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APPLICATION NUMBER:

125527Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology BLA Review	
BLA	125527
Submission Date (Rolling)	December 22, 2014 (Completed)
Type/Category	Type 9/ Original BLA
Brand (generic) Name	Opdivo (nivolumab)
Dosage Form /Strength	40 mg/4 mL (10 mg/mL) & 100 mg/10 mL (10 mg/mL) in a single-use vial
Dosing Regimen	3 mg/kg IV infusion over 1 hour every 2 weeks (Q2W).
Proposed Indication	Advanced squamous non-small cell lung cancer after prior platinum-based therapy (b) (4)
Applicant	BMS
Clinical Pharmacology Reviewer	Xianhua (Walt) Cao, Ph.D.
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
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PDUFA Goal Date (Priority Review)	June 22, 2015
Action Goal Date	March 4, 2015

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1 EXECUTIVE SUMMARY

A type 9 BLA is submitted for Nivolumab for treatment of advanced squamous non-small cell lung cancer after prior platinum-based therapy (b) (4). The clinical pharmacology package is identical to that in the previous submitted BLA 125554, which received an accelerated approval on December 22, 2014, for the treatment of patients with unresectable or metastatic melanoma after prior treatment of ipilimumab and/or a BRAF inhibitor.

Efficacy, safety, pharmacokinetic (PK), and immunogenicity data for the current application are based on multiple clinical studies with nivolumab administered over the dose range of 0.1-20 mg/kg, where study CA209063 supports the marketing application of nivolumab with 3 mg/kg every 2 weeks (Q2W) dosing regimen. The major findings of the clinical pharmacology review are listed below.

- The apparent flat exposure-response (E-R) relationship for both efficacy and safety supports the use of the 3 mg/kg Q2W dosing regimen for the indicated patient population.
- Treatment emergent anti-nivolumab antibodies were detected in 24 of the 281 evaluable patients (8.5%) who received nivolumab of 3 mg/kg Q2W using an electrochemiluminescence (ECL) based assay. Neutralizing antibodies were detected in two patients (0.7%).
- Population PK analyses suggested that age, gender, race, baseline LDH, PD-L1 expression, anti-nivolumab antibody formation, tumor type, and tumor size did not have clinically meaningful effects on the exposure of nivolumab.

The applicant does not propose any clinical pharmacology related changes to the approved product label.

1.1 RECOMMENDATIONS

BLA 125527 is acceptable for approval from a clinical pharmacology perspective.

1.2 POST MARKETING REQUIREMENTS AND COMMITMENTS

1.2.1 Post Marketing Requirements

None.

1.2.2 Post Marketing Commitments

None.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Nivolumab is a humanized IgG4 monoclonal anti-PD-1 antibody. Its molecular weight is 146 kDa.

Mechanism of Action: Programmed death 1 (PD-1) receptor is a type I membrane protein of 268 amino acids. PD-1 is expressed on the surface of activated T cells, B cells, and macrophages. The binding of PD-1 and its ligands (PD-L1 and PD-L2) on a tumor cell contributes to inhibition of active T-cell immune surveillance of tumors. By inhibiting the PD-1 receptor from binding to its ligands, nivolumab reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity.

Clinical Dose Selection: The selection of nivolumab dose and schedule of 3 mg/kg Q2W was based on the observed clinical safety and efficacy from 306 patients in trial MDX1106-03 across different dose levels and tumor types. In addition, an integrated assessment of data from in vitro, preclinical, other confirmative clinical studies including CA209063, and exposure-response in multiple tumor types supports the dose selection.

Pharmacokinetics: Based on data from 909 patients who received 0.1-20 mg/kg of nivolumab as a single or multiple doses every 2 or 3 weeks, the population PK mean (CV%) estimates are as follows:

- Clearance, 9.5 mL/h (49.7%)
- Volume of distribution at steady-state, 8.0 L (30.4%)
- Half-life, 26.7 days (101%).
- Time to reach steady state concentrations of nivolumab, 12 weeks after 3 mg/kg Q2W and the systemic accumulation, approximately 3-fold.

Population Pharmacokinetic Analysis: Population PK analyses (n=909) showed that the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The following factors had no clinically important effect on the clearance of nivolumab: age, gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

Exposure/Dose-Response Relationship for Efficacy and Safety: Trough concentration after first dose (C_{min1}) of 3 mg/kg nivolumab was not a significant predictor of probability of objective response (OR) in advanced squamous NSCLC. Risk of Grade 3+ drug related -AEs and AEs-leading discontinuation did not increase with average concentration at steady state (C_{avgss}) over the dose range of 3 to 10 mg/kg nivolumab Q2W in advanced squamous NSCLC.

Immunogenicity: A total of 24 out of the 281 evaluable patients (8.5%) who received nivolumab of 3 mg/kg Q2W tested positive for treatment emergent anti-nivolumab antibodies using an electrochemiluminescence (ECL) based assay. Neutralizing antibodies were detected in two patients (0.7%). No apparently altering or clinically meaningful difference in PK, safety and efficacy profiles were observed with the anti-nivolumab antibodies development.

Signatures:

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2 QUESTION BASED REVIEW

The clinical pharmacology component of the rolling submission for BLA 125527 was originally submitted on June 20, 2014 and was updated with population PK and exposure-response analysis with additional safety/efficacy data from study CA209037 for the treatment of patients with unresectable or metastatic melanoma after prior treatments under BLA 125554. The clinical pharmacology package is identical to that submitted in BLA 125554. The clinical pharmacology review are updated accordingly for ER analysis based on the data from registration study CA209063 for the proposed indication in advanced squamous NSCLC. The detail of other clinical pharmacology information can be found in the previous clinical pharmacology review for BLA 125554 dated 12/5/2014 (reference ID: 3668463).

2.1 GENERAL ATTRIBUTES

2.1.1 *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

Nivolumab is a humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4) kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The molecular weight of nivolumab is approximately 146 kDa.

Nivolumab drug product is supplied as a sterile, non-pyrogenic, single-use, preservative-free, isotonic aqueous solution with strength of 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) for intravenous (IV) administration. It may be administered undiluted at a concentration of 10 mg/mL or further diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to nivolumab concentrations as low as 1 mg/mL.

2.1.2 *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

By blocking the PD-1 receptor from binding to its ligands PD-L1 and PD-L2, nivolumab reactivates tumor- specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity.

The proposed indication is for the treatment of advanced squamous non-small cell lung cancer after prior platinum-based therapy (b) (4).

2.1.3 *What are the proposed dosage(s) and route(s) of administration?*

The proposed dosing regimen of nivolumab is 3 mg/kg administered via intravenous infusion over 60 minutes every 2 weeks (Q2W).

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims? What is the clinical outcome in terms of efficacy and safety?

Clinical Pharmacology Studies

The clinical pharmacology program included PK data from 1040 patients enrolled in eight completed and ongoing clinical trials as described in Table 1. MDX1106-03 included dose escalation and dose expansion cohorts in multiple tumor types and had intensive PK sampling. A monotherapy dose regimen of 3 mg/kg Q2W was selected for later stage clinical development across tumor types including the advanced squamous NSCLC in study CA209063. The PK profile of nivolumab was described using population PK analysis based on data collected from 909 patients with solid tumors. Data for E-R analyses for safety (n=640) were collected from MDX1106-03, CA209063 and CA209037. Data for E-R analyses for clinical activity were collected and evaluated separately from study CA209063 (n=91) and study CA209037 (n=115). Immunogenicity data were collected from 524 nivolumab-treated patients with solid tumors.

Table 1. Clinical pharmacology studies in the submission				
Study No.	Population	Assessment	Dosage and Regimen	N
MDX1106-01 (CA209001)	NSCLC, Melanoma, RCC, CRC and mPRC	Single-dose PK and PPK	0.3, 1, 3 or 10 mg/kg	39
MDX1106-03 (CA209003)	NSCLC, Melanoma, RCC, CRC and mPRC	Multiple-dose PK, PPK, PD, Immuogenicity, E- R,Dose selection	0.1, 0.3, 1, 3, or 10 mg/kg Q2W	306 (melanoma= 107)
CA209009	RCC	PD, drug interaction potential	0.3, 2, 10 mg/kg Q3W	91
CA209010	RCC	PPK, QT prolongation potential	0.3, 2, 10 mg/kg Q3W	167
CA209063	Refractory SQ NSCLC	PPK, E-R, immunogenicity, Dose justification	3 mg/kg Q2W	117
CA209037	Melanoma	PPK, E-R, immunogenicity, dose justification	3 mg/kg Q2W	268
ONO-4538-01	Japanese subjects with solid tumors	PPK	1, 3, 10 and 20 mg/kg 3-week for 1 st dose, followed by Q2W	17
ONO-4538-02	Japanese subjects with advanced melanoma	PPK	2 mg/kg Q2W	35

Abbreviations: NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; CRC: colorectal cancer; mCRPC: metastatic castration-resistant

prostate cancer; PK: pharmacokinetics; PPK: population pharmacokinetics; PD: pharmacodynamics; Q2W: every 2 weeks; Q3W: every 3 weeks; QTc: corrected QT interval

Clinical Studies

Advanced Squamous NSCLC

The proposed indication in the current BLA is primarily supported by the results from 117 nivolumab treated patients in study CA209063, together with supportive data from study MDX1106-03 (n=129 nivolumab-treated) (**Table 2**).

Table 2. Description of clinical studies:		
Study No.	Study Design	Endpoint¹
CA209063 (Registrational)	Open-label, single-arm study of nivolumab (3 mg/kg every 2 weeks [Q2W]) in patients with advanced NSCLC with at least 1 platinum doublet-based chemotherapy and 1 additional system therapy. There were 117 patients who received at least 1 infusion of nivolumab.	The ORR was 14.5% (95% CI: 8.7, 22.2) with range of DOR from 1.9+ to 11.5+ months (median DOR not reached at the time of database lock). 1-year PFS rate of 20.0% (95% CI: 12.7, 28.5). Median OS was 8.21 months (95% CI: 6.05, 10.91).
MDX1106-03 (phase 1b) (Supportive)	One hundred and twenty nine (129) patients with NSCLC received nivolumab at doses of 1, 3, or 10 mg/kg Q2W. Patients were with at least 1 prior systemic therapy.	The ORR (crossing dose group) was 17.1% (95% CI: 11, 24.7) with a median duration of response (DOR) of 17 months (range: 1.4+ to 30.8+). Median OS across all doses was 9.9 months (95% CI: 7.8, 12.4).

¹As reported by BMS;

For Study CA209063, the primary endpoint was ORR. The ORR is defined with a best overall response (BOR) of confirmed complete or partial response (CR or PR), confirmed by an Independent Review Committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST) V1.1. The primary analysis of ORR was based on the 117 nivolumab-treated patients with minimum follow-up of approximately 11 months. PFS in the ORR population was also described. For Study MDX1106-03, the responses were centrally assessed by the sponsor using RECIST V1.0 based on the tumor measurements collected by investigators in the expansion cohorts.

In study CA209063, the IRC-assessed confirmed ORR was 14.5%, which was consistent with the investigator-assessed ORR observed in MDX1106-03 (all dose levels: 17.1% and 3 mg/kg: 22.2%). At the time of the CA209063 database lock, the median DOR among responders had not been reached with a minimum of 11 months follow-up, with a range of 1.9+ to 11.5+ months (Table 3). With a median OS follow-up of 8 months and a maximum followup of 17.3 months in CA209063, the median OS was 8.2 months, and the 1-year OS rate was 41% (Table 3).

Table 3. Overall efficacy summary with nivolumab monotherapy in NSCLC

Endpoint	CA209063		MDX1106-03		
	SQ NSCLC	All NSCLC	SQ NSCLC	SQ NSCLC	
	3 mg/kg		All doses	All doses	3 mg/kg
All doses	N=117	N=129	N=54	N=18	
ORR, n (%) ^a	17 (14.5)	22 (17.1)	9(16.7)	4 (22.2)	
95% CI	8.7, 22.2	11.0; 24.7	7.9; 29.3	6.4, 47.6	
DOR, Median (95% CI)	NR (8.31, NR)	17.0 (8.7, NR)	NR (3.7, NR)	NR (NR, NR)	
Range (Months) ^{b,c}	1.9+ - 11.5+	1.4+ - 30.8+	3.7 - 30.8+	3.7+ - 30.8+	
PFS					
Median (95% CI) (Months)	1.87 (1.77, 3.15)	2.3 (1.8, 3.7)	3.8 (1.8, 7.2)	3.7 (1.7, 12.8)	
Rate (95% CI) (%)					
At 6 Months (~24 weeks)	25.9 (18.0, 34.6)	33 (25, 42)	41 (27, 55)	38 (15, 60)	
At 1 Year (~48 weeks)	20.0 (12.7, 28.5)	22 (15, 30)	27 (15, 41)	30 (10, 53)	
At 2 Years (~96 weeks)	NA	9 (4, 15)	13 (5, 26)	23 (6, 46)	
OS					
Median (95% CI) (Months)	8.21 (6.05, 10.91)	9.9 (7.8, 12.4)	9.2 (7.3, 12.5)	9.5 (5.3, NR)	
Rate (95% CI) (%)					
At 6 Months (~24 weeks)	60.1 (50.5, 68.4)	66 (57, 73)	71 (57, 81)	76 (47, 90)	
At 1 Year (~48 weeks)	40.8 (31.6, 49.7)	42 (34, 51)	40 (27, 54)	49 (23, 71)	
At 2 Years (~96 weeks)	NA	24 (16, 32)	24 (13, 37)	41 (17, 64)	

^a Based on IRC-assessed confirmed PR or CR for CA209063 and sponsor-assessed for MDX1106-03.

^b Per IRC assessment for CA209063 and per sponsor assessment for MDX1106-03.

^c For responders who did not have reported progression or death date, DOR was censored at the last tumor assessment date and is denoted by a + symbol.

Source: sponsor's clinical overview Table 4.3-1 page 20

MTD was not reached at the dose up to 10 mg/kg. In CA209063, the most frequent ($\geq 10\%$ of subjects) drug-related AEs were: fatigue (32.5%), decreased appetite (18.8%), nausea (15.4%), asthenia (12.0%), rash (11.1%), and diarrhea (10.3%). Drug-related Grade 3-4 AEs were observed in 17.1% of subjects, with the following events reported in $>2\%$ of subjects: fatigue (4.3%), pneumonitis (3.4%), and diarrhea (2.6%). Serious drug-related AEs and drug-related AEs leading to treatment discontinuation were reported in 10.3% and 12.0% of subjects respectively. The most frequently reported drug-related AE leading to discontinuation was pneumonitis (4.3%).

2.2.2 Exposure-response

2.2.2.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

No dose or exposure-efficacy relationship has been identified across the dose range of 3-10 mg/kg Q2W for nivolumab in the proposed patient population based on the primary endpoint of ORR in Study MDX1106-03 and CA209063.

In the dose escalation and expansion study MDX1106-03 in patients with malignant NSCLC, a flat exposure-ORR relationship was identified over the dose range of 3-10 mg/kg, with a greater percent of ORR (>20%) than 1 mg/kg (ORR of 3%) (Table 4).

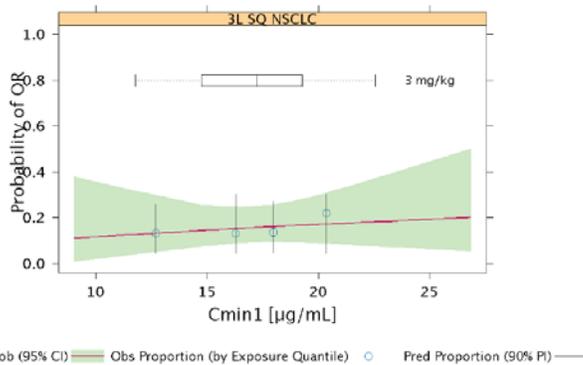
Table 4. Overview of ORR of nivolumab in advanced NSCLC in study MDX1106-03

Dose (mg/kg)	0.1	0.3	1	3	10	Overall
All NSCLC	NA	NA	3.0 (0.1, 15.8) N=33	24.3 (11.8, 41.2) N=37	20.3 (11.0, 32.8) N=59	17.1 (11.0, 24.7) N=129

Source: Tables 7.2.1-1 of MDX1106-03 CSR

There is apparently flat exposure-efficacy relationship between individual exposures derived from population PK modeling and the primary endpoint of ORR from 91 patients in Study CA209063 with nivolumab administered at 3 mg/kg Q2W (Figure 1). Population PK model predicted trough concentrations (7- 28 $\mu\text{g/mL}$) after first nivolumab dose ($C_{\text{min}1}$) were used as the measure of nivolumab exposure.

Figure 1. Flat exposure-response relationship of ORR versus nivolumab $C_{\text{min}1}$ at 3 mg/kg Q2W for patients with advanced NSCLC



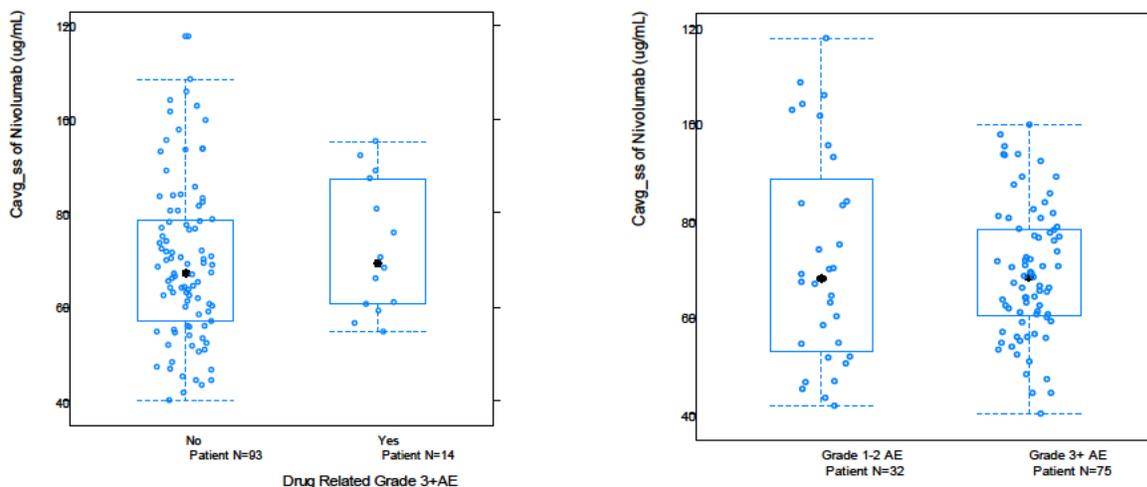
Source: Sponsor's PPK report, Figure 5.2.2-1

2.2.2.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

The relationship between $C_{\text{avg, ss}}$ and the incidence rate of Grade 3+ DR-AEs, or AEs leading to discontinuation was characterized with data from 410 patients from study CA209063 and MDX1106-03. There were 17.3% and 19.3% of patients with reported Grade 3+ drug related-

AEs and AEs leading to discontinuation, respectively in the analysis dataset. In general, there appeared to be no exposure-safety relationships between exposure ($C_{avg,ss}$) and the incidence rate of Grade 3+ drug related-AEs, AEs leading to discontinuation and any grade 3+AEs for nivolumab at 3 mg/kg Q2W based on the currently available clinical safety data (Figure 2).

Figure 2. No exposure-response relationship between drug-related or any grade 3+ adverse events and steady-state average concentration ($C_{avg,ss}$) of nivolumab at 3 mg/kg Q2W in study CA209063



Left: Drug –related 3+ AEs of interest; Right: any grade 3+ AEs.
Source: Pharmacometrics Review, Figure 2 and 3

2.2.2.3 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?

The clinical dose of 3 mg/kg IV Q2W was selected based on ex vivo receptor binding study, animal tumor models, and clinical dose escalation study MDX1106-03 across different tumor types. Nivolumab 3 mg/kg dose was able to saturate the PD-1 receptor binding and the preclinical efficacious doses in multiple tumor mouse studies suggested the human equivalent dose of 1-3 mg/kg Q2W. In the dose escalation and expansion study MDX1106-03 in patients with malignant NSCLC or other solid tumors with doses up to 10 mg/kg Q2W, maximum tolerable dose (MTD) was not reached and 3 mg/kg Q2W appeared to be safe and efficacious in the patients with malignant NSCLC. Furthermore, no trend in exposure-efficacy or safety relationship was observed in study CA209063 at 3 mg/kg Q2W and therefore 3 mg/kg Q2W is considered appropriate as the recommended dose and schedule for the proposed indication.

[Reviewer notes: Please see clinical pharmacology review for BLA 125554 dated 12/5/2014 \(reference ID: 3668463\) for the following sections except Table 5 is updated with OC sample plans for study CA209063.](#)

2.2.3 *What are the PK characteristics of the drug?*

2.3 **INTRINSIC FACTORS**

2.3.1 *What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

2.3.2 *Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dose regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.*

2.3.2.1 *Elderly Patients*

2.3.2.2 *Gender*

2.3.2.3 *Body weight*

2.3.2.4 *Race*

2.3.2.5 *Renal Impairment*

2.3.2.6 *Hepatic Impairment*

2.3.2.7 *What pregnancy and lactation use information is in the application?*

2.3.3 *Immunogenicity*

2.3.3.1 *What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?*

2.3.3.2 *Does the immunogenicity affect the PK and/or PD of the therapeutic protein?*

2.3.3.3 *Do the anti-product antibodies have neutralizing activity?*

2.3.3.4 *What is the impact of anti-product antibodies on clinical efficacy?*

2.3.3.5 *What is the impact of anti-product antibodies on clinical safety (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?*

2.4 EXTRINSIC FACTORS

2.4.1 *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?*

2.4.2 *What are the drug-drug interactions?*

2.4.2.1 *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 *What are the manufacturing differences between the to-be-marketed formulation and the formulation used in the pivotal clinical trial?*

2.5.2 *What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?*

2.6 ANALYTICAL SECTION

2.6.1 *What bioanalytical methods are used to assess therapeutic protein concentrations?*

2.6.1.1 *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

2.6.1.2 *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

2.6.1.3 *What are the accuracy, precision and selectivity at these limits?*

2.6.1.4 *What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)*

2.6.1.5 *What is the QC sample plan?*

For assay ICD 416, each analytical run included low (0.600 µg/mL), mid (1.50 µg/mL), high (4.80 µg/mL) and dilutional QCs (100 µg/mL) of nivolumab. If study samples required dilution, a minimum of three replicates of a dilutional QC were analyzed in each run. About two-thirds of the QCs pool replicates included in each run appropriately needed to have a calculated concentration within $\pm 20.0\%$ of the theoretical concentration for the analytical run to be accepted. QC runs of assay ICD416 for study CA209063 is summarized in Table 5 below.

Table 5. Summary of QC runs for assay ICD416 in study CA209063

	QC 1 - Dil 1	QC 2 - Dil 1	QC 3 - Dil 1	QC 7 - Dil 50	QC 7 - Dil 100	QC 7 - Dil 200
$\mu\text{g/mL}$	0.600 $\mu\text{g/mL}$	1.50 $\mu\text{g/mL}$	4.80 $\mu\text{g/mL}$	100 $\mu\text{g/mL}$	100 $\mu\text{g/mL}$	100 $\mu\text{g/mL}$
Mean Observed Conc., $\mu\text{g/mL}$	0.659	1.58	4.79	108	108	82.6
%Dev	9.78	5.09	-0.252	7.58	7.80	-17.4
Between Run Precision (%CV)	6.87	5.60	7.01	4.55	6.81	10.8
Within Run Precision (%CV)	7.05	10.5	14.7	8.89	8.86	10.8
n	59	62	62	21	60	3
Number of Runs	31	31	31	7	20	1

Source: Table 8b of (b) (4) Serum Bionalytical Study Report for study CA209063
 Statistical outliers with values greater than 3S.D. from the mean value for that QC level excluded

3 APPENDICES

3.1 PHARMACOMETRICS REVIEW

**OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW**

BLA Number	125527
Drug Name	OPDIVO® (Nivolumab)
Dose Regimen	3 mg/kg IV infusion over 60 minutes every 2 weeks
Indication	Advanced squamous non-small cell lung cancer after prior platinum-based therapy (b) (4)
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Liang Zhao, Ph.D.
Sponsor	Bristol-Myers Squibb Company

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1 SUMMARY OF FINDINGS

In general, the nivolumab dose of 3 mg/kg Q2W appeared to be reasonable for patients with advanced squamous non-small cell lung cancer (NSCLC) after prior platinum-based therapy ^{(b) (4)}

No evident exposure-efficacy relationship for the objective response rates (ORR) was identified across the dose range of 3-10 mg/kg Q2W for the proposed indication based on the clinical efficacy data currently available.

In general, no clear exposure-safety relationships was found following the nivolumab 3 mg/kg Q2W dosing regimen for the proposed indication based on the clinical safety data of Study CA209063. However, there may be a signal for increase in specific AEs with increasing exposure as shown in **Table 2**.

The effect of PD-L1 status on ORR and whether systemic administration of corticosteroids affects the efficacy of nivolumab were not evaluated due to data limitation in the patient population.

1.1 KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions.

1.1.1 Is the nivolumab dose of 3 mg/kg Q2W dosing regimen appropriate for the indicated patient population?

In general, the nivolumab dose of 3 mg/kg Q2W appeared to be reasonable for patients with advanced squamous NSCLC after prior platinum-based therapy ^{(b) (4)}

The nivolumab dose of 3 mg/kg Q2W was selected based on ex vivo receptor binding study, animal studies involving tumor models, and Phase II human clinical trials in the advanced squamous NSCLC patients. Below are the main supports from sponsor for the proposed dosing regimen.

- First, the clinical dose of 3 mg/kg was initially selected based on the ex vivo receptor binding study. Nivolumab binds to native PD-1 molecules expressed on activated human peripheral T cells, and the nivolumab EC₅₀ for the receptor binding was identified to be 0.1 µg/mL. In the Phase 1 multiple dose PK study in human, the trough concentration of the first dose was > 16 µg/mL for the 3 mg/kg Q2W dose (Table 9.2-2 of MDX1106-03 CSR), which was > 160 times of the binding EC₅₀.
- Second, the clinical dose of 3 mg/kg was selected based on PK-PD studies in animals. The studies involved different mouse tumor models, MC38 model (BMS DCN 930046571) and Sa1/N fibrosarcoma model in AJ mice (BMS DCN 930046567), and 10-

30 mg/kg dose was found to be efficacious. Based on the human equivalent dose calculations, the sponsor predicted nivolumab to demonstrate PD-1 blockade and clinical activity at doses of approximately 1 mg/kg or higher in humans.

- Third, 3 mg/kg Q2W was selected based on the efficacy and safety data of a Phase 1b trial (MDX1106-03). In this Phase 1 dose escalation study in 306 patients with NSCLC, melanoma or RCC, maximum tolerable dose (MTD) was not reached at 10 mg/kg.
- Finally, 3 mg/kg Q2W was selected based on the efficacy and safety data of the Phase 2 registration trial. In the Phase 2 registration trial (CA209063), 3 mg/kg dose demonstrated to be efficacious with acceptable safety profile in the NSCLC patients.

1.1.2 Was there any exposure-efficacy relationship following the nivolumab Q2W treatment for the proposed indication?

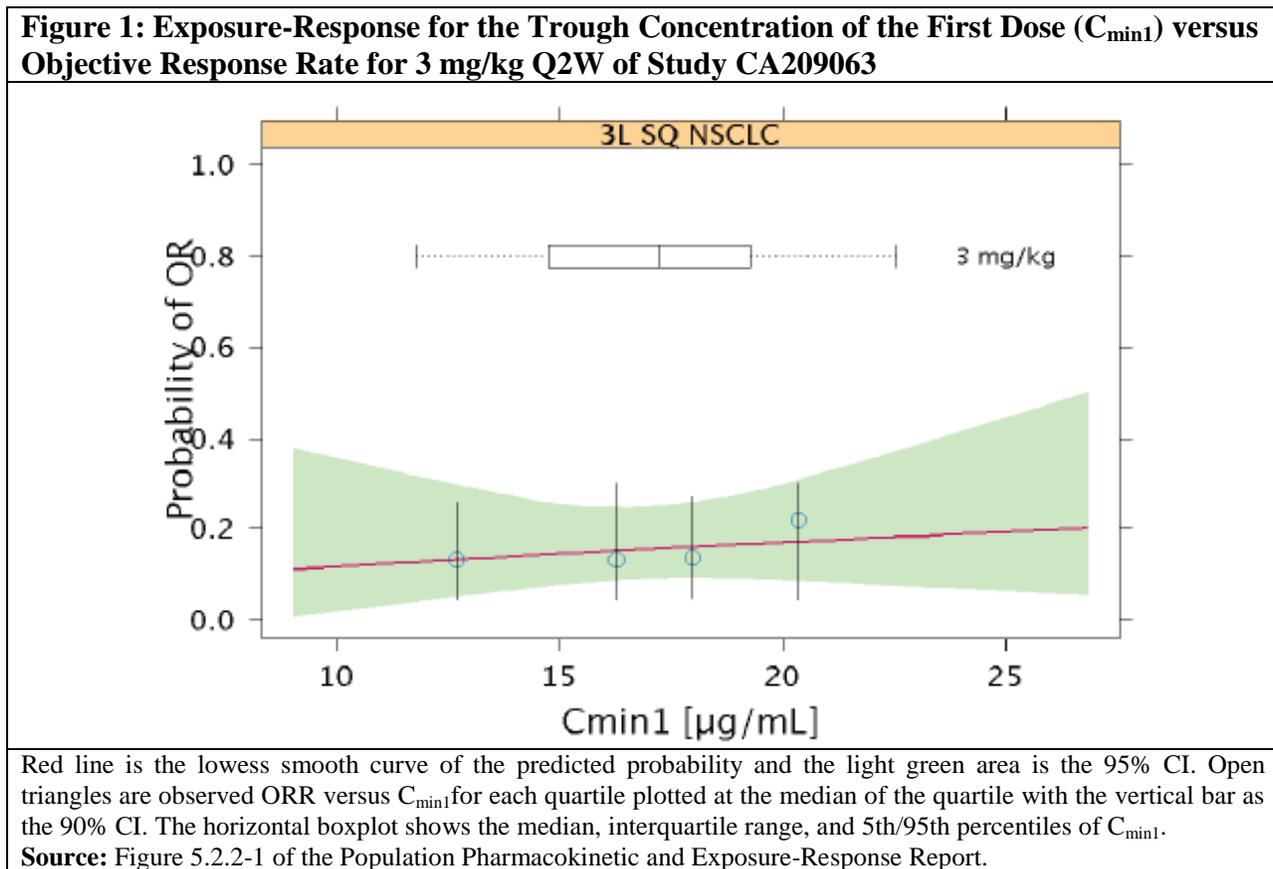
There appeared to be no exposure-efficacy relationship for the objective response rates (ORR) across the dose range of 3-10 mg/kg Q2W for the proposed indication based on the clinical efficacy data currently available.

- In the Phase I dose escalation study (MDX1106-03), the ORR of nivolumab in NSCLC patients were 3% (N=33), 24.3% (N=37), and 20.3% (N=59) for doses of 1, 3 and 10 mg/kg doses Q2W, respectively. Nivolumab PK was linear across the dose range, so the exposure-ORR relationship was flat for the dose range of 3-10 mg/kg, while the effect of 1 mg/kg appeared to be not desirable. Numerically, 3 mg/kg Q2W appeared to be better than 10 mg/kg (**Table 1**).
- In the Phase 2 trial (CA209063), ORR was also flat across the trough concentration range of 9-27 µg/mL for the 3 mg/kg Q2W dose after the covariate effect was adjusted (**Figure 1**).

•

Dose (mg/kg)	0.1	0.3	1	3	10	All
All NSCLC	NA	NA	3.0 (0.1, 15.8) N=33	24.3 (11.8, 41.2) N=37	20.3 (11.0, 32.8) N=59	17.1 (11.0, 24.7) N=129
Melanoma	35.3 (14.2, 61.7) N=17	27.8 (9.7, 53.5) N=18	31.4 (16.9, 49.3) N=35	41.2 (18.4, 67.1) N=17	20.0 (5.7, 43.7) N=20	30.8 (22.3, 40.5) N=107
RCC	NA	NA	27.8 (9.7, 53.5) N=18	NA	31.3 (11.0, 58.7) N=16	29.4 (15.1, 47.5) N=34

Source: Tables 7.2.1-1, 7.3.1-1 and 7.4.1-1 of MDX1106-03 CSR



In general, the exposure-ORR relationship for nivolumab appeared to be flat across the dose range of 3-10 mg/kg Q2W, and 3 mg/kg Q2W was shown to be efficacious for the proposed indication.

1.1.3 Were there any exposure-safety relationships following the nivolumab 3 mg/kg Q2W dosing regimen for the proposed indication?

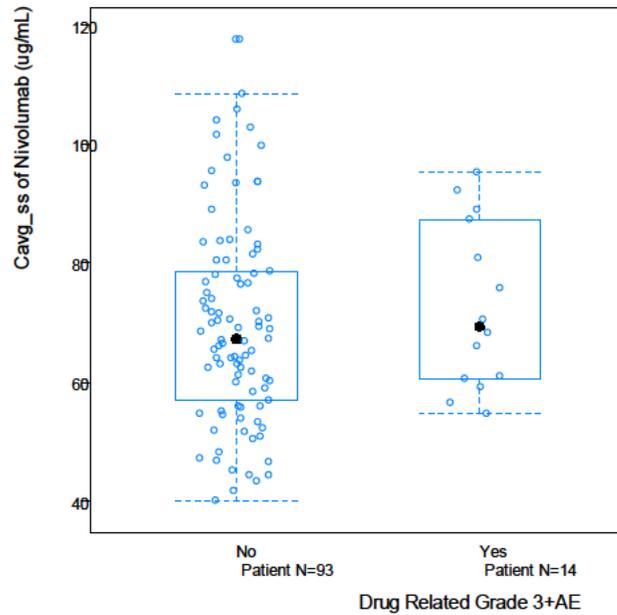
Overall, there appeared to be no clear exposure-safety relationships following the nivolumab 3 mg/kg Q2W dosing regimen for the proposed indication based on the clinical safety data of Study CA209063. However, there may be a signal for increase in specific AEs (diarrhea and fatigue) with increasing exposure as shown in **Table 2**.

- **Figure 2** presents a summary of exposures for patients with (n=14) and without (n=93) drug related Grade 3+ AEs in Study CA209063. The distributions of the exposures were not significantly different between the 2 subgroups.
- **Figure 3** presents a summary of exposures for patients with any AEs in CA209063. Patients were divided into 2 subgroups: Grade 1-2 AE (N=32) and Grade 3-5 AE (N=75). Of note, 70% patients experienced Grade3+ AEs. The distributions of the exposure were not significantly different between the 2 subgroups.

In Studies **MDX1106-03** and **CA209063**, the safety risk did not increase with exposure in the dose range of 3-10 mg/kg Q2W for time to the first event of Grade3+ drug-related-AEs (**Table 3**) and for drug AE-related discontinuations (**Table 4**). As shown in **Table 2**, high exposure (defined by quartiles of $C_{avg,ss}$ with Q1 to Q4 indicating increasing exposure) was associated with 2 types of drug related Grade 3+ adverse events, diarrhea and fatigue. Refer to **Table 10** for more information about all drug related Grade 3+ AEs.

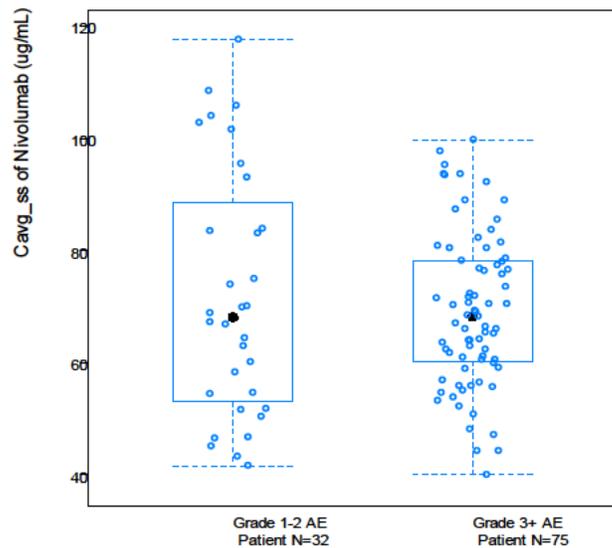
Table 2: The Distribution of Number of Drug Related Grade 3+ Adverse Events in the 4 Quartiles of $C_{avg,ss}$ ($\mu\text{g/mL}$) for 3 mg/kg Q2W in Phase II Study CA209063				
	Nivolumab $C_{avg,ss}$ Quartile, Patient Number & $C_{avg,ss}$ Range ($\mu\text{g/ml}$)			
	Q1 (n=26) 40.0-56.8	Q2 (n=30) 56.8-68.8	Q3 (n=25) 68.8-80.4	Q4 (n=26) 80.4-117.5
Diarrhea			1 (ID: 9-63068)	2 (IDs: 15-63079, 17-63065)
Fatigue			2 (IDs: 37-63145, 9-63068)	3 (IDs: 14-63022, 17-63065, 2-63084)
Note: blank cell means there was no drug-related Grade 3+ adverse events found in the quartile.				
Source: FDA reviewer's analysis based on data "adae.xpt" and "aedata.xpt" for CA209063.				

Figure 2: Summary for Steady-State Average Concentrations ($C_{avg,ss}$) for Patients with and without Drug Related Grade 3+ Adverse Events



Source: FDA reviewer's analysis based on adae.xpt and aedata.xpt for Study CA209063.

Figure 3: Summary of Steady-State Average Concentrations ($C_{avg,ss}$) for Patients with Different Grades of Adverse Events for 3 mg/kg Q2W in Phase III Study CA209063



Source: FDA reviewer's analysis based on adae.xpt and aedata.xpt for Study CA209063.

Table 3: Model Estimated Hazard Ratio of Grade 3+ Drug Related AEs¹ (Relative to Median C_{avg,ss} at 3 mg/kg)		
C_{avg,ss} (µg/mL)	HR	95% CI of HR
Median 1 mg/kg (27.27)	1.05	0.87 - 1.26
Median 10 mg/kg (237.62)	0.94	0.74 - 1.20
5th percentile 3 mg/kg (44.34)	1.02	0.94 - 1.12
95th percentile 3 mg/kg (116.06)	0.98	0.88 - 1.08

¹ There were 14 out of 107 patients in Study CA209063 experienced drug-related Grade 3+ AEs.
Source: Table 5.3.3-1 of the Population Pharmacokinetic and Exposure-Response Report

Table 4: Model Estimated Hazard Ratio of AEs Leading to Discontinuation (Relative to Median C_{avg,ss} at 3 mg/kg)		
C_{avg,ss} (µg/mL)	HR	95% CI of HR
Median 1 mg/kg (27.27)	0.91	0.74-1.12
Median 10 mg/kg (237.62)	1.13	0.87 - 1.48
5th percentile 3 mg/kg (44.34)	0.96	0.86 - 1.05
95th percentile 3 mg/kg (116.06)	1.05	0.94 - 1.18

Source: Table 3.2.1-2 of Summary of Clinical Pharmacology Studies

1.2 RECOMMENDATIONS

From pharmacometrics perspective, nivolumab 3 mg/kg Q2W seems reasonable for the proposed indication.

2 PERTINENT REGULATORY BACKGROUND

The nivolumab development program for advanced pretreated NSCLC has received advices from the regulatory agencies in the US and the EU.

Nivolumab has been granted Fast Track Designation in refractory NSCLC for the demonstration of durable objective responses in patients who have progressed following platinum doublet-based chemotherapy and at least 1 additional systemic therapy. Two meetings were held between the FDA and the sponsor to discuss the Phase 3 NSCLC program in both squamous (SQ) and non-squamous (NSQ) NSCLC, including the potential for accelerated approval regulatory pathway for SQ NSCLC. In order to support this request for seeking accelerated approval, the FDA suggested the conduct of an additional, single-arm study of nivolumab for the third-line treatment of patients with SQ NSCLC. This resulted in the design and conduct of CA209063, a global Phase 2, multi-center, single-arm study

of nivolumab monotherapy in a prospectively defined population of subjects with advanced, refractory, SQ NSCLC. The outcome of CA209063, with supporting data from MDX1106-03, was discussed at a pre-BLA meeting held 28-Apr-2014 with the FDA.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 PIVOTAL TRIAL (STUDY CA209063)

Study (CA209063) was a single-arm Phase 2 study of Nivolumab in subjects with advanced or metastatic squamous cell NSCLC who have received at least two prior systemic regimens. The primary objective was to assess the clinical activity of nivolumab, as measured by the independent radiology review committee (IRC)-assessed objective response rate (ORR), in subjects with advanced or metastatic squamous non-small cell lung cancer (SQ NSCLC) who have progressed during or after both platinum doublet-based chemotherapy and at least one additional systemic therapy. The secondary objectives were to estimate the ORR based on investigator assessment of response. And the exploratory objectives were to assess the overall safety and tolerability of nivolumab, as measured by frequency and severity of adverse events (AEs), and specific laboratory abnormalities; To estimate the progression-free survival (PFS) of nivolumab in all treated subjects; To estimate the overall survival (OS) of nivolumab in all treated subjects; and to characterize the immunogenicity of nivolumab. A total of 140 subjects were enrolled and 117 (83.6%) subjects were treated.

The IRC-assessed confirmed ORR in the treated subjects among the ORR population (primary objective population) for the nivolumab group was 12.0% (14/117 subjects, 95% CI: 6.7, 19.3). Nivolumab treatment led to objective responses across subgroups of age, gender, region, or ECOG. The median DOR was not reached with a minimum of 5.5 months of follow up. Duration of response ranged from 2.8 to 6.9+ months. For subjects who responded to nivolumab, the median time to response was 3.0 months (range: 1.7 months to 4.8 months). Of the 14 subjects with confirmed responses, 7 (50.0%) experienced a target lesion tumor burden reduction of at least 50%. In addition, 34 (29.1%) subjects experienced disease stabilization (SD), with 14 subjects achieving tumor burden reduction of greater than 10% from baseline.

The analysis of PFS as assessed by the IRC demonstrated a median PFS of 1.9 months and a 6-month PFS rate of 26.6%.

Two (1.7%) deaths were attributed to study drug toxicity: drug-related hypoxic pneumonia reported within 30 days of last nivolumab dose and drug-related ischemic stroke within 100 days of last nivolumab dose. Adverse events leading to discontinuation of study drug were reported in 34 (29.1%) subjects. The most frequently reported AEs leading to discontinuation of study drug were malignant neoplasm progression (3.4%) and pneumonitis (3.4%).

Drug-related AEs leading to discontinuation of study drug were reported in 11 (9.4%) subjects. Most drug-related events were Grade 3-4 in severity. Pneumonitis was the most frequently reported drug-related AE leading to discontinuation of study drug (3.4% of subjects).

Grade 3-4 AEs were reported in 47.9% of subjects. The most frequently reported Grade 3-4 AEs included dyspnea (9.4%), fatigue (6.8%), and hyponatremia (5.1%). Grade 3-4 drug-related AEs were reported in 15.4% of subjects. The most frequently reported Grade 3-4 drug-related AEs were fatigue (4.3%), diarrhea (2.6%), and pneumonitis (2.6%). SAEs were reported in 65 (55.6%) subjects. Drug-related SAEs were reported in 11 (9.4%) subjects. Pneumonitis was the most frequently reported drug-related SAE (3.4% of subjects).

All subjects experienced at least 1 AE of any grade. The most frequently reported AEs included fatigue (48.7%), dyspnea (35.9%), decreased appetite (33.3%), cough (29.1%), nausea (28.2%), and constipation (23.1%). The majority of subjects (70.9%) experienced at least 1 drug-related AE of any grade. The most frequently reported drug-related AEs were fatigue (32.5%), decreased appetite (17.9%), nausea (15.4%), asthenia (11.1%), and rash (10.3%).

During treatment, anti-nivolumab ADAs were not detected in 89/101 subjects (88.1%) with evaluable ADA data at baseline and post-baseline, and were detected in 12/101 (11.9%) of the subjects with evaluable ADA data at baseline and post baseline, of whom no subjects were persistent positive (ADA positive sample at 2 or more sequential timepoints at least 8 weeks apart). No samples were positive for neutralizing antibodies. Based on the available data, the immunogenicity of nivolumab appears to be low and not clinically meaningful.

3.2 POPULATION PHARMACOKINETICS (PPK) AND EXPOSURE-RESPONSE (E-R) ANALYSIS

3.2.1 Objectives and Studies Included in the Analysis

The objectives of the PPK and E-R analysis were to characterize: the pharmacokinetics (PK) and key covariates of nivolumab exposure, the relationship between nivolumab exposure and efficacy in post anti-CTLA4 advanced melanoma subjects, and the relationship between nivolumab exposure and safety in post anti-CTLA4 advanced melanoma subjects, as measured by drug-related Grade 3 or greater adverse events (Grade 3+ DR-AEs) and AEs leading to discontinuation or death (AEs leading to DC/D).

The PPK analysis included 7710 nivolumab serum concentration values from 909 subjects with solid tumors involving 7 clinical studies: three Phase 1 studies (MDX1106-01, N=39, ONO-4538-01, N=17 and MDX1106-03, N=304), 3 Phase 2 studies (CA209010, N=167, ONO-4538-02, N=35, and CA209063, N=115), and 1 Phase 3 study (CA209037, N=232). The E-R analyses of efficacy (OR) were conducted with data from subjects in CA209037 for whom measures of nivolumab exposure and IRRC assessed OR were evaluable (N=115). The E-R analyses of safety

(Grade 3+ DR-AEs and AEs leading to DC/D) were conducted with data from subjects in CA209037 (N=230).

3.2.2 PPK and E-R Analysis Method

Population Pharmacokinetic Analysis Method: There were 3 steps in the PPK analysis. First, a base model was developed to describe the PK of nivolumab without consideration of covariate effects. Second, a full model was developed by incorporating the effect of all pre-specified covariate parameter relationships, and in the third step, the final PPK model was developed by retaining covariates that improved the goodness-of-fit statistic (Bayesian Information Criterion [BIC]). The baseline covariates examined were body weight (BW), age, sex, race, tumor type, estimated glomerular filtration (eGFR) rate, Eastern Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH), hepatic function status, tumor burden, immunogenicity (anti-drug antibodies, ADA), and PD-L1 expression. All the covariate effects other than baseline tumor burden, PD-L1 expression, and tumor burden were assessed by a full model. The effect of immunogenicity on clearance was assessed as a time-varying covariate in an ad-hoc analysis to account for the possibility that anti-drug antibodies (ADA) are not present at all times in immunogenic subjects. The effect of PD-L1 expression was assessed by graphical analysis for subjects from CA209063 and CA209037, as data were not available in all subjects in PPK analysis dataset. The effect of baseline tumor burden was assessed by graphical analysis only for subjects from CA209037, as the effect might be different across tumor types. Covariate effects were examined for nivolumab clearance (CL) and central volume of distribution (VC). No covariates were considered for the peripheral volume of distribution (VP) and inter-compartmental clearance (Q). Visual predictive check with and without bias correction was used to evaluate the prediction performance of the final PPK model.

Exposure-OR Analysis: The exposure-OR was characterized by a logistic regression model relating $C_{\min 1}$ to the probability of achieving a IRRC assessed OR, defined as Best Overall Response (BOR) of complete or partial response (CR or PR). There were 3 steps in the analysis. First, a base model was developed to correlate nivolumab exposure and probability of OR (Pr(OR)). Second, potential covariates were examined: sex, ECOG status, BRAF status, prior anti CTLA-4 benefit, PD-L1 status, body weight, age, baseline tumor burden (sum of longest diameters of all target lesions) and baseline LDH. A full model incorporating all the potential covariates was developed. Third, the final model was developed by backward elimination to only retain covariates that were significant based on BIC criteria. The E-R model of OR was evaluated by visual predictive check with respect to the predictor variables in the final model.

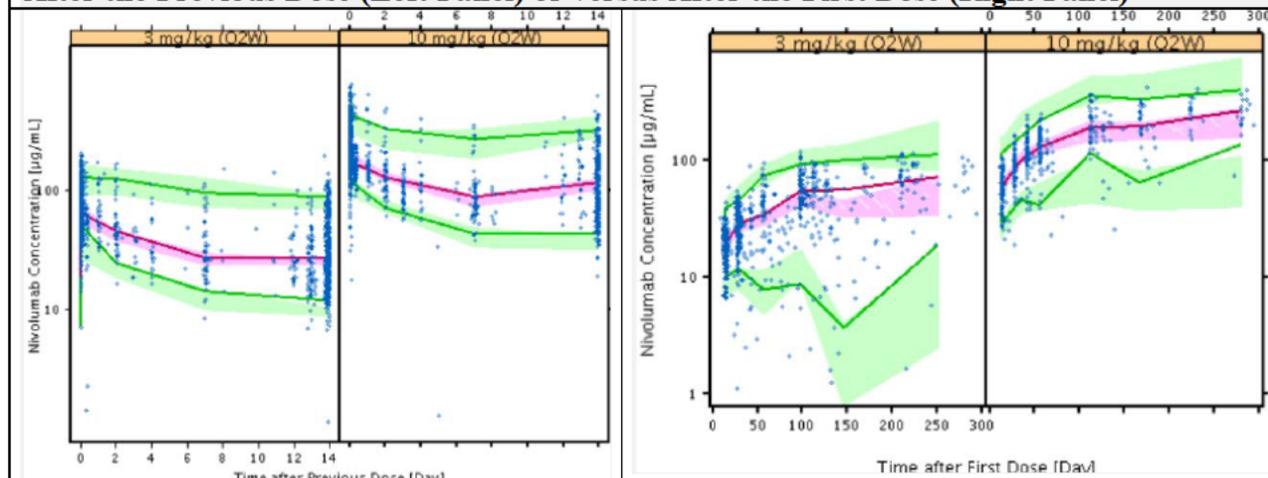
Exposure-Safety Response Analysis: Grade 3+ DR-AEs and AEs leading to DC/D: The E-R of safety analyses (Grade 3+ DR-AEs and AEs leading to DC) was characterized by two separate semi-parametric Cox Proportional-Hazards (CPH) models. The CPH models were developed in 3 stages. First, the relationship between nivolumab exposure (time-averaged steady state

concentration, $C_{avg,ss}$) and time-to-event was characterized in a base CPH model. Second, a full model was developed by incorporating the effect of baseline LDH in addition to that of nivolumab exposure. Third, the final model was obtained by retaining only the statistically significant predictors, with appropriate functional forms of their relationships with the events of interest. The CPH model was evaluated by comparing model predicted cumulative probability of Grade 3+ DR-AEs and AEs leading to DC/D vs. time with that obtained by Kaplan-Meier (KM) analyses.

3.2.3 PPK and E-R Analysis Result

Population Pharmacokinetic Analysis: Nivolumab PK was described with a linear two-compartment model with zero-order IV infusion parameterized in terms of clearance (CL), volume of central compartment (VC), inter-compartmental clearance (Q), and volume of peripheral compartment (VP). Inter-individual variability in CL, VC and VP were characterized with lognormal distributions, and a proportional error model was used to characterize the residual error. Covariate analysis revealed that baseline BW and ECOG status were potentially clinically relevant predictors of CL, and BW and sex were potentially clinically relevant predictors of VC. Both CL and VC increase with body weight, however nivolumab exposures (dose normalized $C_{min,ss}$ and $C_{avg,ss}$) are comparable across the range of body weight (34-162 kg), supported BW-normalized dose regimen is appropriate. Sex was a significant covariate on VC and male subjects had higher VC relative to female subjects. The effect was however, not clinically relevant, as nivolumab exposure was shown to be similar between male and female subjects. CL in subjects with ECOG status>0 was higher than that of subjects with ECOG status=0. Patients with higher ECOG status had higher clearance and therefore lower exposure levels. However, the effect is unlikely to be clinically relevant. The effect of eGFR on CL was statistically significant. It was however, unlikely to be clinically relevant, as the distribution of dose normalized $C_{avg,ss}$ of nivolumab was similar across the renal function groups. Age, race, LDH, tumor type and hepatic function were found not to be statistically significant or clinically relevant predictors of nivolumab PK. No association was found between CL, baseline tumor burden and PD-L1 expression in subjects with advanced melanoma based on graphical analysis. The immunogenicity effect was not considered to be clinically relevant based on post-hoc analysis showing substantial overlap of CL estimates. In the final model, BW, eGFR, and ECOG were the covariates of CL, and BW and Sex were the covariates of Vc, with all covariates in power models. Parameter estimates from the final PPK model are provided in **Table 5**. The results of the visual predictive check revealed that the model adequately described the observed data (**Figure 4**).

Figure 4: Visual Predictive Check of Trough Concentration (Log Scale) versus Actual Time After the Previous Dose (Left Panel) or versus After the First Dose (Right Panel)



Note: Dots are observed data. The solid lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% confidence intervals for the 5th, 50th and 95th percentiles of the predicted data.

Source: Pages 78-79 of sponsor's population pharmacokinetics and exposure-response report.

Exposure-OR Analysis: C_{min1} produced by 3 mg/kg nivolumab was not a significant predictor of Pr(OR) in subjects with advanced NSCLC (Table 6) in study CA209063. The final model was evaluated by visual predictive check with respect C_{min1} (Figure 5). No predictor variable was identified for OR.

Exposure-Safety Response Analysis: Grade 3+ DR-AEs and AEs leading to DC: Nivolumab exposure ($C_{avg,ss}$) did not appear to have a significant effect on the hazard of Grade 3+ DR-AEs or AEs leading to DC/D for subjects in CA209063. The hazard of Grade 3+ DRAEs and AEs leading to DC increased by 0.98-fold and 1.07-fold for every 1 µg/mL increase of $C_{avg,ss}$, respectively (Table 7, Table 8). Baseline LDH was a significant predictor of the AE risk Grade 3+ DRAEs (HR=2.29) and AE related DC (HR=1.78).

Table 5: Parameter Estimates of PPK Final Model

Parameter ^a [Units]	Estimate ^b	95% Confidence Interval ^c
Structural Model Parameters		
CL_{REF} [L/h]	0.00878	0.00824 - 0.00935
VC_{REF} [L]	3.83	3.70 - 3.96
Q_{REF} [L/h]	0.0298	0.0269 - 0.0330
VP_{REF} [L]	3.67	3.41 - 3.94
CL_{BW}	0.560	0.398 - 0.709
CL_{Sex}	0.108	0.0196 - 0.190
CL_{LDH}	0.519	0.0943 - 0.931
CL_{ALB}	-0.958	-1.27 - -0.642
VC_{BW}	0.518	0.443 - 0.601
VC_{sex}	0.157	0.113 - 0.202
Inter-Individual Variability Model Parameters		
ω^2_{CL}	0.164 (0.405)	0.131 - 0.198
ω^2_{VC}	0.0521 (0.228)	0.0428 - 0.0625
ω^2_{VP} [-]	0.338 (0.581)	0.245 - 0.434
$\omega_{CL:VC}$	0.0380 (0.411)	0.0252 - 0.0516
Residual Error Model Parameters		
Proportional error [-]	0.205	0.194 - 0.216

^a Eta shrinkage: η_{CL} : 8.83, η_{VC} : 14.7, η_{VP} : 24.5 and Eps shrinkage (%): 9.73. CL_{REF} and VC_{REF} are typical value of CL and VC at the reference values. Covariate effect was estimated relative to a female reference weighing 80kg (median value in the PPK dataset), LDH of 180 [IU/L] (median), and ALB of 4 g/dL (median).

^b Estimate values in parentheses are *standard deviation* for estimated variances and *correlation* for estimated covariances

^c Confidence Interval values are taken from bootstrap calculations (934 successful out of a total of 1000)

Source: Page 76 of sponsor's population pharmacokinetics and exposure-response report.

Table 6: Parameter Estimates of E-R OR Final Model

Predictor	Estimate	SE	RSE%	Odds Ratio Coefficient (95% CI) ^a
log(C _{min1})	0.666	1.48	223	1.947 (0.106, 35.7)

^a C_{minss} was log-transformed. log(C_{minss}) increases by one unit for approximately 2.7-fold increase in C_{minss}.

Source: Page 5 of sponsor's population pharmacokinetics and exposure-response report.

Figure 5: Visual Predictive Check of Marginal Probability of OR versus Nivolumab C_{min1}

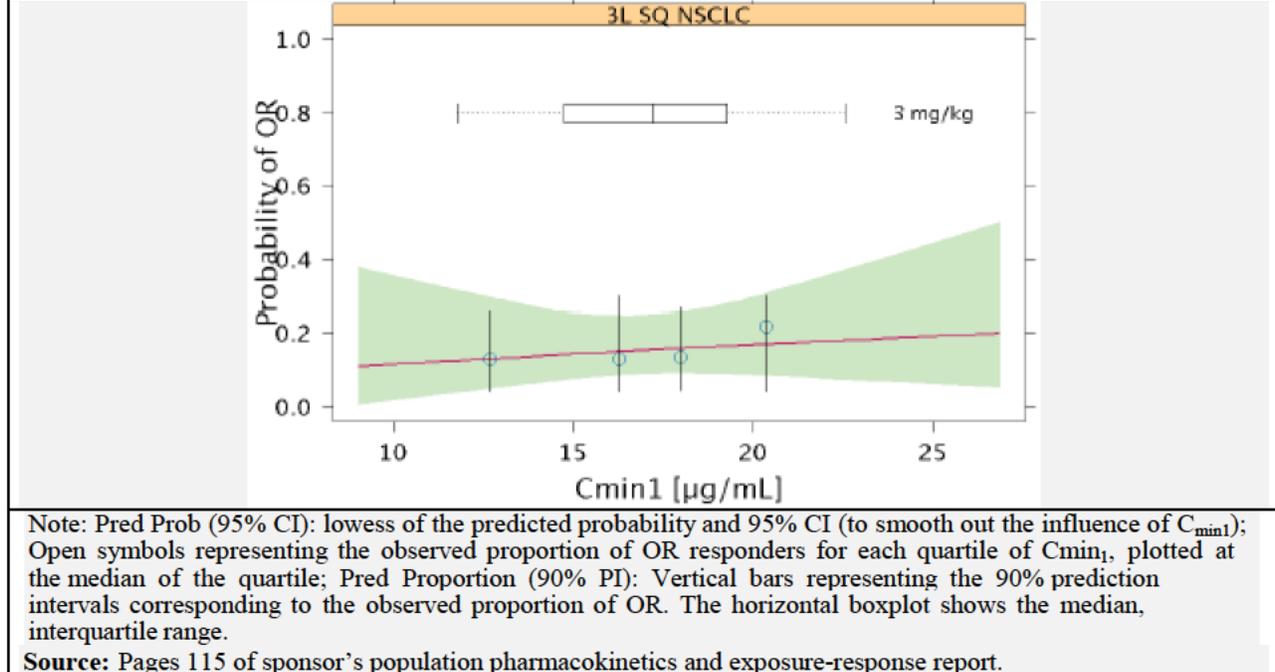


Table 7: Parameter Estimates of E-R (Grade 3+ DR-AEs) Final Model

Predictor	Estimate	SE	RSE%	Hazard Ratio Coefficient ^a (95% CI)
Log(Cavg _{ss}) [μg/mL]	-0.0201	0.0929	-463	0.98 (0.817, 1.18)
LDH [IU/L]	0.827	0.189	22.8	2.29 (1.58, 3.31)

^a increase in hazard for every unit increase in continuous predictor variables (both Cavg_{ss} and LDH were log-transformed, which increased by one unit for approximately 2.7-fold increase in Cavg_{ss} and LDH, respectively)

Source: Page 120 of sponsor's population pharmacokinetics and exposure-response report.

Table 8: Parameter Estimates of E-R (AEs Leading to DC) Final Model

Predictor	Estimate	SE	RSE%	Hazard Ratio Coefficient ^a (95% CI)
log(Cavg _{ss}) [μg/mL]	0.071	0.109	154	1.07 (0.867, 1.33)
LDH [IU/L]	0.575	0.201	35	1.78 (1.2, 2.64)
Tumor Type ^b	-0.975	0.265	-27.2	0.377 (0.224, 0.634)

^a increase in hazard for every unit increase in continuous predictor variables (both Cavg_{ss} and LDH were log-transformed, which increased by one unit for approximately 2.7-fold increase in Cavg_{ss} and LDH, respectively)

^b reference: subjects with NSCLC

Source: Page 126 of sponsor's population pharmacokinetics and exposure-response report.

3.2.4 Conclusion

PPK Analysis

- The PK of nivolumab is linear and time invariant.
- Nivolumab CL increases with increasing BW, and LDH; and decreases with increasing baseline albumin.

- Body weight normalized (mg/kg) dosing produced approximately uniform exposures (Cavgss and Cmin1) over the observed range of body weights
- Age, gender, race, ECOG status, renal impairment, mild hepatic impairment, immunogenicity, tumor type, manufacturing process, tumor size, and PD-L1 expression did not have clinically relevant (<20%) effects on nivolumab CL.

Exposure-OR

- Cmin1 produced by 3 mg/kg nivolumab was not a significant predictor of efficacy as measured by probability of OR in treatment refractory squamous NSCLC.

Exposure-Safety: Grade 3+ DR-AEs and AE-DC

- Risk of Grade 3+ DR-AEs and AEs leading to DC did not increase with Cavgss produced by doses ranging from 0.1 to 10 mg/kg nivolumab.
- The risk of both Grade 3+ DR-AEs and AEs leading to DC increased with increasing baseline LDH values.
- Subjects with NSCLC appeared to have higher risk of AEs leading to DC than subjects with other tumor types, including melanoma.

Reviewer's Comments: The applicant's population PK and exposure-response analyses appear reasonable. However, probability of drug-related Grade 3+ specific AE versus exposure was not explored, which could be important for labeling regarding dose modification.

4 REVIEWER'S ANALYSIS

4.1 OBJECTIVE

The analysis objectives are

- To compare the exposure distributions between different grades of AEs.
- To explore exposure-response relationship for each specific drug-related Grade 3+ AE.

4.2 METHODS

4.2.1 Data Sets

Data sets used are summarized in Table 9.

Table 9: Analysis Datasets for FDA Reviewer’s Analysis		
Study Number	Name	Link to EDR
CA209063	aedata.xpt	\\cdsesub1\evsprod\bla125527\0001\m5\datasets\population-pk\analysis\legacy\datasets\
CA209063	adae.xpt	\\cdsesub1\evsprod\bla125527\0007\m5\datasets\ca209063\analysis\adam\datasets\

4.2.2 Software

R and S-plus were used for the reviewer’s analysis.

4.3 RESULTS

The exposure distributions vs AE categories of Study CA209063 are presented in **Figure 2** and **Figure 3**. In **Figure 3**, the distributions were not different between Grade 1-2 AE patients (N=32) and Grade 3+ AE patients (N=75). In **Figure 2**, the distributions were not different between the 14 patients who experienced drug-related Grade 3+ AEs and the 93 patients who did not experience any drug-related Grade 3+ AEs.

High exposure (Quartile 4 of $C_{avg,ss}$) was associated with 2 types of drug related Grade 3+ adverse events, diarrhea and fatigue. These AEs did not occur with Quartile 1 or 2 although a few occurred in Q3 (**Table 2**). **Table 10** lists drug related Grade 3+ AEs for nivolumab for the patient population of Study CA209063.

Overall, efficacy and safety data of Study CA209063 appeared to support the proposed nivolumab 3 mg/kg Q2W dosing regimen for the indicated population. As listed in **Table 2**, some drug related Grade 3+ AEs occurred in patients with high nivolumab exposure, although the safety risk was not high.

5 APPENDIX

Table 10: Nivolumab Related Grade3+ Adverse Events

USUBJID	Adverse Event	Grade	Cavg,ss (µg/ml)	Quartile	Discontinue Flag
CA209063-10-63086	ADRENAL INSUFFICIENCY	3	68.15465817	Q2	
CA209063-17-63075	ANAEMIA	3	56.45391745	Q1	
CA209063-9-63055	ANAPHYLACTIC REACTION	3		NA	Y
CA209063-15-63079	DIARRHOEA	3	87.30487261	Q4	
CA209063-17-63065	DIARRHOEA	3	99.75031822	Q4	
CA209063-9-63068	DIARRHOEA	3	80.39794181	Q3	Y
CA209063-14-63022	FATIGUE	3	80.84517006	Q4	
CA209063-17-63065	FATIGUE	3	99.75031822	Q4	
CA209063-2-63084	FATIGUE	3	92.21724084	Q4	Y
CA209063-37-63145	FATIGUE	3	70.52308978	Q3	
CA209063-9-63068	FATIGUE	3	80.39794181	Q3	
CA209063-14-63022	HERPES ZOSTER	3	80.84517006	Q4	
CA209063-34-63074	HYPERSENSITIVITY	4	89.05340107	Q4	Y
CA209063-28-63142	HYPONATRAEMIA	3	72.27471443	Q3	
CA209063-9-63068	HYPONATRAEMIA	3	80.39794181	Q3	
CA209063-35-63124	ISCHAEMIC STROKE	5	60.51552135	Q2	
CA209063-2-63095	LYMPHOCYTE COUNT DECREASED	3	54.65303504	Q1	
CA209063-2-63084	LYMPHOPENIA	3	92.21724084	Q4	
CA209063-2-63095	LYMPHOPENIA	3	54.65303504	Q1	
CA209063-37-63145	MYALGIA	3	70.52308978	Q3	
CA209063-14-63035	PNEUMONIA	5	59.19058843	Q2	
CA209063-12-63117	PNEUMONITIS	3	81.34472751	Q4	Y
CA209063-32-63054	PNEUMONITIS	3	65.96634472	Q2	Y

CA209063-7-63026	PNEUMONITIS	3	95.32308738	Q4	Y
CA209063-35-63124	POLYNEUROPATHY	4	60.51552135	Q2	Y
CA209063-14-63041	PRURITUS	3	75.78131386	Q3	
CA209063-17-63042	RASH	3	60.97496033	Q2	Y
CA209063-35-63124	VASCULITIS	4	60.51552135	Q2	

Source: FDA reviewer's analysis based on adae.xpt and aedata.xpt for Study CA209063

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

/s/

XIANHUA W CAO
02/24/2015

HONGSHAN LI
02/24/2015

LIANG ZHAO
02/24/2015

HONG ZHAO
02/24/2015
I concur.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR BLA 125527**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125527	Brand Name	OPDIVO
OCP Division (I, II, III, IV, V)	OCP Division V	Generic Name	Nivolumab, BMS-936558/MDX1106
Medical Division	DOP2	Drug Class	Fully human IgG ₄ monoclonal antibody
OCP Reviewer	Xianhua(Walt) Cao, Ph D.	Indication(s)	Advanced squamous NSCLC
OCP Team Leader	Hong Zhao Ph.D. (CP); Liang Zhao, Ph.D. (PM)	Dosage Form	10 mg/mL solution (40 mg/4 mL & 100 mg/10 mL single-use vials)
Pharmacometrics Reviewer	Hongshan Li, Ph.D.	Dosing Regimen	3 mg/kg every 2 weeks (Q2W)
Date of Submission	12/22/14 (completed) Rolling, 06/20/2014 (ClinPharm)	Route of Administration	Intravenous (IV) over one hour
Estimated Due Date of OCP Review	3/2/15	Sponsor	Bristol-Myers Squibb
Medical Division Due Date	3/4/15	Priority Classification	Type 9 BLA, Priority, Expedited
PDUFA Due Date	6/22/15		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	x			
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	x	1		Study MDX1106-01 (CA209001); same as in BLA125554
multiple dose:	x	1		Study MDX1106-03 (CA209003); same as in BLA125554
Dose proportionality -				

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fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	2		MDX1106-03; CA209009 (same as in BLA125554)
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x	3		MDX1106-01 MDX1106-03 Ono-4538-01 (CA209005) (same as in BLA125554)
Data sparse:	x	4		CA209010 CA209037 CA209063 Ono-4538-02 (CA209051) (same as in BLA125554)
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Immunogenicity assessment	x	3		MDX1106-03 CA209063 CA209037 (same as in BLA125554)
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		8		(same as in BLA125554)

On **initial** review of the NDA/BLA application for filing:

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for BLA
125527_nivolumab

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR BLA 125527**

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			Analytical comparability for (b) (4) (to-be-marketed) and (b) (4) (used in clinical trials). Same as in BLA 125554.
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			Applicant states lack of CYP enzyme related cytokine modulation up to 10 mg/kg. same as in BLA 125554
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			x	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	x			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code,	x			

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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	input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?				
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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR BLA 125527**

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
3	Is the appropriate pharmacokinetic information submitted?	x			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			E-R for efficacy: CA209063 E-R for safety: MDX1106-03 and CA209063
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Waivered from the pediatric study requirement
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Waivered from the pediatric study requirement
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR BLA 125527**

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology 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.

Xianhua (Walt) Cao Ph.D.	January 28, 2015
Reviewing Clinical Pharmacologist	Date
Hong Zhao Ph.D.	January 28, 2015
Team Leader/Supervisor	Date

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

/s/

XIANHUA W CAO
01/30/2015

HONGSHAN LI
02/02/2015

LIANG ZHAO
02/02/2015

HONG ZHAO
02/02/2015
I concur.