CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s000

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 1

NDA/BLA #:	BLA 125514
Drug Name:	MK-3475 (Pembrolizumab)
Indication(s):	Unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab
Applicant:	Merck Sharp & Dohme Corp.
Date(s):	Receipt: 04/30/2014 PDUFA: 10/28/2014
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Emmanuel Sampene
Concurring Reviewers:	Kun He, Team Leader Rajeswari Sridhara, Division Director
Medical Division:	Division of Oncology Products 2
Clinical Team:	Jennie Chang, Reviewer Meredith Chuk Marc Theoret, Team Leader Patricia Keegan, Division Director
Project Manager:	Sharon Sickafuse

Keywords: Objective response rate

There was a typographical error in Table 7 titled "Response Duration". This is an addendum to BLA 125514, submitted on 7/31/2014. The follow-up time was changed from weeks to months.

By the time of data cut-off for the final analysis, the median duration of responses was not reached with a lower bound of 95% confidence interval of 6 weeks. Eighteen out of 21 responders still maintained their responses as the date of the data cut-off for the CSR.

Table 7 shows the response duration in weeks for the 2 mg/kg treatment arm.

Table 1 Response Duration

Patient	Follow-up (months) MK-3475 2 mg/kg Q3W
0011000315	1.4
0019000279	2.8*
0021000369	2.8
0001000284	2.8
0019000380	2.8
0010000253	2.9*
0019000338	3.0
0021000324	4.7
0020000318	5.1
0020000322	5.1
0016000346	5.6
0010000341	5.6
0011000307	5.9
0010000274	8.3*
0020000290	8.3
0016000306	8.3
0010000255	8.4
0015000294	8.4
0021000287	8.4
0023000269	8.5
0023000280	8.5

* means patient dropped out of study

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/s/

EMMANUEL SAMPENE

08/01/2014

This is an addendum To BLA 125514 sumitted on 7/31/2014. Response duration in Table 7 was changed from weeks to months

KUN HE

08/01/2014

RAJESHWARI SRIDHARA

08/01/2014

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

In this Biologics License Application (BLA), the applicant is seeking an accelerated approval for pembrolizumab in patients with advanced melanoma and refractory to ipilumumab.

The study P001 Part B2 was a multi-center, open-label, Phase I trial in patients with locally advanced or metastatic melanoma. Although P001 is labelled a Phase I study due to its initial dose escalation component, it evolved into multiple Phase II-like sub-studies in melanoma and NSCLC through a series of expansion cohorts in these types of cancer. The key patient population to support the proposed indication is the ipilumumab (IPI) refractory patients in the all patients as treated (APaT) population, referred to as, Part B2 population. A total of 173 patients form the Part B2 cohort. The primary endpoint was objective response rate (ORR) per independent radiology review with integrated oncology assessment (IRO) using RECIST 1.1. The key secondary endpoints were overall response rate (ORR) per immune-related response criteria (irRC) per investigator and overall response rate (ORR) per independent review committee (IRC).

Although Study P001 Part B2 was a randomized study with study arms MK-3475 2 mg/kg Q3W and MK-3475 10 mg/kg Q3W, in this submission, only 2 mg/kg Q3W data and analyses are relevant. The data and analysis for patients in the MK-3475 2 mg/kg Q3W treatment arm of Part B2 study population demonstrated an ORR of (23.6%, 95% CI: 15.2, 33.8). Although the median response duration was not reached, the response durations ranged from 6+ to 37+ weeks at the data cut-off date.

Whether the data and analyses from the current submission demonstrated an overall favorable benefit vs. risk profile is deferred to the clinical team reviewing this application.

2 INTRODUCTION

MK-3475 (previously known as SCH 900475) is a highly selective humanized mAb of the IgG4/kappa isotope designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. In this Biologics License Application, the applicant is seeking an accelerated approval of MK-3475. This submission included efficacy and safety data in patients with locally advanced metastatic melanoma who are refractory to ipilimumab.

2.1 Overview

2.1.1 Class and Indication

Malignant melanoma is the second fastest growing cancer worldwide. This type of cancer is the most lethal, although melanoma only accounts for 5% of skin cancer cases. Some of the risk factors for melanoma include exposure to UV rays, white ethnicity, and advanced age. The median age of diagnosis is 61 years old. The 5-year survival of patients with metastatic melanoma is about 15%.

Prior to 2011, the standard treatment option for patients with unresectable advanced melanoma was single-agent dacarbazine. However, the current recommended treatment options for BRAF-mutant melanoma are the three approved agents (vemurafenib, dabrafenib, trametinib), which produce response rates of 22-57%

Also, ipilimumab (IPI), which is an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) mAb, has demonstrated that immune modulation could be an effective treatment of metastatic melanoma. A recent study has shown the decrease in the risk of death when IPI is used in a combination therapy with dacarbazine in a first line setting.

MK-3475 is designed to directly block PD-1 and its ligands. It enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients and primates. On January 17, 2013, FDA granted MK-3475 a breakthrough designation

2.1.2 History of Drug Development

This study P001, titled "Phase 1 Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma and Non-Small Cell Lung Carcinoma" was initially submitted to IND 110080 on December 9, 2010. This BLA was submitted to FDA on February 27, 2014, while an expanded access protocol was opened on February 28, 2014. The original protocol was amended 50 times. The key amendments related to statistics were:

- Amendment 2:
    - P001 Part B1 was initiated under this amendment.
    - The sample size was increased to include more IPI-treated patients and included a 2 mg/kg Q3w dose level

- Patients were not randomly assigned, but were enrolled under sequential but overlapping amendments.

- Amendment 5:
  - P001 Part B2 and D were initiated under this amendment.

- Amendment 6:
  - The sample size was increased to 84 subjects in the MK-3475 10 mg/kg Q3W treatment arm of P001 Part B2
  - Changed the allocation schedule to achieve a final 1:1 randomization between treatment arms MK-3475 2 mg/kg Q3W and MK-3475 10 mg/kg Q3W.

- Amendment 8:
  - The primary method of assessment of the ORR primary efficacy endpoint was changed from immune-related response criteria (irRC) to RECIST 1.1 by independent central review.

A pre-BLA meeting was held on October 25, 2013. Agreements were made on the format and content for BLA for study P001.

2.2 Data Sources

The electronic submission including protocols, statistical analysis plan, study reports, analysis datasets, and SAS programs for this submission are located on the network with network path: \\Cdsesub1\bla\eCTD_Submissions\STN125514

3 STATISTICAL EVALUATION

Part of the text, tables and figures presented in this review were adapted from the CSR.

3.1 Data and Analysis Quality

This reviewer was able to reproduce the analysis dataset, duplicate the analysis variable derivation and summary statistics. No further data resubmission was requested.

3.2 Evaluation of Efficacy

3.2.1 Objective

The primary efficacy objective of study P001 Part B2 was to determine the best overall response rate (ORR) by independent central radiologic review of disease assessment based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. An additional method used to assess efficacy included determination of best overall response using immune-mediated response criteria (irRC) by both investigators and independent review. The key secondary efficacy objectives included response duration, PFS and OS.

3.2.2 Study Design and Endpoints

P001 is a Phase 1 multi-center, open-label study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics and anti-tumor activity of MK-3475 in patients with locally advanced or metastatic melanoma (IPI-naïve or previously treated with IPI), NSCLC, or carcinoma. Study P001 evolved into multiple Phase II-like sub-studies in melanoma and NSCLC through a series of expansion cohorts, namely, Parts A, B, C, D and F. Table 1 presents the different patient distributions for the expansion cohorts.

Table 1 P001 Patient Distribution

	Cohort	Disease Indication	MK-3475 Dose	Dose Frequency	IPI status	Enrollment Status	Allocation method	PD-L1 Status	Total N[2]
Part A	A	Solid Tumors	1, 3 and 10 mg/kg	Q2W	NA	Completed	Non-randomized	NA	10
	A1	Solid Tumors	10 mg/kg	Q2W	NA	Completed	Non-randomized	NA	7
	A2	Solid Tumors	2 or 10 mg/kg[1]	Q3W	NA	Completed	Randomized	NA	13
Part B	B1	Melanoma	2 or 10 mg/kg	Q2W or Q3W	Naïve or Treated	Completed	Non-randomized	All comers	135
	B2	Melanoma	2 or 10 mg/kg	Q3W	Refractory	Completed	Randomized	All comers	173
	B3[3]	Melanoma	10 mg/kg	Q2W or Q3W	Naïve or Treated or Refractory	Completed	Randomized	All comers	248
Part C		NSCLC	10 mg/kg	Q3W	NA	Completed	Non-randomized	All comers	38
Part D		Melanoma	2 or 10 mg/kg	Q3W	Naïve	Completed	Randomized	All comers	103
Part F[3]	F1	NSCLC	10 mg/kg	Q2W or Q3W	NA	Ongoing	Randomized	Positive	43
	F2	NSCLC	10 mg/kg	Q2W or Q3W	NA	Ongoing	Randomized	Positive or Negative	200

Source: CSR Table 2

The P001 study was initially designed as a standard dose escalation trial, and was the first in human study of MK-3475. This portion of the trial constitutes Part A of P001 study. The Part B sub-cohort is made up of the melanoma patient population, while Parts C and D are comprised of NSCLC patients. However, Parts D and F cohorts are still ongoing.

In addition, P001 Part B1 was initially designed to evaluate and confirm the efficacy of MK-3475. This sub-group includes patients who were naïve to IPI or who had been previously treated with IPI. Also, Part B1, which consists of 135 patients, compared three different dosing regimens of MK-3475 2mg/kg every 3 weeks or 10mg/kg every 2 or 3 weeks.

Likewise, Part D, which consists of 103 patients, was designed to evaluate the efficacy of MK-3475 in a patient population who were naïve to IPI. However, Part B2 is the sub-study in IPI refractory melanoma that forms the primary basis for approval consideration in the proposed indication in this application.

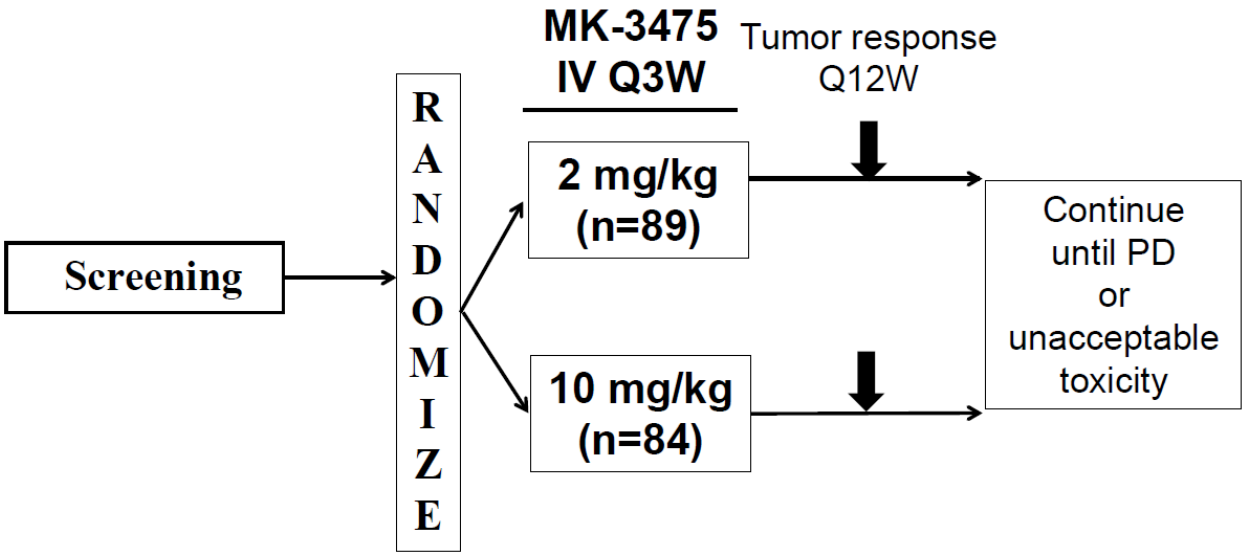
3.2.3 P001 Part B2

This study was designed to evaluate the efficacy of MK-3475 in a population of patients who had progressed on prior IPI, and for those patients with BRAF V600E mutations, had also received a prior BRAF or MEK inhibitor.

Treatment was administered over 30 minutes in 3 weeks cycles of MK-3475 with a dose of 2mg/kg. Disease assessment was performed every 12 weeks, and treatment continued until disease progression or unacceptable toxicity.

The primary endpoint was assessed by independent central radiologic review of disease assessment based on RECIST 1.1, while the secondary endpoint was assessed using immune-related response criteria per investigator. Figure 1 presents the study schema.

Figure 1: Trial design of P001 Part B2



P001 Part B2, which consists of 173 IPI-refractory patients, is the key patient population to support the proposed indication for the use of MK-3475 in the treatment of melanoma in the all patient as treated (APaT) population. The APaT population consists of all patients who received at least 1 dose of study treatment. Thus, the primary efficacy analysis was based on the APaT population.

The main inclusion criteria were:

- Advanced unresectable melanoma
- Progression after at least 2 doses of IPI within 6 months of last dose of IPI, documented on 2 separate assessments
- BRAF V600 mutant patients must have received prior BRAFi or MEKi
- No limit on number of prior therapies

3.2.4 Statistical Methodologies

3.2.4.1 Efficacy Measures

ORR was defined as the percentage of subjects with complete response (CR) or partial response (PR) documented by independent central radiologic review and immune-mediated response by investigator or independent review

Response Duration was only determined for confirmed responses and was defined as the time from first documentation of response to first documentation of disease progression.

PFS was measured from the start of treatment to documentation of definitive disease progression or death due to any cause, whichever occurs first. PFS was assessed with disease progression defined by RECIST 1.1 by independent central review, by irRC by independent central review, and by irRC based on investigator assessment.

OS was defined as time from treatment initiation to death due to any cause.

3.2.4.2 Sample Size Consideration

Eligible patients were randomly assigned to MK-3475 at a dose of 2mg/kg or 10mg/kg. Initially, randomization was 2:1 in favor of the 2mg/kg Q3W dose, but the allocation schedule was changed to achieve a final 1:1 randomization after a series of amendments. As a result, there were 89 subjects in the MK-3475 2mg/kg Q3W arm compared with 84 subjects in the MK-3475 10mg/kg Q3W arm. Consequently, 173 subjects were used for analysis.

Also, melanoma patients from Parts B1, B2 and D (N=411 treated patients) of P001 were part of an interim analysis. These cohorts of patients form the basis for the indication of MK-3475 for melanoma in patients who were previously treated with IPI

3.2.4.3 Efficacy Analysis

The key patient population to support the use of MK-3475 in the treatment of melanoma previously treated with IPI is the all patient as treated (APaT) population. This population was the primary population for evaluating efficacy results.

Efficacy Analysis Method for ORR

The planned analysis of ORR was originally designed to compare the 2 mg/kg Q3W and 10 mg/kg Q3W treatment arms using a 2-sided Miettinen and Nurminen's method. However, since only the 2 mg/kg arm is considered in this submission, point estimates and binomial exact confidence intervals will be performed.

Efficacy Analysis Method for Response Duration

Response duration analysis was assessed by Kaplan-Meier methodology based on confirmed responses from integrated radiology and oncology (IRO) assessment using RECIST 1.1.

Efficacy Analysis Method for PFS

The analysis of PFS was performed using log-rank test. The median PFS with corresponding 95% CIs and survival curves were estimated using the Kaplan-Meier (KM) method.

Efficacy Analysis Method for OS

The OS analysis method was identical to PFS analysis.

Reviewer's Comments:
Since in this submission only 2 mg/kg Q3W data are relevant, any time-to-event analyses are uninterpretable. Even if it is considered as RCT, there are numerous adaptations that have occurred to conduct a valid hypothesis testing

3.2.5 Patient Disposition, Demographic and Baseline Characteristics

3.2.5.1 Patient Disposition

Tables 2 presents patient disposition which includes unknown disposition status at the time of data cutoff for study Parts B2.

Table 2 P001 Part B2 Patient Disposition

	MK-3475 2 mg/kg Q3W n	MK-3475 10 mg/kg Q3W n
Patients in population	89	84
Subject Study Medication Disposition		
Discontinued	54	46
Adverse Event	12	17
Lost To Follow-Up	1	1
Physician Decision	3	1
Progressive Disease	34	25
Protocol Violation	2	0
Withdrawal By Subject	2	2
Unknown	35	38

Table 3 presents the patient disposition for Part D.

Table 3 P001 Part D Patient Disposition

	MK-3475 2 mg/kg Q3W n	MK-3475 10 mg/kg Q3W n
Patients in population	51	52
Subject Study Medication Disposition		
Discontinued	26	28
Adverse Event	4	8
Physician Decision	1	0
Progressive Disease	18	20
Protocol Violation	1	0
Withdrawal By Subject	2	0
Unknown	25	24

3.2.5.2 Demographic and Baseline Characteristics

Table 4 presents the study and patient characteristics.

Table 4 P001 B2 Patient Demographics

	MK-3475 2 mg/kg Q3W n	(%)	MK-3475 10 mg/kg Q3W n	(%)
Patients in population	89		84	
Gender				
Male	48	(53.9)	57	(67.9)
Female	41	(46.1)	27	(32.1)
Age (Years)				
< 65	59	(66.3)	52	(61.9)
>=65	30	(33.7)	32	(38.1)
Mean	57.0		60.7	
SD	15.0		12.7	
Median	59.0		62.5	
Range	18 to 88		27 to 86	
Race				
Asian	1	(1.1)	2	(2.4)
Black Or African American	1	(1.1)	0	(0.0)
Multiracial	0	(0.0)	1	(1.2)
White	87	(97.8)	81	(96.4)
Geographic Region				
United States	70	(78.7)	62	(73.8)
Canada	5	(5.6)	9	(10.7)
Australia	6	(6.7)	4	(4.8)
France	8	(9.0)	9	(10.7)

Table 5 presents the baseline characteristics.

Table 5 P001 B2 Baseline Characteristics

	MK-3475 2 mg/kg Q3W n	(%)	MK-3475 10 mg/kg Q3W n	(%)
BRAF Mutation				
Mutant	12	(13.5)	18	(21.4)
Wild Type/Normal	77	(86.5)	66	(78.6)
Brain Metastases				
Yes	7	(7.9)	8	(9.5)
No	81	(91.0)	75	(89.3)
UNK	1	(1.1)	1	(1.2)
Number of Prior Systemic Therapies				
1	29	(32.6)	19	(22.6)
2	31	(34.8)	34	(40.5)
3 or more	29	(32.6)	31	(36.9)
Baseline Lactate Dehydrogenase				
Normal	49	(55.1)	55	(65.5)
Elevated	39	(43.8)	29	(34.5)
NULL	1	(1.1)	0	(0.0)

Reviewer's Comments:
There were no apparent differences with respect to demographic and baseline disease characteristics.

3.2.6 Results and Conclusions

3.2.6.1 Primary Efficacy Endpoint - ORR

The randomization scheme was not strictly adhered to, with regards to the treatment schedules. In particular, two patients who were initially randomized to receive 2 mg/kg Q3W were wrongly administered the 10 mg/kg Q3W dose schedule. Since in this submission only 2 mg/kg Q3W was considered, the efficacy analysis population would consist of all patients who actually received 2 mg/kg Q3W. In this section, all reported results are based on all patients who actually received 2 mg/kg Q3W instead of randomized to 2 mg/kg Q3W arm.

Table 6 presents the applicant's efficacy analysis for ORR based on the IRC measurements. The ORR was approximately 24% in both arms. Although the median response duration was not reached, the range of the response duration was 6+ to 37+ weeks. Also, at the 2 mg/kg Q3W treatment arm, 86% (18/21) of the responding patients had an ongoing response at the time of data cut-off.

Table 6 ORR Results for P001 Part B2

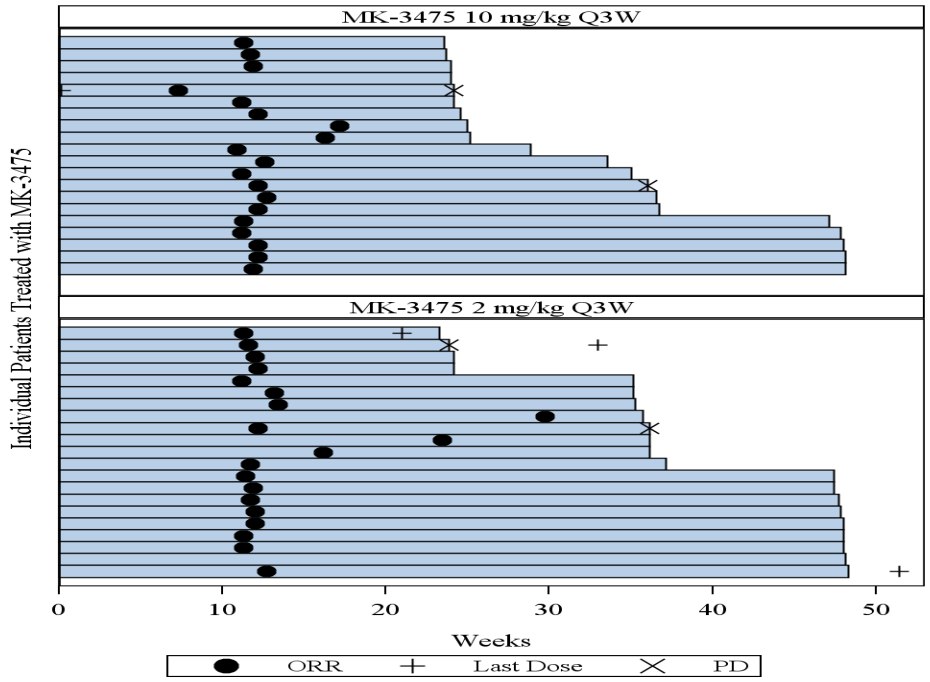
	MK-3475 2 mg/kg Q3W (N=89)	MK-3475 10 mg/kg Q3W (N=84)
ORR	23.6%	23.8%
CR	1	1
PR	20	19
95% CI	(15.2-33.8)	(15.2-34.3)
Response Duration Median in weeks (range)	Not reached (6+, 37+)	Not reached (8+, 37+)
Response ongoing	86%	90%

CR= Complete Response, PR= Partial Response

Response duration was estimated by the Kaplan-Meier method based on confirmed responses from IRO assessment using RECIST 1.1, by measuring the interval from the first recorded response of a confirmed best response until disease progression.

Figure 2 presents the graphical display of the response duration analysis, showing the number of patients with a confirmed objective response (N=41).

Figure 2 Plot of Time to Response and Time to Progression



By the time of data cut-off for the final analysis, the median duration of responses was not reached with a lower bound of 95% confidence interval of 6 weeks. Eighteen out of 21 responders still maintained their responses as the date of the data cut-off for the CSR.

Table 7 shows the response duration in weeks for the 2 mg/kg treatment arm.

Table 7 Response Duration

Patient	Follow-up (Weeks) MK-3475 2 mg/kg Q3W
0001000284	12
0010000253	12*
0010000255	36
0010000274	35
0010000341	24*
0011000307	26
0011000315	6
0015000294	36
0016000306	36
0016000346	24
0019000279	12
0019000338	13
0019000380	12
0020000290	36
0020000318	22
0020000322	22
0021000287	36
0021000324	20
0021000369	12
0023000269	37
0023000280	37

* means patient dropped out of study

There were different measures used to assess patient responses. In particular, IRC assessment was based on independent central review using RECIST 1.1 but without the integrated oncology assessment, while IRO per RECIST included the oncology assessment.

Table 8 presents the comparison of the efficacy results of study P001 Part B2 using different disease assessment

Table 8 Comparison of ORR in P001 Part B2

	IRO by RECIST		IRO by irRC		IRC by RECIST		INV by irRC	
	MK-3475 2 mg/kg Q3W (N=89)	MK-3475 10 mg/kg Q3W (N=84)	MK-3475 2 mg/kg Q3W (N=89)	MK-3475 10 mg/kg Q3W (N=84)	MK-3475 2 mg/kg Q3W (N=74)	MK-3475 10 mg/kg Q3W (N=75)	MK-3475 2 mg/kg Q3W (N=79)	MK-3475 10 mg/kg Q3W (N=73)
ORR	24%	24%	19%	24%	28%%	27%	30%	37%
CR	1	1	0	1	1	1	3	0
PR	20	19	17	19	20	19	21	27
(95% CI)	(15-34)	(15-34)	(12-29)	(15-34)	(19-40)	(17-38)	(21-42)	(26-49)
Response Duration Median	NR	NR	NR	NR	NR	NR	NR	NR
Range (Weeks)	(6+, 37+)	(8+, 37+)	(6+, 37+)	(6+, 37+)	(6+, 37+)	(8+, 37+)	(12+,42+)	(8+, 37+)

NR= Not Reached

Reviewer's Comments:
There were different sets of response criteria used to assess measurements, and therefore discordance analysis between IRC and INV cannot be performed.

Table 9 presents sensitivity analysis of patients, who at baseline, had only one first line IPI-treatment compared to patients who had more than one IPI-treatment.

Table 9 Sensitivity analysis of 1st line IPI vs greater than 1st line

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W	
Variable	1st line IPI	>1st line	1st line IPI	>1st line
Ipilumumab:	N=40	N=44	N=29	N=45
ORR	28%	27%	28%	33%
CR	1	1	0	0
PR	10	11	8	15
(95% CI)	(15, 44)	(15, 43)	(13, 47)	(20, 49)

Reviewer's Comments:
The sensitivity analysis suggests that there was no differential response among patients who had more than one line of IPI treatment compared with patients with only first line IPI.

3.2.6.2 Secondary Endpoint – PFS

The Kaplan-Meier methodology was used to estimate PFS for patients in this study. The primary method of assessment of PFS is based on RECIST 1.1 measurements by IRO. The median PFS for the 2 mg/kg Q3W and 10 mg/kg Q3W treatment arms are 22 weeks and 14 weeks, respectively. The PFS analyses are presented in Table 10 and Figure 3 below:

Table 8 PFS Based on IRO Assessment per RECIST 1.1

	MK-3475 2 mg/kg Q3W (N=89)	MK-3475 10 mg/kg Q3W (N=84)	MK-3475 2 mg/kg Q3W Versus MK-3475 10 mg/kg Q3W		
			Hazard Ratio[†]	95% CI for Hazard Ratio[†]	p-Value[‡]
Number (%) of PFS Events	54 (60.7)	53 (64.3)	--	--	--
Number of progression events	38	46			
Deaths	16	8			
Person-Weeks	1987	1562	--	--	--
Event Rate/100 Person-Weeks (%)	2.7	3.5	--	--	--
Median PFS (Months)[§]	5.5	3.5	0.84	(0.57,1.23)	0.355
95% CI for Median PFS[§]	(3.0,9.0)	(3.0,6.0)	--	--	--
PFS rate at 12 Weeks in % [§]	65.5	58.9	--	--	--
PFS rate at 24 Weeks in % [§]	44.5	37.1	--	--	--

Source: CSR Table 56

Reviewer's Comments:
Please note that PFS results, although presented for both arms, are uninterpretable for 2 mg/kg Q3W.

3.2.6.3 Secondary Endpoint – OS

Table 11 presents the efficacy analysis for OS with a total of 54 (31%) death events across both treatment arms. The median OS was approximately 13 months (95% CI: 10.1, NR) for the 2 mg/kg Q3W arm.

Table 9 OS Analysis

	MK-3475 2 mg/kg Q3W (N=89)	MK-3475 10 mg/kg Q3W (N=84)
Death (%)	32 (36.0)	22 (26.2)
Median Survival (Months)[§]	12.7	Not reached
95% CI for Median Survival[§]	(10.1,.)	(.,.)
OS rate at 6 Months in % [§]	78.8	78.7
OS rate at 12 Months in % [§]	53.0	66.9

Source: CSR Table 65

Reviewer's Comments:
Please note that OS results, although presented for both arms, are uninterpretable for 2 mg/kg Q3W.

3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Since 98% of the study population was of white ethnicity, subgroup analysis based on race was omitted. Table 12 summarizes ORR subgroup analysis results by age, gender and geographic region per IRC assessment.

Table 10 ORR Results based on Age, Sex and Region

Variable	MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W			
Age:	<65 (N=59)		>=65 (N=30)		<65 (N=52)		>=65 (N=32)	
ORR	27%		17%		23%		25%	
CR	0		1		1		0	
PR	16		4		11		8	
(95% CI)	(16, 40)		(6, 35)		(13, 39)		(11, 43)	
Sex:	Male (N=48)		Female (N=41)		Male (N=57)		Female (N=27)	
ORR	23%		24%		23%		26%	
CR	1		0		0		1	
PR	10		10		13		6	
(95% CI)	(12, 37)		(12, 40)		(13, 36)		(11, 46)	
Geographic Region:	USA (N=70)	CAN (N=5)	FRA (N=8)	AUS (N=6)	USA (N=62)	CAN (N=9)	FRA (N=9)	AUS (N=4)
ORR	19%	60%	38%	33%	26%	22%	0	50%
CR	1	0	0	0	0	0	0	1
PR	12	3	3	2	16	2	0	1
(95% CI)	(10, 30)	(15, 95)	(9, 76)	(4, 78)	(16, 39)	(3, 60)	NA	(7, 93)

Reviewer's Comments:
These subgroup analyses are exploratory.

4.2 Other Special/Subgroup Populations

Table 13 summarizes ORR subgroup analysis results per important baseline disease characteristics based on IRC assessments.

Table 11 ORR Results Based on Baseline Disease Characteristics

Variable	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W	
ECOG:	0	1	0	1
	(N=59)	(N=30)	(N=57)	(N=27)
ORR	25%	20%	21%	30%
CR	0	1	1	0
PR	15	5	11	8
(95% CI)	(15, 38)	(8, 39)	(11, 34)	(14, 50)
Brain Metastases:	Yes	No	Yes	No
	(N=7)	(N=81)	(N=8)	(N=75)
ORR	29%	23%	25%	24%
CR	0	1	0	1
PR	2	18	2	17
(95% CI)	(4, 71)	(15, 34)	(3, 65)	(15, 35)
Lactate Dehydrogenase (LDH):	Elevated	Normal	Elevated	Normal
	(N=39)	(N=49)	(N=29)	(N=55)
ORR	31%	18%	14%	29%
CR	1	0	0	1
PR	11	9	4	15
(95% CI)	(17, 48)	(9, 32)	(4, 32)	(18, 43)
BRAF Mutation:	Wildtype	Mutant	Wildtype	Mutant
	(N=77)	(N=12)	(N=66)	(N=18)
ORR	25%	17%	26%	17%
CR	1	0	1	0
PR	18	2	16	3
(95% CI)	(16, 36)	(2, 48)	(16, 38)	(4, 41)

4.2.1 Other Findings to Support Efficacy

Since P001 Parts B1 and D trials were initiated to confirm efficacy in Part B2, Tables 14 and 15 present the efficacy results for ORR based on IRO assessments.

Table 12 ORR Results for P001 Part B1 IPI-treated

	MK-3475 10 mg/kg Q3W (N=31)	MK-3475 10 mg/kg Q2W (N=16)
ORR	22.6%	56.2%
CR	0	3
PR	7	6
95% CI	(9.5-41.1)	(29.8-80.2)
Response Duration Median in weeks (range)	Not reached (34+, 72+)	Not reached (22+, 76+)
Response ongoing	100%	89%

Reviewer's Comments:
The above analysis to confirm efficacy used a different dosing schedule different than that in Part B2. In particular, Part B1 IPI-treated patients were given MK-3475 10 mg/kg for every 2 weeks or 3 weeks. There was no 2 mg/kg dose administered in this part of the study.

Table 13 ORR Results for P001 Part D IPI-naive

	MK-3475 2 mg/kg Q3W (N=51)	MK-3475 10 mg/kg Q3W (N=52)
ORR	33.3%	36.5%
CR	4	2
PR	13	17
95% CI	(20.7-47.9)	(23.6-51.0)
Response Duration Median in weeks (range)	Not reached (7+, 36+)	Not reached (6+, 39+)
Response ongoing	100%	89%

5 SUMMARY AND CONCLUSIONS

In this Biologics License Application (BLA), the applicant is seeking an accelerated approval in patients with unresectable or metastatic melanoma who have been previously treated with ipilimumab based on an open-label, single-arm Phase 1 study P001 Part B2.

5.1 Statistical Issues

Although Study P001 Part B2 was a randomized study, in this submission, only 2 mg/kg Q3W data and analyses are relevant. For single arm data, a key issue is whether the analyses from the current submission demonstrated an overall favorable benefit vs. risk profile which is deferred to the clinical team reviewing this application.

5.2 Collective Evidence

The data and analyses from study P001 Part B2 shows that ORR was approximately 24% CI (15, 34) for both MK-3475 2 mg/kg Q3W and MK-3475 10 mg/kg Q3W treatment arms, with ranges of the duration of response 6+ to 37+ weeks and 8+ to 37+ weeks, respectively. Eighteen out of 21 responders still maintained their responses as the date of the data cut-off for the CSR.

5.3 Conclusions and Recommendations

No statistical inference can be drawn from this single arm study. All statistics presented are for descriptive purposes only. Whether the data and analyses from the current submission demonstrated an overall favorable benefit vs. risk profile is deferred to the clinical team reviewing this application.

5.4 Labeling Recommendations

PFS and OS results should not be included in the lable since the results are uninterpretable when evaluating only single arm.

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/s/

EMMANUEL SAMPENE
07/31/2014

KUN HE
07/31/2014

RAJESHWARI SRIDHARA
07/31/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125514 **Applicant: Merck Sharp & Dohme Corp.** **Stamp Date: 2/27/2014**

Drug Name: MK-3475 **NDA/BLA Type: Breakthrough**

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.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

EMMANUEL SAMPENE
04/17/2014
This is the statistical review done prior to filing action scheduled for 4/28/2014

KUN HE
04/17/2014