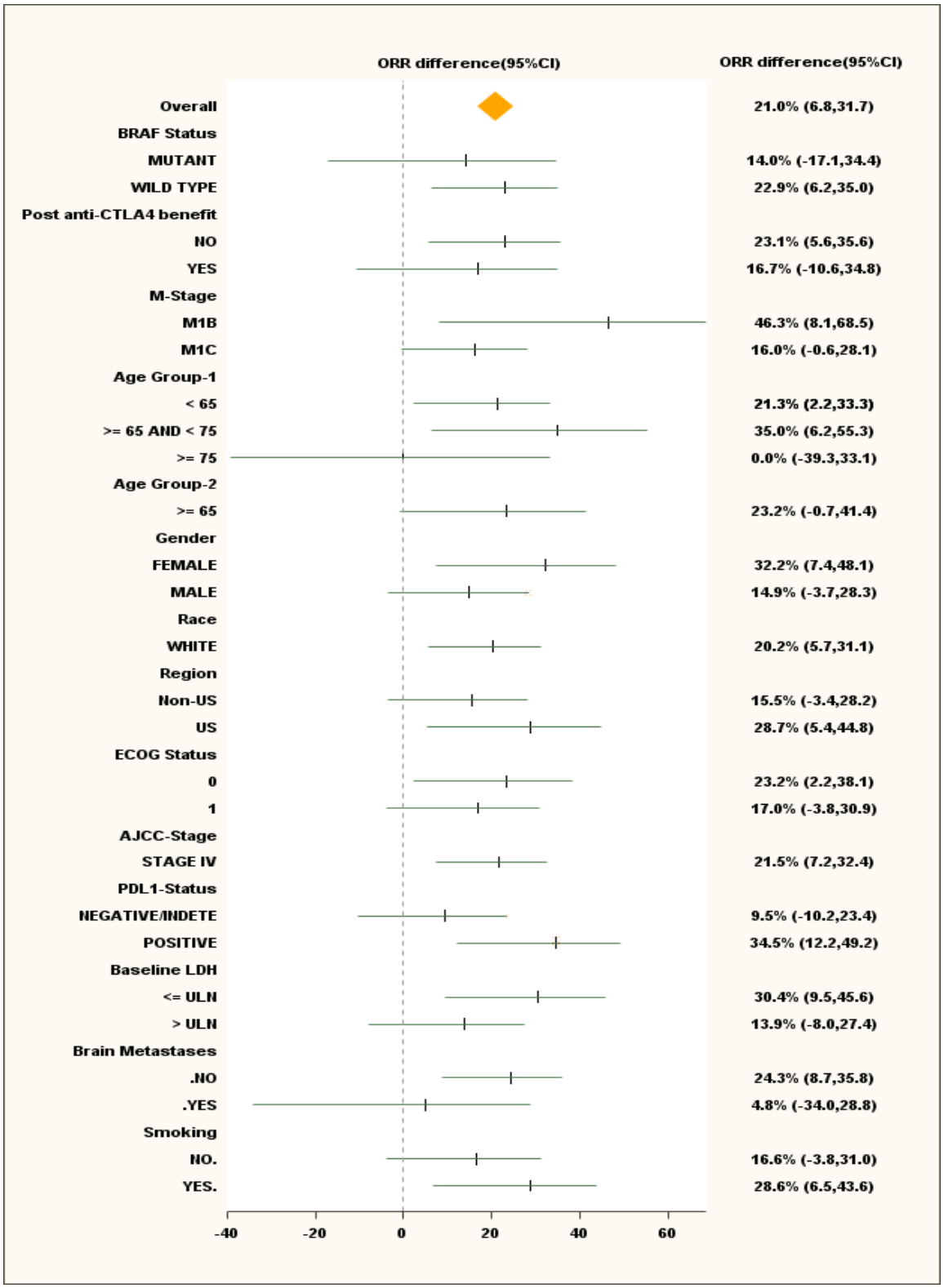
All subgroup efficacy analyses were performed for the primary analysis data of ORR and only the subgroups with sufficient sample size are presented in this report. The unweighted differences in the ORR between the treatment and the control arm and the corresponding 95% exact confidence intervals computed using the Newcomb method are summarized in Table 18 and Figure 8 displays the corresponding forest plot.

Table 19: Subgroup analysis results of ORR based on the ORR treated population

Subgroup Variable	Subgroup Level	Nivolumab		Investigator's Choice		Unweighted ORR Diff (95% CI)
		#Resp/n	%Resp (95% CI)	#Resp/n	%Resp (95% CI)	
Overall		38/120	31.7% (23.5, 40.8)	5/47	10.6% (3.5, 23.1)	21.0% (6.8,31.7)
BRAF Status	Mutant	6/26	23.1% (9.0, 43.6)	1/11	9.1% (0.2, 41.3)	14.0% (-17.1,34.4)
	Wild Type	32/94	34.0% (24.6, 44.5)	4/36	11.1% (3.1, 26.1)	22.9% (6.2,35.0)
Post Anti-CTLA4 therapy benefit	No	26/80	32.5% (22.4, 43.9)	3/32	9.4% (2.0, 25.0)	23.1% (5.6,35.6)
	Yes	12/40	30.0% (16.6, 46.5)	2/15	13.3% (1.7, 40.5)	16.7% (-10.6,34.8)
M stage at study entry	M0	1/5	20.0% (0.5, 71.6)			
	M1a	3/8	37.5% (8.5, 75.5)	0/2		
	M1b	9/16	56.3% (29.9, 80.2)	1/10	10.0% (0.3, 44.5)	46.3% (8.1,68.5)
	M1c	25/91	27.5% (18.6, 37.8)	4/35	11.4% (3.2, 26.7)	16.0% (-0.6,28.1)
Age group 1	< 65	24/82	29.3% (19.7, 40.4)	2/25	8.0% (1.0, 26.0)	21.3% (2.2,33.3)
	>= 65 And < 75	10/24	41.7% (22.1, 63.4)	1/15	6.7% (0.2, 31.9)	35.0% (6.2,55.3)
	>= 75	4/14	28.6% (8.4, 58.1)	2/7	28.6% (3.7, 71.0)	
Age group 2	< 65	24/82	29.3% (19.7, 40.4)	2/25	8.0% (1.0, 26.0)	21.3% (2.2,33.3)
	>= 65	14/38	36.8% (21.8, 54.0)	3/22	13.6% (2.9, 34.9)	23.2% (-0.7,41.4)
Gender	Female	16/42	38.1% (23.6, 54.4)	1/17	5.9% (0.1, 28.7)	32.2% (7.4,48.1)
	Male	22/78	28.2% (18.6, 39.5)	4/30	13.3% (3.8, 30.7)	14.9% (-3.7,28.3)

Subgroup Variable	Subgroup Level	Nivolumab		Investigator's Choice		Unweighted ORR Diff (95% CI)
		#Resp/n	%Resp (95% CI)	#Resp/n	%Resp (95% CI)	
Race	Asian	1/2	50.0% (1.3, 98.7)			
	Black Or Africa			0/1		
	Other			0/1		
	White	37/118	31.4% (23.1, 40.5)	5/45	11.1% (3.7, 24.1)	20.2% (5.7,31.1)
Region	Non-US	16/68	23.5% (14.1, 35.4)	2/25	8.0% (1.0, 26.0)	15.5% (-3.4,28.2)
	Us	22/52	42.3% (28.7, 56.8)	3/22	13.6% (2.9, 34.9)	28.7% (5.4,44.8)
ECOG PS	0	27/70	38.6% (27.2, 51.0)	4/26	15.4% (4.4, 34.9)	23.2% (2.2,38.1)
	1	11/50	22.0% (11.5, 36.0)	1/20	5.0% (0.1, 24.9)	17.0% (-3.8,30.9)
Brain Metastases	No	34/99	34.3% (25.1, 44.6)	4/40	10.0% (2.8, 23.7)	24.3% (8.7,35.8)
	Yes	4/21	19.0% (5.4, 41.9)	1/7	14.3% (0.4, 57.9)	4.8% (-34.0,28.8)
Smoking	No	18/63	28.6% (17.9, 41.3)	3/25	12.0% (2.5, 31.2)	16.6% (-3.8,31.0)
	Yes	20/53	37.7% (24.8, 52.1)	2/22	9.1% (1.1, 29.2)	28.6% (6.5,43.6)
AJCC Stage at study entry	Stage III	1/5	20.0% (0.5, 71.6)			
	Stage IV	37/115	32.2% (23.8, 41.5)	5/47	10.6% (3.5, 23.1)	21.5% (7.2,32.4)
PD L1 Status (IVRS)	Negative/Indeterminate	14/65	21.5% (12.3, 33.5)	3/25	12.0% (2.5, 31.2)	9.5% (-10.2,23.4)
	Positive	24/55	43.6% (30.3, 57.7)	2/22	9.1% (1.1, 29.2)	34.5% (12.2,49.2)
Baseline LDH	<= ULN	22/53	41.5% (28.1, 55.9)	3/27	11.1% (2.4, 29.2)	30.4% (9.5,45.6)
	> ULN	16/67	23.9% (14.3, 35.9)	2/20	10.0% (1.2, 31.7)	13.9% (-8.0,27.4)

Figure 8: Forest plot for subgroup analysis of ORR based on the ORR treated population



5 SUMMARY AND CONCLUSIONS

5.1 Summary

In summary, based on Study CA209037, the interim analysis results based on the 120 nivolumab treated patients, patients who received at least one dose of nivolumab and were followed for at least 6 months, the percentage of responders was 31.7% (38/120) with 95% exact confidence interval as (23.5, 40.8). Among the 38 responders, 4 patients had a complete response and 34 had a partial response. By the time of the data cutoff for the ORR analysis, the median response of duration was not reached and the response durations ranged from 1.4+ to 10.0+ months. Approximately 95% (36/38) of responders maintained their response with 84.2% (32/38) remained on treatment including 78.9% (30/38) with ongoing response at the time of analysis.

5.2 Statistical Issues

The interim study report is a single arm analysis of nivolumab treated subjects and no statistical issues were encountered during the analysis.

5.3 Conclusions and Recommendations

In conclusion, this statistical reviewer confirms the applicant's efficacy results submitted. The overall favorable benefit to risk assessment of nivolumab in supporting an indication for advanced (unresectable or metastatic) melanoma progressing post anti-CTLA-4 therapy is deferred to the clinical review team.

5.4 Labeling Recommendations

This statistical reviewer supports the inclusion of results based on the primary analysis of objective response rate for the indication of advanced melanoma based on nivolumab treatment. The discussions for the labelling are still ongoing and any further recommendations will be included in the labelling insert.

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/s/

SIRISHA L MUSHTI
12/05/2014

KUN HE
12/05/2014

THOMAS E GWISE
12/05/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125554 **Applicant: Bristol-Meyers Squibb** **Stamp Date: 30 July 2014**

Drug Name: Nivolumab **NDA/BLA Type: Priority**

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? ✓

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: 5_Statistics Filing Checklist for a New NDA_BLA110207

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SIRISHA L MUSHTI
09/11/2014

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