CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology BLA Review	
BLA	125554
Submission Date	July 30, 2014
Type/Category	NME, Original BLA
Brand (generic) Name	Opdivo (nivolumab)
Dosage Form /Strenth	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 melanoma (unresectable or metastatic) in patients who have progressed on or after anti-CTLA-4 therapy, regardless of BRAF stautus.
Applicant	BMS
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OCP Division	DCPV
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Orphan Drug Designation	Januray 23, 2013
Breakthrough Designation	September 11, 2014
PDUFA Goal Date (Priority Review)	March 30, 2015
Action Goal Date	December 19, 2014

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1 EXECUTIVE SUMMARY

Nivolumab is submitted as a new molecular entity (NME) BLA for treatment of unresectable or metastatic melanoma in patients whose disease progressed on or after treatment with ipilimumab and, if BRAF V600 mutation positive, received treatment with a BRAF inhibitor in addition of ipilimumab.

Efficacy, safety, pharmacokinetic (PK), and immunogenicity data for this application are based on multiple clinical studies with nivolumab administered over the dose range of 0.1-20 mg/kg, where study CA209037 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.

1.1 RECOMMENDATIONS

BLA 125554 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 CA206037, 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 melanoma. Risk of time to first 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 0.1 to 10 mg/kg nivolumab Q2W in advanced melanoma.

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 diference in PK, safety and efficacy profiles were observed with the anti-nivolumab antibodies development.

Signatures:

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2 QUESTION BASED REVIEW

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 unresectable or metastatic melanoma in patients who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor in addition to anti-CTLA-4-therapy.

2.1.3 *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 melanoma in study CA209037. 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 separeately 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 1st 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 Melanoma

The proposed indication in the current BLA is primarily supported by the results from first 120 nivolumab treated patients in study CA209037 (n=268 nivolumab-treated), together with supportive data from study MDX1106-03 (n=107 nivolumab-treated) and CA209066 (n=197 nivolumab-treated) (**Table 2**).

Table 2. Description of clinical studies:

Study No.	Study Design	Endpoint[1]
CA209037 (Registrational)	Open-label, rondamized study of nivolumab (3 mg/kg every 2 weeks [Q2W]) versus investigator's choice (dacarbazine or carboplatin and paclitaxel) in patients with advanced melanoma on or after previously treatment with ipilimuab. There were 268 patients who received at least 1 infusion of nivolumab.	The ORR (first 120 nivolumab-treated patients with at least 6 months of follow-up) was 31.7% (95% CI: 23.5, 40.8) with range of DOR from 1.4+ to 10.0+ months (median DOR not reached at the time of database lock). Median exposure was 5.3 months (95% CI: 3.29, 6.47).
MDX1106-03 (phase 1b) (Supportive)	One hudred and seven (107) patients with melanoma received nivolumab at doses of 0.1, 0.3, 1, 3, or 10 mg/kg Q2W. Subjects were without prior anti-CTLA-4 therapy.	The ORR (crossing dose group) was 31% (95% CI: 22, 41) with a median duration of response (DOR) of 22.9 months (range: 3.9+ to 26.9+). Median OS across all doses was 17.3 months (95% CI: 12.5, 36.7).
[2]CA209066 (Supportive)	Randomized, double-blind randomized study of nivolumab versus dacarbazine in patients with previously untreated, BRAF wildtype advanced melanoma (n=197 nivolumab-treated).	Median OS in patients receiving nivolumab vs. dacarbzine was >14 months vs. 11.8 months, with HR=0.46

[1]As reported by BMS; [2] As summary report provided by DMC (data monitoring committee)

For Study CA209037, the co-primary endpoints were ORR and OS. The ORR is defined as complete or partial response (CR or PR), assessed by an Independent Radiologic Review Committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST) V1.1. The primary analysis of ORR was based on the first 120 nivolumab-treated patients with at least 6 months of follow-up. 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 investigatiors in the expansion cohorts.

In study CA209037, the IRRC-assessed confirmed ORR in the nivolumab group was 31.7%, which was consistent with the investigator-assessed ORR observed in MDX1106-03 (all dose levels: 31% and 3 mg/kg: 41%). In CA209037, 4 (3.3%) responses were CRs and in MDX1106-03, 1 (0.9%) CR was observed. At the time of the CA209037 database lock, the median DOR among responders had not been reached, with a range of 1.4+ to 10.0+ months (Table 3). The median OS across all doses in MDX1106-03 was 17.3 months (Table 3).

Table 3. Overall efficacy summary with nivolumab monotherapy in melanoma

	CA209037		MDX1106-03	
Endpoint **Efficacy parameter**	**Nivolumab 3 mg/kg**	**Investigator's choice (Reference arm)**	**Nivolumab 3 mg/kg**	**Nivolumab All doses**
	N=120	**N=47**	**N=17**	**N=107**
ORR,[a,b] n (%) (95% CI)	38 (31.7) (23.5, 40.8)	5 (10.6) (3.5, 23.1)	7 (41.2) (18.4, 67.1)	33 (30.8) (22.3, 40.5)
DOR,[b,c] n Median (Range) (Months)	38 NR (1.4+,10.0+)	5 3.6 (1.3+, 3.5)	7 17.5 (9.3, NR) (9.2+ - 26.5+)	34[d] 22.9 (17.0, NR) (3.9+ - 26.9+)
			N=17	**N=107**
OS				
Median (95% CI) (Months)	NA	NA	20.3 (7.2, -)	17.3 (12.5, 36.7)
Rate (95% CI)				
At 6 months	NA	NA	88% (61, 97)	82% (74, 88)
At 12 months (1 y)	NA	NA	65% (38, 82)	63% (53, 71)
At 24 months (2 y)	NA	NA	47% (23, 68)	48% (38, 57)
At 36 months (3 y)	NA	NA	41% (19, 63)	41% (31, 51)

a Based on IRRC-assessed confirmed PR or CR for CA209037 based on RECIST v1.1 and sponsor-assessed for MDX1106-03 based on RECIST v1.0.

b In CA209037, ORR and DOR were assessed in the Treated Subjects Among ORR Population, and PFS was assessed in all randomized subjects in the ORR Population.

c Per IRRC assessment for CA209037 and per sponsor assessment for MDX1106-03. 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.

d One additional subject was reported as a responder after 05-Mar-2013 (database lock for the MDX1106-03 CSR).

Abbreviations: DOR: duration of response; mo: month; NA: not available; NR: not reached; ORR: objective response rate; PFS: progression-free survival; y: year.

Source: sponsor's clinical overview report Table 4.3.1-1 page 22

MTD was not reached at the dose up to 10 mg/kg. The overall pattern of adverse events observed in melanoma patients, fit a profile expected for an immune checkpoint inhibitor. The most frequently reported drug-related AEs in the nivolumab group included fatigue (25%) and pruritus (16%). A lower proportion of patients in the nivolumab group compared with the investigator's choice group in CA209037 experienced at least 1 drug-related SAE (6.3% vs 9.8%). Drug-related AEs leading to discontinuation occurred less frequently in the nivolumab group compared with the investigator's choice chemotherapy group in CA209037 (2.2% vs 7.8%).

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 for nivolumab in the proposed patient polulation based on the primary endpoint of ORR in Study MDX1106-03 and CA209037.

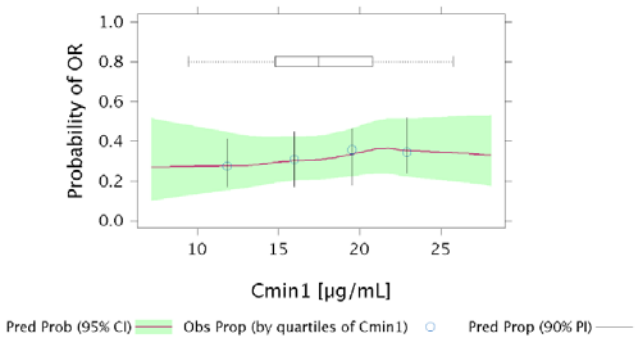
In the dose escalation and expansion study MDX1106-03 in patients with malignant melanoma, a flat exposure-ORR relationship was identified over the dose range of 0.1-10 mg/kg (Table 4).

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

Dose (mg/kg)	0.1	0.3	1	3	10	Overall
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
Source: Tables 7.2.1-1, 7.3.1-1 and 7.4.1-1 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 in Study CA209037 with nivolumab administered at 3 mg/kg Q2W (Figure 1). Population PK model predicted trough concentrations (7- 28 µg/mL) after first nivolumab dose (C_{min1}) were used as the measure of nivolumab exposure.

Figure 1. Flat exposure-response relationship of ORR versus nivolumab C_{min1} at 3 mg/kg Q2W for patients with advanced melanoma



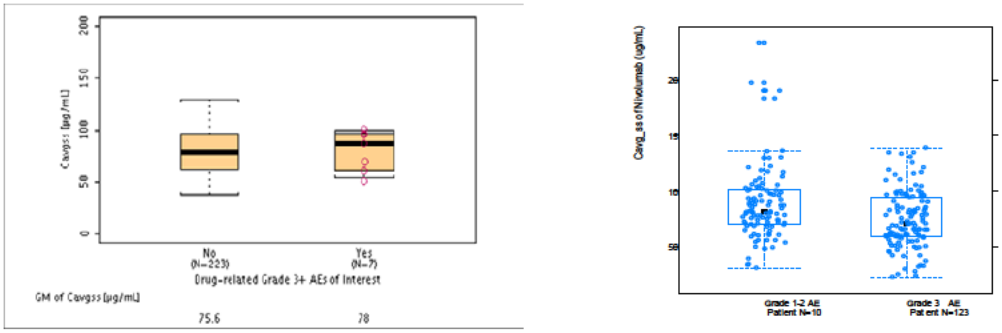
Source: Sponor's PPK report, Figure 5.2.2-1

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 $C_{avg,\ ss}$ and the time to first Grade 3+ DR-AEs, or AEs leading to discontinuation was characterized with data from 230 patients from study CA209037. There were 9.6% and 8.7% 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 time to first Grade 3+ drug related-AEs, AEs

leading to discontinuation and all 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 all grade 3+ adverse events and steady-state average concentration (Cavg,ss) of nivolumab at 3 mg/kg Q2W in study CA209037



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

2.2.2.3 *Does this drug prolong the QT/QTc interval?*

A QT substudy of CA209010 was conducted to determine whether nivolumab has QT prolongation potential. CA209010 was a randomized, blinded, 3-arm dose-ranging study of nivolumab (0.3, 2, and 10 mg/kg Q3W) in solid tumors. Evaluation of QTc was done at first dose and at seventh dose to cover effect of nivolumab at steady state exposure and also potential delayed effect on QT prolongation. There was no dose response for QTcF, ΔQTcF or change from baseline in heart rate, PR interval or QRS interval after either first dose or seventh dose. No patients had a QTcF interval > 470 msec or a ΔQTcF > 45 msec. In addition, there was no relationship between QTcF change from baseline and nivolumab serum concentration. This result is expected as large molecule monoclonal antibodies such as nivolumab has low potential to cause QT prolongation.

2.2.2.4 *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 melanoma 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 melanoma. Furthermore, no trend in exposure-efficacy or safety relationship was observed in study CA209037 at 3 mg/kg Q2W and therefore 3 mg/kg Q2W is considered appropriate as the recommended dose and schedule for the proposed indication.

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

The PK profile of nivolumab has been characterized by non-compartment analysis (NCA) and population PK (PPK) analysis based on the data from clinical studies as described in Table 1. PPK analysis (with n=909 nivolumab treated patients) indicates that the PK of nivolumab is time-invariant and linear in the dose range of 0.1 to 20 mg/kg. The volume of distribution of nivolumab at steady state is 8 L with a variability of 30.4%. The systemic clearance (CL) is 9.5 mL/hr with a variability of 50%. The terminal half-live ($t_{1/2}$) was estimated to be 26.7 days and steady-state was achieved by 12 weeks of Q2W repeated dosing. The accumulation index (AI) of 3 mg/kg Q2W dosing regimen is estimated to be approximately 3-fold.

Single dose PK

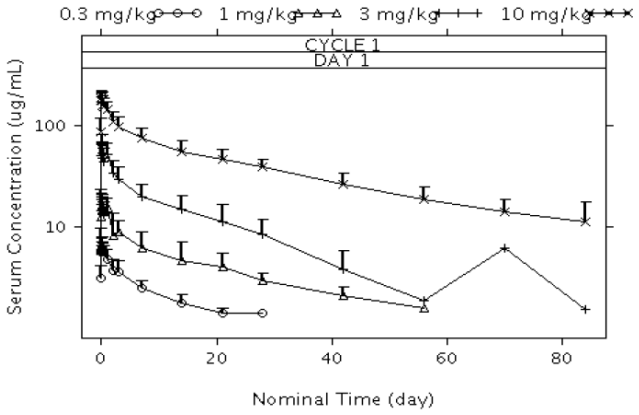
The single dose PK of nivolumab was evaluated following doses of 0.3, 1, 3 and 10 mg/kg in Study MDX1106-01. The median T_{max} across single doses ranged from 1.6 to 3.1 hours with individual values ranging from 0.9 to 7 hours. Mean $t_{1/2}$ ranged between 17 and 25 days across the studied dose cohorts. Geometric mean CL_T varied from 0.13 to 0.19 mL/h/kg, while mean V_z varied between 83 to 113 mL/kg across doses. The summary of nivolumab single-dose PK parameters by dose level is presented in Table 5, and the mean (+SD) serum concentration-time profiles are shown in Figure 3.

Table 5. Summary of nivolumab PK parameters after single dose IV infusion

Dose (mg/kg)	Cmax (µg/mL) Geo. Mean [N] (%CV)	Tmax (h) Median [N] (Min-Max)	AUC(0-T) (µg*h/mL) Geo. Mean [N] (%CV)	AUC(INF) (µg*h/mL) Geo. Mean [N] (%CV)	T-HALF (day) Mean [N] (SD)	CLT (mL/h/kg) Geo. Mean [N] (%CV)	Vz (mL/kg) Mean [N] (SD)
0.3	6.7 [6]	3.0[6]	970 [6]	2343 [3]	18.9 [3]	0.13 [3]	82.8 [3]
	(21.6)	(1.0-6.8)	(47)	(16)	(7.05)	(16.93)	(27.19)
1	16.0 [6]	1.9 [6]	3244 [6]	6014 [4]	17.0 [4]	0.17 [4]	99.6 [4]
	(32.1)	(1.0-7.0)	(62)	(30)	(2.36)	(29.80)	(23.04)
3	60.0 [5]	3.1 [5]	13909 [5]	15813 [5]	17.0 [5]	0.19 [5]	112.7 [5]
	(27.6)	(1.0-5.0)	(44)	(44)	(4.70)	(42.66)	(39.50)
10	196.3 [21]	1.6 [21]	55324 [21]	76541 [19]	24.8 [19]	0.13 [19]	109.4 [19]
	(19.5)	(0.9-7.0)	(39)	(27)	(7.22)	(28.42)	(26.70)

Source: Table S.8.2.2 of MDX 1106-01 CSR

Figure 3. Mean (+SD) serum concentration versus time profiles of nivolumab following a single IV infusion at various doses



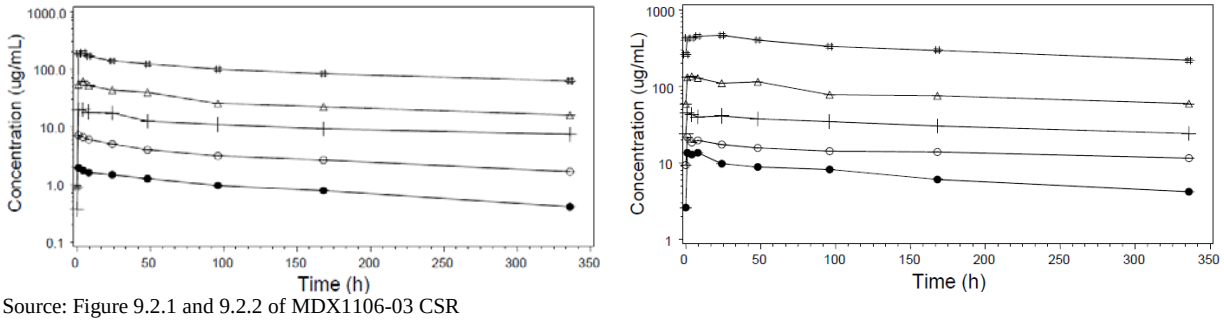
Source: Figure S.8.2.1 of MDX1106-01 CSR

Multiple doses PK

The multiple-dose PK of nivolumab given Q2W over the dose range of 0.1 to 10 mg/kg was assessed by NCA in trial MDX1106-03 at first dose (Cycle 1 Day 1) and ninth dose (Cycle 3 Day 1). The mean serum concentration-time profiles for nivolumab are shown in Figure 4 for first dose and ninth dose, respectively. The summary statistics for nivolumab PK parameters by dose group are provided in Table 6.

With Q2W administration schedule, a dose-proportional increase in nivolumab C_{max} and AUC_{TAU} was observed after first and ninth dose. A moderate variability (approximately 30% CV%) was observed in nivolumab exposure parameters (C_{max} and AUC_{TAU}). Geometric mean CL_T following Cycle 3/Day 1 dose ranged from 6.9 to 10.3 mL/h and was independent of dose in the dose range studied. Nivolumab accumulation index (AI) following Q2W administration was in the range of 2.9 to 3.3 based on AUC_{TAU}, 2.0 to 2.4 based on C_{max}, and 3.1 to 4.8 based on C_{min}. There was no dose-related trend in the AI of AUC_{TAU}, C_{max}, or C_{min}. The mean effective $t_{1/2}$ was in the range of 23.1 to 27.5 days.

Figure 4. Mean (+SD) serum concentration versus time profiles of nivolumab after first (left) and ninth (right) IV infusion with a Q2W dosing schedule at 0.1, 0.3,1,3, and 10 mg/kg



Source: Figure 9.2.1 and 9.2.2 of MDX1106-03 CSR

Table 6. Summary statistics for pharmacokinetic parameters of nivolumab administered Q2W

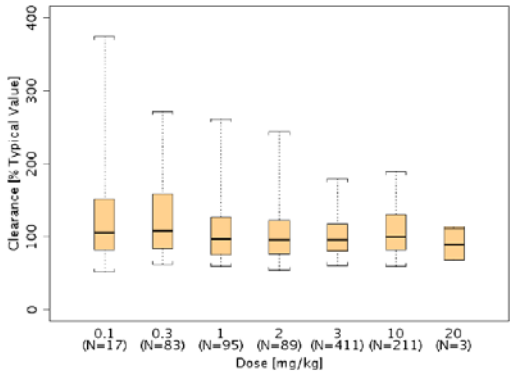
Nivolumab Dose	Dose Number	Cmax (μg/mL) GEO.MEAN[N] (%CV)	Tmax (h) MEDIAN[N] (MIN-MAX)	AUC(TAU) (μg*h/mL) GEO.MEAN[N] (%CV)	AI_Cmax GEO.MEAN[N] (%CV)	AI_AUC GEO.MEAN[N] (%CV)	CLT (mL/h) GEO.MEAN[N] (%CV)	Effective T-HALF (h) Mean [N] (SD)
0.1 mg/kg	First	1.9[15] (23.6)	1.1[15] (0.3-51.0)	279.4[13] (32.5)				
	Ninth	3.7[5] (42.2)	8.0[5] (0.6-24.0)	1104.4[4] (26.6)	2.3[4] (13.0)	3.1[4] (31.0)	8.3[4] (40.0)	622 [4] (235)
0.3 mg/kg	First	7.0[17] (32.3)	1.2[17] (0.9-24.3)	954.7[15] (26.9)				
	Ninth	17.8[2] (26.6)	24.7[2] (1.3-48.0)	3406.1[2] (12.8)	2.0[2] (26.7)	2.9[2] (6.1)	6.9[2] (17.8)	555 [2] (42)
1 mg/kg	First	19.6[17] (29.5)	1.2[17] (0.9-48.0)	3589.6[10] (23.8)				
	Ninth	46.9[10] (26.1)	1.0[10] (0.9-24.1)	10190.4[9] (25.8)	2.4[9] (21.4)	3.1[9] (34.7)	8.0[9] (31.1)	636 [9] (267)
3 mg/kg	First	61.3[13] (26.4)	2.1[13] (0.8-8.0)	8785.8[13] (22.7)				
	Ninth	132.0[7] (19.8)	4.0[7] (1.0-8.0)	30640.3[5] (17.5)	2.4[5] (13.6)	3.3[5] (25.5)	10.3[5] (18.1)	661 [5] (202)
10 mg/kg	First	191.2[14] (40.0)	3.9[14] (1.0-48.2)	31095.1[12] (25.4)				
	Ninth	475.0[5] (24.6)	22.3[5] (1.0-24.5)	99621.7[3] (26.0)	2.4[3] (12.6)	3.1[3] (11.0)	8.5[3] (6.4)	595 [3] (80)

Source: Table 9.2.1 of MDX1106-03 CSR

Dose linearity and accumulation

Nivolumab exhibited linear PK in a dose range of 0.1 to 20 mg/kg. PK linearity was examined in the PPK analysis by testing the effect of dose on CL, as well as by estimating the parameters in a model in which CL was described by a combination of linear and nonlinear (Michaelis-Menten) terms. The kinetics of nivolumab were established to be linear as dose did not have a significant effect on CL, and the nonlinear model did not result in a significant improvement in the fit of the model to the data. The dose linearity in nivolumab PK is illustrated in Figure 5, which presents CL of nivolumab by dose levels.

Figure 5. Linear PK indicated by PPK based estimates of individual nivolumab clearance



Source: Figure 3.1.2-1 summary of clinical pharmacology

Following Q2W administration, accumulation of nivolumab C_{min} from first to ninth dose was in the range of 3.1 to 4.8, whereas accumulation of concentration at the end of infusion (C_{eoinf}) was in the range of 1.5 to 2.2 as indicated in Table 7. There was no dose-related trend in accumulation of C_{min} and C_{eoinf}.

Table 7. Summary statistics for trough (Cmin) and end of infusion (Ceoinf) concentrations of nivolumab administered Q2W

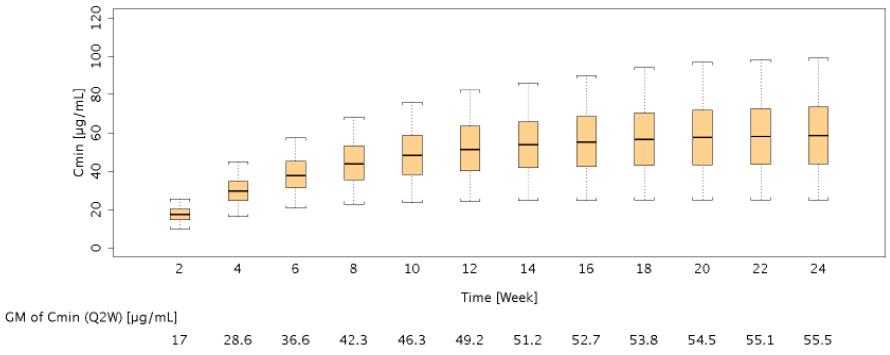
Nivolumab Dose	Dose Number	Cmin (µg/mL) GEO.MEAN[N] (%CV)	Ceoinf (µg/mL) GEO.MEAN[N] (%CV)	AI Cmin GEO.MEAN[N] (%CV)	AI Ceoinf GEO.MEAN[N] (%CV)
0.1 mg/kg	First	0.3[16] (56.9)	1.9[16] (27.7)		
	Ninth	2.5[7 (27.7)	2.8[4] (53.1)	4.8[7] (26.2)	1.5[4] (58.9)
0.3 mg/kg	First	1.4[15] (47.6)	6.9[18] (32.8)		
	Ninth	6.4[5] (47.1)	17.2[2] (31.3)	4.7[5] (102.3)	1.9[2] (31.5)
1 mg/kg	First	5.5[72] (42.8)	19.7[82] (31.3)		
	Ninth	19[35] (38.8)	39.7[38] (30.1)	3.1[35] (34.5)	1.9[36] (32.6)
3 mg/kg	First	16.6[46] (34.4)	58.6[50] (28.3)		
	Ninth	57[21] (35.9)	121.5[23] (20.7)	3.2[20] (25.3)	2.2[23] (49.4)
10 mg/kg	First	56.5[116] (30.6)	179.6[120] (26.3)		
	Ninth	188.8[44] (36.9)	331.4[43] (33.6)	3.2[44] (34.6)	1.8[42] (39.4)

Cmin and Ceoinf data shown are based on Day 1 samples, except for the Cycle1 Cmin which is based on Day 15 samples

Source: Table 9.2.2 of MDX1106-03 CSR

The PK parameters (CL and V_{ss}) do not change following the administration of multiple doses of 0.1 to 20 mg/kg Q2W, which is supported by the population PK analysis. With 3 mg/kg Q2W doses, the steady state is achieved approximately at 6th dose (12 weeks) with AI of approximately 3 folds as indicated in Figure 6.

Figure 6. PPK predicted nivolumab trough concentration (C_{min}) as function of time at 3 mg/kg Q2W during first six months dosing



Note: The box plot represent median (bold line), 25th and 75th percentile of Cmin distribution. The whiskers represent 5th and 95th percentile of the distribution.

Source: Figure 5.1.3.2-1 of the PPK and Exposure-Response Report.

PK parameter covariates and variability

In the final PPK model, body weight, ECOG status and baseline eGFR were covariates for CL; body weight and gender were covariates for volume of distribution of central compartment (Vc). None of the covariates tested had a clinically meaningful impact on exposure to nivolumab with the body weight based dosing schedules. For the final model, the parameters and unexplained inter-individual variability are listed in the Table 8 below.

Table 8. Paremeter estimates of the final population PK model

Parameter[a] [Units]	Estimate[b]	95% Confidence Interval[c]
Structural Model Parameters		
CL_{REF} [L/h]	0.00866	0.00826 - 0.00905
VC_{REF} [L]	3.87	3.75 - 3.99
Q_{REF} [L/h]	0.0296	0.0267 - 0.0329
VP_{REF} [L]	3.80	3.6 - 4.04
CL_{BW} *(REF=80 [kg])*	0.700	0.576 - 0.809
CL_{eGFR}, *(REF=80 mL/min/1.73m^2)*	0.172	0.067 - 0.276
CL_{ECOG} *(REF= 0)*	0.174	0.113 - 0.235
VC_{BW} *(REF=80 [kg])*	0.534	0.463 - 0.607
VC_{sex}, *REF=Female*	0.130	0.0937 - 0.167
Inter-Individual Variability Model Parameters		
ω^2CL	0.188 (0.434)	0.16 - 0.218
ω^2VC	0.0488 (0.221)	0.0403 - 0.0577
ω^2_{VP} [-]	0.294 (0.542)	0.227 - 0.371
ω_{CL}:ω_{VC}	0.0438 (0.457)	0.0335 - 0.0551
Residual Error Model Parameters		
Proportional error [-]	0.207	0.197 - 0.218

[a] Eta shrinkage: ETA_CL: 9.92, ETA_VC: 17.8, ETA_VP: 28.5 and Eps shrinkage (%): 10.9.

[b] Estimate values in parentheses are *standard deviation* for estimated variances and c*orrelation* for estimated covariances

[c] Confidence Interval values are taken from bootstrap calculations (1897 successful out of a total of 2000)

Source: Page 4 of Sponsor's PPK reports ; Table 8 of Pharmacometrics Review; .

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?*

The effects of various covariates on the pharmacokinetics of nivolumab were assessed in population pharmacokinetic analyses. The CL of nivolumab increased with increase in

bodyweight and ECOG status. Nivolumab exposures (dose normalized $C_{avg,ss}$ and $C_{min,ss}$) were approximately uniform with body weight normalized (mg/kg based) dosing of nivolumab and slightly lower in patients with ECOG status > 0. The following factors had no clinically important effect on the CL of nivolumab: age (range 23 to 87 years) , gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, immunogenicity, renal impairment and mild hepatic impairment.

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***.

No clinically meaningful PK differences have been identified in specific patient populations; therefore, no dosing regimen adjustments are recommended for specific patient populations

2.3.2.1 ***Elderly Patients***

None. Age was not identified as a significant covariate influencing nivolumab PK based on a population PK analysis ,which included patients range of 23-87 years of age (n=909), mean of 61 years of age, and median of 62 years of age.

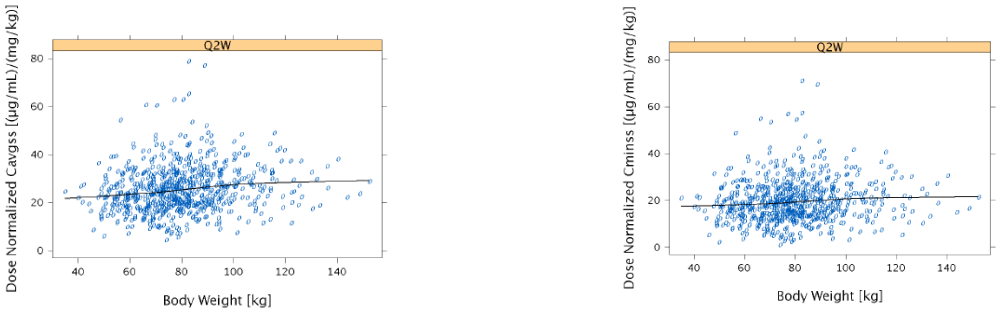
2.3.2.2 ***Gender***

None. The population PK dataset included 603 men (66%) and 306 women (34%). Although gender was identified as a statistically significant covariate on Vc, but had no clinically relevant effect on CL and no influence on the nivolumab exposure (dose normalized $C_{avg,ss}$) for male and female subjects.

2.3.2.3 ***Body weight***

None. Based on population PK analyses, body weight was identified as a statistically significant covariate on nivolumab CL and V_C (ranged from 34 to 162 kg with a mean weight of 81 kg). However nivolumab exposures (dose normalized $C_{avg,ss}$ and $C_{min,ss}$) were approximately uniform with body weight based (mg/kg based) dosing of nivolumab (Figure 7). Body weight based dosing is generally acceptable considering the flat exposure-response relationship in terms of efficacy and safety for nivolumab (refer to Figure 1 and 2).

Figure 7. Nivolumab dose normalized exposure (Cavg,ss and Cmin,ss) vs body weight for body weight-based dose regimens

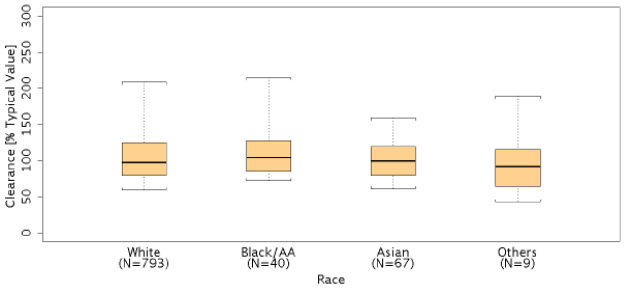


Source: Figure 5.1.3.4-1 PPK and ER report

2.3.2.4 *Race*

None. Based on population PK analyses, race was not a significant covariate on the PK of nivolumab and it had no clinical relevance on nivolumab CL as shown in Figure 8.

Figure 8. Effect of race on nivolumab clearance.



Note: The box plots represent median (bold line), 25th, and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution.
Source: Figure 5.1.3.10-1 PPK and ER report

2.3.2.5 *Renal Impairment*

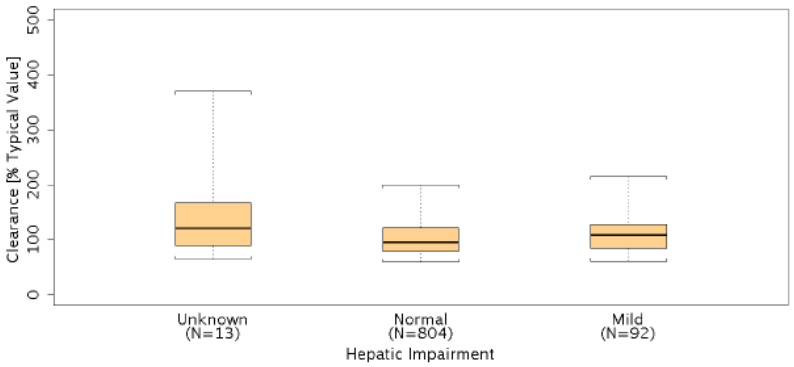
No dedicated clinical studies were conducted to evaluate the effect of renal impairment on the PK of nivolumab. Based on a population PK analysis which included patients with mild (eGFR 60-90 mL/min/1.73m^2, n=313), moderate (eGFR 30-59 mL/min/1.73m^2, n=140), and severe (eGFR 15-29 mL/min/1.73m^2, n=3) renal impairment, the effect of mild and moderate renal impairment on CL of nivolumab was minor. Data is not sufficient for drawing a conclusion on severely renal impaired patients.

2.3.2.6 *Hepatic Impairment*

No dedicated clinical studies were conducted to evaluate the effect of hepatic impairment on the PK of nivolumab. Based on a population PK analysis which included patients with mild hepatic impairment (total bilirubin (TB) ≤ ULN and AST > ULN or TB < 1.0 to 1.5 x ULN and any AST n=92) and normal hepatic function (TB and AST less than or equal to ULN; n=804), there was no clinically important differences in the CL of nivolumab between patients with mild hepatic impairment and patients with normal hepatic function. Model-derived CL values in patients with mild hepatic impairment were similar to those in patients with normal hepatic

function (Figure 9). Nivolumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe hepatic impairment (TB greater than 3 times ULN and any AST).

Figure 9. Effect of hepatic function on nivolumab clearance.



Note: The box plots represent median (bold line), 25th, and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution.
Source: Figure 5.1.3.8-1 PPK and ER report

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

Nivolumab is categorized as Pregnancy Category (b) (4) The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels either 8 or 35 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, dose-dependent increases in fetal losses and increased neonatal mortality in infants with extreme prematurity were observed. There are no adequate and well-controlled studies with nivolumab in pregnant women. Nivolumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether nivolumab is excreted in human milk. No studies have been conducted to assess nivolumab's impact on milk production or its presence in breast milk. Because antibodies are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from nivolumab, a decision should be made whether to discontinue nursing or to discontinue nivolumab, taking into account the importance of nivolumab to the mother.

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?*

Three assays were used to detect the presence of APA in the patinets treated in the clinical program. Only the 3rd generation of ECL assay has sufficient drug tolerance. With the 3rd generation ECL assay and at clinical relavant dose of 3 mg/kg Q2W, 24 of 281 patients (8.5%)

were tested positive for the treatment emergent anti-nivolumab antibodies; 2 (0.7%) patients were persistently positive (positive at two consecutive time points at least 8 weeks apart) for the presence of APA (Table 9). Neutralizing antibodies were detected in 2 (0.7%) of the positive APA samples. There was no apparent altered pharmacokinetic profile or toxicity profile associated with APA development based on the population pharmacokinetic and exposure-response analysis.

Table 9. Summary of immunogenicity results for nivolumab

Assay Generation /Drug tolerance level (ug/mL)	Study	Dose (mg/kg) Q2W	N	Number(%)Subjects				
				Baseline positive	On-Treatment positive [a]			ADA Negative
					Persistent positive b	Only last sample postitive	Any positive	
2^{nd}/ 12.5	MDX1106-03	0.1	14	0	1 (7.1)	4 (28.6)	6 (42.9)	8(57.1)
		0.3	14	1(7.1)	0	1(7.1)	2(14.3)	12(85.7)
		1	66	3(4.5)	1(1.5)	5(7.6)	7(10.6)	59(89.4)
		3	46	2(4.3)	0	1 (2.2)	2 (4.3)	44(95.7)
		10	103	1(1)	0	3(2.9)	4(3.9)	99(96.1)
Subtotal			243	7(2.9)	2 (0.8)	14(5.8)	21(8.6)	222(91.4)
3^{rd} / 800	CA209063	3	101	11(10.9)	0	6(5.9)	12 (11.9)	89 (88.1)
	CA209037	3	180	9(5.0)	2 (1.1)	4 (2.2)	12 (6.7)	168(93.3)
Subtotal			281	20(7.1)	2(0.7)	10 (3.6)	24(8.5)	257(91.5)

Source: Table 4.2.2-1, Table 4.2.3-1 and Table 4.2.4-1 of clinical pharmacology summary

APA samples were colleceted at baseline and during the treatment of nivolumab at 3 mg/kg Q2W in Study CA209063 and CA209037 according to the following schedule in Table 10, which appears to be adequate.

Table 10. Immunogenicity sampling schedules for nivolumab at 3 mg/kg Q2W with cycle of 14 days

Phase	Time
Baseline	Predose on Cycle 1 Day 1
Early treatment phase	Predose on Day 1 of Cycle 2, 3 and 8
Later treatment phase	Every 8^{th} Cycle after Cycle 8 Day 1 until discontinuation
Follow up visit	First 2 Follow-up Visits up to 100 days from the end of treatment

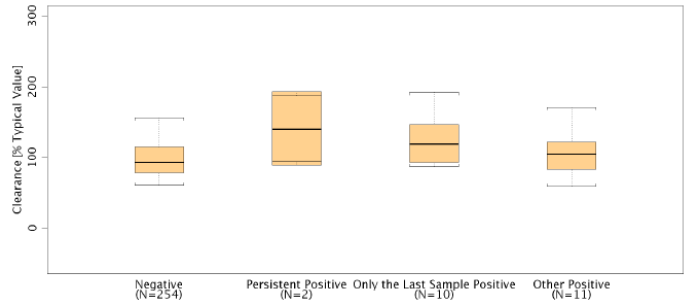
The initial ECL assay (STM 4669) lacked a confirmatory testing, and therefore the immunogenicity data evaluated by the initial assay was not included in the immunogenicity statistical analysis. The second generation ECL method (ICDIM 44 V3.00) was used to detect the APA in patients samples for study MDX1106-03, which included a three-tiered testing approach (screen, confirm, and titer) with the drug tolerance up to 12.5 μg/mL of nivolumab. The true

occurrence of immunogenicity at higher doses may be underestimated in MDX1106-03, as the observed geometric mean steady state trough concentration of nivolumab at ≥ 1 mg/kg dose, was higher than the drug tolerance level of 12.5 µg/mL. The samples from CA209063 and CA209037 were analyzed by the third generation ECL method (ICDIM 140 V1.00/V2.02), with drug tolerance of up to 800 µg/mL, exceeded the expected drug trough levels with the recommended nivolumab dosing regimen of 3 mg/kg Q2W. Samples that were confirmed positive from CA209063 and CA209037 were tested for presence of neutralizing antibodies using a validated cell based functional assay (Method 15400).

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

Nivolumab clearance for the patients whose samples tested positive for treatment emergent APA was in the range of clearance for patients tested negative of APA treated with the same dose of 3 mg/kg Q2W (Figure 10).

Figure 10. Effect of immunogenicity on nivolumab clearance at 3 mg/kg Q2W (3rd generation assay).



Note: The box plots represent median (bold line), 25th, and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution.
Source: Figure 5.1.3.13-1 PPK and ER report

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

Out of 12 APA positive patients in Study CA209037, 2 patients (1 persistent positive, 1 other positive) each had 1 ADA positive sample with neutralizing antibodies (Nabs) detected. Nivolumab concentrations increased at subsequent APA assessment for both patients when Nabs were not detectable. A clear cause-effect relationship cannot be established between the presence of Nabs and loss of efficacy and/or AEs.

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

There was no evidence of apparent impact of treatment-emergent APA on the clinical efficacy profile for nivolumab due to lack of effect of immunogenicity on pharmacokinetic profile and flat exposure-response relationship (refer to Figure 1 and Figure 10).

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.)?*

The patients who had a post-dose sample tested positive for treatment-emergent APA did not have any hypersensitivity events associated with APA, such as anaphylaxis, urticarial, angioedema or injection site reactions.

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?*

No dedicated studies were conducted to evaluate the impact of extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) on the PK of nivolumab.

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?*

No. Given nivolumab is a therapeutic monoclonal antibody, it is expected to be catabolized into amino acids by general protein degradation process. As nivolumab is not a cytokine modulator, it is unlikely to have an effect on drug metabolizing enzymes or transporters in terms of inhibition or induction.

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?*

Three manufacturing processes were used in the development of nivolumab drug substance (DS) and drug product (DP) as listed in Table 11. Products from (b) (4) were determined to be analytically comparable. (b) (4) The results of analytical tests including statistical analysis (tolerance limit analysis) demonstrated that (b) (4) DS is comparable to both (b) (4) DS. Please refer to the CMC review. Nivolumab DS (b) (4) were used in clinical studies CA209063 and CA209037. (b) (4) is the intended process for nivolumab DS that will be used to produce marketed DP.

Table 11. Manufacturing processes for nivolumab

(b) (4)

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?*

(b) (4) DS will be used to produce marketed DP, which is analytical comparable to (b) (4) DS used in the registration trial. Please refer to CMC review. No relative PK comparability study was conducted to compare the (b) (4) DP to the to-be-marketed (b) (4) DP and it is deemed unnecessary based on the minor low risk manufacturing changes between the two products. Populaton PK analysis indicated manufacturing switch from (b) (4) had no impact on nivolumab clearance as indicated in Figure 11.

Figure 11. Effect of manufacturing (b) (4) on nivolumab clearance.

Note: The box plots represent median (bold line), 25th, and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution. Subjects who did not have available manufacturing information were not presented in the boxplot.
Source: Figure 3.1-1 of Summary of Biopharmceutic Studies and Associated Analytic Methods

2.6 ANALYTICAL SECTION

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

Two quantitative enzyme-linked immunosorbent assays (ELISA) (ICD 316 and (b) (4) and one electrochemiluminescence (ECL) assay (ICD 416) were validated to quantify nivolumab levels in human serum. The ELISA assays supported early BMS and ONO studies (MDX1106-01, part of MDX1106-03 and ONO-4538-01). The ECL method has greater sensitivity, and supported the later BMS and ONO studies (part of MDX1106-03, CA209010, CA209063, CA209037, and ONO-4538-02). The summary of bioanalytical assays for nivolumab quantification is listed in Table 12 below.

Table 12. Bioanalytical methods summary for nivolumab quantification

Validated Method	ELISA (ICD 316)	ECL (ICD 416)	ELISA (b) (4)
Species and Matrix	Human Serum	Human Serum	Human Serum
Analyte	Nivolumab	Nivolumab	Nivolumab
Capture	(b) (4)		
Detector			
Regression Model, Weighting:	4 parameter logistic, no weighting	4 parameter logistic, no weighting	4 parameter logistic, no weighting
Standard Curve			
LLOQ	1.2 µg/mL	0.2 µg/mL	1.2 µg/mL
ULOQ	10 µg/mL	6.5 µg/mL	21 µg/mL
QC Precision (% CV)			
Intra Assay	≤ 14.6%	≤ 3.87%	≤ 6.35 %
Inter Assay	≤ 15.5%	≤ 10.1%	≤ 13%
QC Accuracy (% Deviation)	Within ± 21%	Within ± 12%	Within ± 10%
Stability			
RT	~24 hours	96 hours	~19 hours
4°C	72 hours	~24 hours	~19 hours
-20°C	Not determined	515 days	Not determined
-70°C or -80°C	1433 days	900 days	~ 465 days
Freeze-Thaw	10 cycles	6 cycles	5 cycles
Studies in Which Method Was Used	MDX1106-01 and MDX1106-03 (cohorts prior to protocol amendment 4)	ONO-4538-02, MDX-1106-03 (cohorts enrolled after protocol amendment 4), CA209010, CA209063, and CA209037	ONO-4538-01

[a] Clone 1106.2438.12B4.E11.D11

[b] Clone 1106.2437.16B10.H7.B8.

[c] Cross Validation is reported in the "Method Comparison" section of the ECL (ICD 416) validation report

ELISA: enzyme-linked immunosorbent assay, ECL: electrochemiluminescence, ICD: Immunochemistry Department, LLOQ: Lower limit of quantification, QC: quality control, RT: room temperature, (b) (4) immunoassay method ULOQ: Upper limit of quantification.

Source: Table 1.3.1-1 of Summary of Biopharmceutic Studies and Associated Analytic Methods

ELISA assays

The ELISA assays (ICD 316 and [redacted] were used to measure nivolumab in human serum in early clinical studies. Assay ICD 316 was validated and performed at [redacted] using [redacted] The range for nivolumab in undiluted human serum for assay ICD 316 was 1.2 to 10 µg/mL. Assay [redacted] was validated and performed at [redacted] in which [redacted] and the range for nivolumab in undiluted human serum was 1.2 to 21 µg/mL.

ECL assay

ECL assay ICD 416 using the MSD platform was developed and validated at [redacted] The assay has further increased sensitivity to quantitate the expected lower drug levels from subjects receiving lesser amounts of drug (0.1 or 0.3 mg/kg). ICD 416 measures nivolumab in human serum [redacted] The detection range of nivolumab for this assay in undiluted human serum is 0.2 µg/mL to 6.5 µg/mL.

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?***

Table 12 above provides the range of the standard curve for each assay. For assay ICD 416, calibrators, controls and samples were diluted to the assay minimum required dilution (MRD) (1:100) in assay buffer. Analyte concentrations were determined by interpolation from the standard curve, which has been fit using a four-parameter logistic regression model. The minimum required sample volume is 20.0 µL. The calibration range of 0.100 to 6.50 µg/mL with a quantification range of 0.200 to 6.50 µg/mL was confirmed in 100% matrix. This standard curve range (0.200, 0.300, 1.00, 2.50, 4.00, 5.50 and 6.50 µg/mL) with MRD of 1:100 was adequate for the purposes of determining serum nivolumab concentrations in the clinical studies.

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

Table 12 above provides the LLOQ and ULOQ for each assay. For assay ICD 416 used in the study CA209037, the LLOQ is 0.2 µg/mL and the ULOQ is 6.5 µg/mL.

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

Accuracy and Precision

A summary of the accuracy and precision for assay ICD 416 is shown below in Table 13. The precision and accuracy at the LLOQ (0.200 µg/mL), back-up LLOQ (0.300 µg /mL), LQC (0.600 µg /mL), MQC (1.50 µg /mL), HQC (4.80 µg /mL), and ULOQ (6.50 µg /mL) were analyzed, which is consistent with the recommendations described in the draft FDA Guidance for Industry entitled, "Bioanalytical Method Validation". Precision was expressed as the percent coefficient of variation (%CV) of each pool. Accuracy was expressed as the percent difference from the theoretical (PDT) concentration.

Table 13. Summary of accuracy and precision for assay ICD 416

Theoretical Concentration (µg/mL)		LLOQ (0.200)	Back-up LLOQ (0.300)	LQC (0.600)	MQC (1.50)	HQC (4.80)	ULOQ (6.50)
Intra-run	n	6	6	6	6	6	6
	Mean	0.195	0.275	0.539	1.64	5.37	6.72
	SD	0.00714	0.00889	0.0209	0.0349	0.187	0.109
	%CV	3.65	3.24	3.87	2.12	3.48	1.62
	PDT(%)	-2.30	-8.43	-10.2	9.65	12.0	3.35
Inter-run	n	12	12	12	12	12	12
	Mean	0.179	0.29	0.609	1.58	4.75	6.35
	SD	0.0181	0.0182	0.0443	0.0863	0.223	0.320
	%CV	10.1	6.28	7.27	5.48	4.69	5.03
	PDT(%)	-10.1	-3.38	1.55	5.02	-0.943	-2.23

Data Source: Table 4 and 5 of the Method Validation Report for assay ICD 416

Selectivity from Matrix Effect

Selectivity was tested in normal human serum samples and the following cancer patient sera: melanoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC). Nivolumab was intitially spiked into each matrix at the high QC (HQC; 4.80 µg/mL) and the LLOQ (0.200 µg/mL). Each individual was also analyzed blank. For selectivity to be considered acceptable, 80% of the high spikes (HQC) were expected to quantitate within 20% of the theoretical value, and 80% of the low spikes (LLOQ) were expected to quantitate within 25% of the theoretical value. The unspiked matrix lots were expected to quantitate below the level of quantitation. A summary of selectivity at LLOQ and HQC is shown in Table 14.

Since only 75% of the samples were recovered in the LLOQ spikes in the melanoma matrix (less than the expected criteria of 80%), LQC with 0.4 µg/mL was further tested in the cancer pataients sera as the estimated minimum concentration (0.4 µg/mL) for a 0.1 mg/kg dose of nivolumab.

Table 14. Summary of selectivity from four matrix at LLOQ, LQC and HQC for assay ICD 416

Matrix	LLOQ (0.200 µg/mL)	LQC (0.4 µg/mL)	HQC (4.80 µg/mL)
Normal serum	100% (10/10)	NA	100% (10/10)
Cancer patients serum			
Melanoma	75% (15/20)	100% (20/20)	80% (95/20)
RCC	83% (10/12)	100% (12/12)	92% (11/12)
NSCLC	85% (17/20)	95% (19/20)	95% (19/20)

Data Source: Table 8-12 of the Method Validation Report for assay ICD 416

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)*

A summary of the sample stability for nivolumab is shown in Table 10. The long-term stability

tests support the shelf life of (b) (4) days at the storage condition of nominal temperature of -(b) (4) claimed by the applicant.

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 ± 20.0% of the theoretical concentration for the analytical run to be accepted. QC runs of assay ICD416 for study CA209037 is summarized in Table 15 below.

Table 15. Summary of QC runs for assay ICD416 in study CA209037

	QC 1 - Dil 1	QC 2 - Dil 1	QC 3 - Dil 1	QC 7 - Dil 50	QC 7 - Dil 100	QC 7 - Dil 200
µg/mL	0.600 µg/mL	1.50 µg/mL	4.80 µg/mL	100 µg/mL	100 µg/mL	100 µg/mL
Mean Observed Conc., µg/mL	0.641	1.52	4.81	103	103	82.6
%Dev	6.79	1.59	0.250	3.18	3.12	-17.4
Between Run Precision (%CV)	7.54	5.57	5.97	8.60	9.35	10.8
Within Run Precision (%CV)	9.73	14.8	15.3	15.5	8.57	10.8
n	105	105	106	123	12	3
Number of Runs	53	53	53	41	4	1

Source: Table 11 of (b) (4) Serum Bionalytical Study Report for study CA209037
Statistical outliers with values greater than 3S.D. from the mean value for that QC level excluded

3 APPENDICES

3.1 PHARMACOMETRICS REVIEW

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

BLA Number	125554
Drug Name	OPDIVO® (Nivolumab)
Dose Regimen	3 mg/kg IV infusion over 60 minutes every 2 weeks
Indication	Unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status
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 reasonable for treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

There appeared to be no exposure-efficacy relationship for the objective response rates (ORR) across the dose range of 0.1-10 mg/kg Q2W for the proposed indication based on the clinical efficacy data currently available.

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 CA209037. 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 remain inconclusive.

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 reasonable for treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status. The nivolumab dose of 3 mg/kg Q2W was selected based on ex vivo receptor binding study, animal studies involving tumor models, and Phase Ib/III human clinical trials in melanoma patients.

- 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 nivolumab EC_{50} 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 EC_{50}.
- 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. In the Phase 1 dose escalation study (MDX1106-03) in 306 patients with NSCLC, melanoma or RCC, maximum tolerable dose (MTD) was not reached at 10 mg/kg. Nivolumab 3 mg/kg dose appeared to be safe and efficacious in the patients with malignant melanoma.
- Finally, 3 mg/kg Q2W was selected based on the efficacy and safety data of the Phase 3 registration trial. In the Phase 3 registration trial (CA209037), 3 mg/kg dose demonstrated to be efficacious with acceptable safety profile in the advanced melanoma 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 0.1-10 mg/kg Q2W for the proposed indication based on the clinical efficacy data currently available.

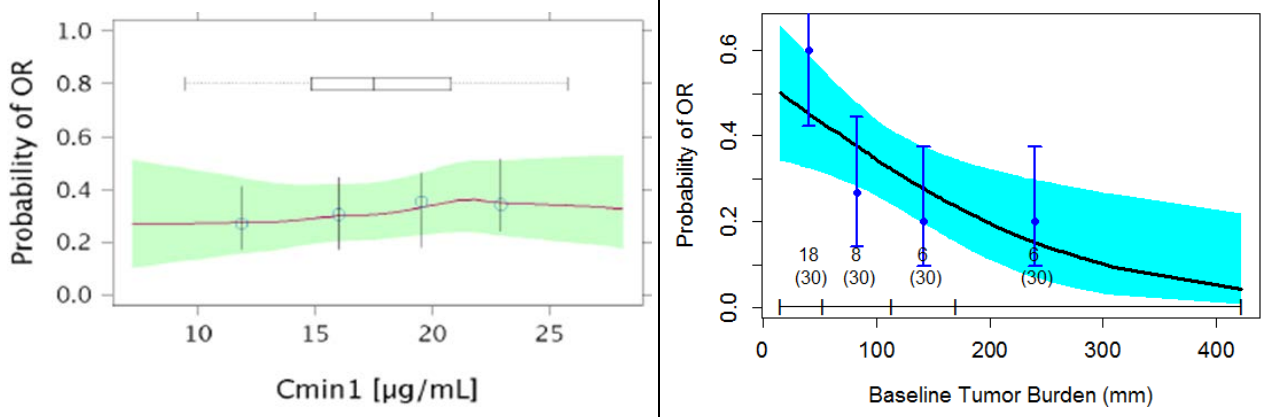
- In the Phase I dose escalation study (MDX1106-03), the ORR of nivolumab in malignant melanoma patients were 35% (N=17), 28% (N=18), 31% (N=35), 41% (N=17) and 20% (N=20) for doses of 0.1, 0.3, 1, 3 and 10 mg/kg doses Q2W, respectively. Nivolumab PK was linear across the dose range, so the exposure-ORR relationship was flat for the dose range of 0.1-10 mg/kg. Numerically, 3 mg/kg Q2W appeared to be the most efficacious dose (**Table 1**).
- In the Phase III trial (CA209037), ORR was also flat across the trough concentration range of 7-28 µg/mL for the first 3 mg/kg Q2W dose after the covariate effect was adjusted (**Figure 1**). The only significant covariate identified for efficacy was the baseline tumor burden: a higher baseline tumor burden resulted in a lower ORR in study CA209037.

Table 1: Objective Response Rates of Nivolumab Across Tumor Types and Dose Levels in Study MDX1106-03

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

Figure 1: Exposure-Response for the Trough Concentration of the First Dose (C_{min1}) versus Objective Response Rate for 3 mg/kg Q2W of Study CA209037



Left Panel: Red line is the lowess smooth curve of the predicted probability and the light green area is the 95% CI. Open circles are observed ORR for each C_{min1} quartile plotted at the median of the quartile with the vertical bar as the 90% CI. The horizontal boxplot shows the median, interquartile range, and 5th/95th percentiles of C_{min1}.
Right Panel: Black line is predicted probability by logistic regression and the cyan area is the 95% CI. Blue dots are observed ORR for each baseline tumor burden quartile plotted at the median of the quartile with the vertical bar as the 95% CI. The horizontal black segments show the boundaries of the 4 quartiles of baseline tumor burden.

Source: The left panel is from Figure 5.2.2-1 of the Population Pharmacokinetic and Exposure-Response Report. The right Panel is from FDA reviewer's analysis based on dataset efforr.xpt for Study CA209037.

In general, the exposure-ORR relationship for nivolumab appeared to be flat across the dose range of 0.1-10 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 CA209037. However, there may be a signal for increase in specific AEs with increasing exposure as shown in **Table 2**.

- **Figure 2** presents a summary of exposures for patients with (n=7) and without (n=223) Grade 3+ AEs of interest in Study CA209037. The distributions of the exposure were not significantly different between the 2 subgroups.
- **Figure 3** presents a summary of exposures for patients with and without any Grade 3+ AEs in CA209037. Patients were divided into 2 subgroups: Grade 1-2 AE (N=104) and Grade 3-5 AE (N=123). Of note, all patients experienced AEs. The distributions of the exposure were not significantly different between the 2 subgroups.

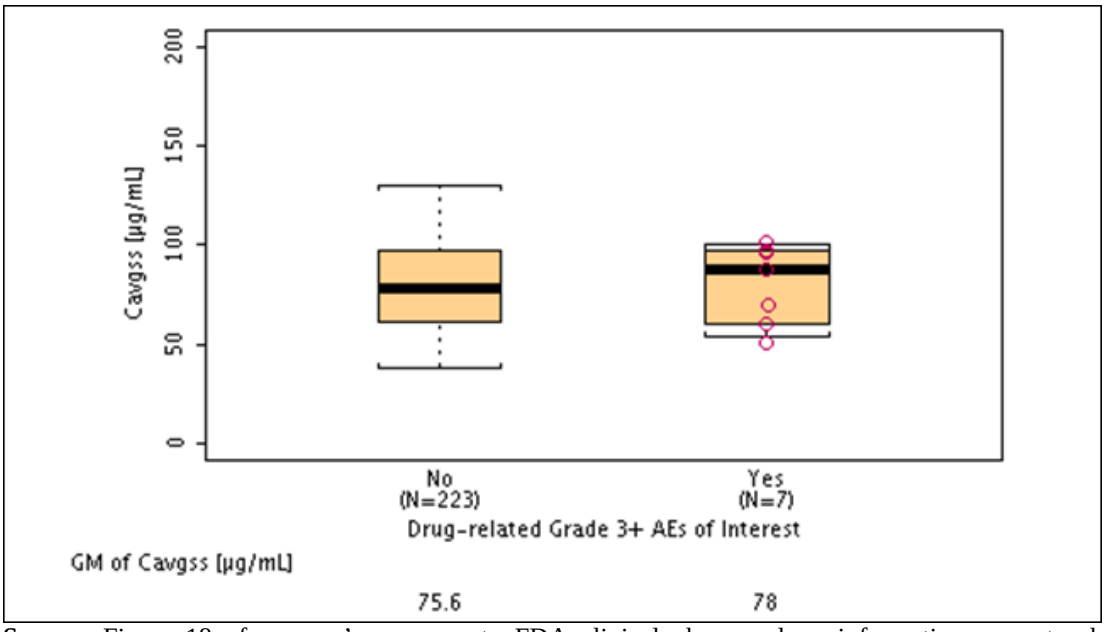
- In Studies **MDX1106-03 and CA209063,** the safety risk did not increase with exposure in the dose range of 0.1-10 mg/kg Q2W for time to the first event of Grade3+ drug-related-AEs (**Table 3**), and for drug AE-related discontinuations (**Table 4**).
- In Study **CA209037,** AE-related discontinuations/deaths appear to increase with exposure following the 3 mg/kg Q2W dosing regimen (**Table 5**). The significance of the trend needs to be further evaluated in future clinical outcome.
- As shown in **Table 2**, high exposure (defined by quartiles of $C_{avg,ss}$ with Q1 to Q4 indicating increasing exposure) was associated with 9 types of drug related Grade 3+ adverse events, including amylase increase, lipase increase, pancreatitis, hyperglycaemia, colitis, pneumonitis, autoimmune neuropathy, rash, and ventricular arrhythmia. These AEs seem to be immune related and did not occur in low exposure groups Q1-2. Refer to **Table 13** and **Table 14** 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 $C_{avg,ss}$ (µg/mL) for 3 mg/kg Q2W in Phase III Study CA209037

	Investigator's Choices (n=98)	Nivolumab $C_{avg,ss}$ Quartile, Patient Number & $C_{avg,ss}$ Range (µg/ml)			
		Q1 (n=66) 22.9-64.4	Q2 (n=65) 64.4-72.3	Q3 (n=65) 72.3-94.9	Q4 (n=66) 94.9-233.0
Amylase Increase					2 (IDs: 17-37259, 43-37239)
Lipase Increase	1(ID: 60-37322)				3 (IDs: 17-37259, 43-37239, 77-37142)
Pancreatitis					1 (ID: 43-37239)
Colitis					2 (IDs: 15-37264,27-37152)
Pneumonitis					1 (ID: 27-37152)
Autoimmune Neuropathy					1 (ID: 10-37276)
Rash					1 (ID: 43-37151)
Hyperglycaemia				1 (ID: 16-37063)	1 (ID: 72-37643)
Ventricular Arrhythmia					1 (ID: 50-37008)

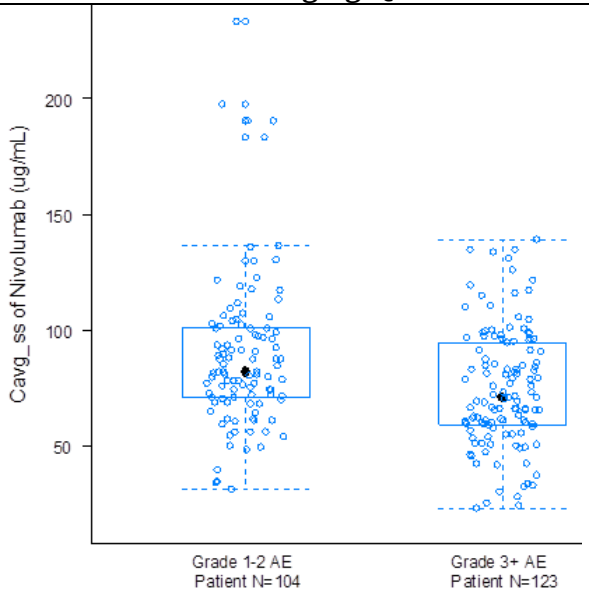
Note: blank cell means there was no drug-related Grade 3+ adverse events found in the quartile.
Source: FDA reviewer's analysis based on data "adae.xpt" and "aedata.xpt" for CA209037.

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



Source: Figure 18 of sponsor's response to FDA clinical pharmacology information request submitted on 21 October 2014.

Figure 3: Summary of Steady-State Average Concentrations ($C_{avg,ss}$) for Patients with and without Any Grade 3+ Adverse Events for 3 mg/kg Q2W in Phase III Study CA209037



Source: FDA reviewer's analysis based on adae.xpt and aedata.xpt for Study CA209037.

Table 3: Model Estimated Hazard Ratio of Grade 3+ Drug Related AEs[1] (Relative to Median $C_{avg,ss}$ at 3 mg/kg) from MDX1106-03 and CA209063		
$C_{avg,ss}$ (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 22 out of 230 patients in Study CA209030 experienced drug-related Grade 3+ AEs. Source: Table 3.2.3.2-1 of the Population Pharmacokinetic and Exposure-Response Report and Table 3.2.1-1 of Summary of Clinical Pharmacology Studies		

Table 4: Model Estimated Hazard Ratio of AEs Leading to Discontinuation (Relative to Median $C_{avg,ss}$ at 3 mg/kg) from MDX1106-03 and CA209063		
$C_{avg,ss}$ (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		

Table 5: Model Estimated Hazard Ratio of AEs Leading to Discontinuation or Death[1] (Relative to Median $C_{avg,ss}$ at 3 mg/kg) from CA209037		
$C_{avg,ss}$ (µg/mL)	**HR**	**95% CI of HR**
5th percentile 3 mg/kg (38.27)	2.19	1.04 - 4.63
95th percentile 3 mg/kg (129.76)	0.37	0.14 - 0.95
[1] 20 out of the 230 patients discontinued or died due to drug-related AEs. Source: Table 3.2.3.2-1 of the Population Pharmacokinetic and Exposure-Response Report and Table 3.2.1-4 of Summary of Clinical Pharmacology Studies		

1.1.4 Was PD-L1 expression status, positive or negative, a covariate of the efficacy?

The effect of PD-L1 status on ORR remains inconclusive. As tabulated in **Table 6**, more ORR responders had a positive PD-L1 status versus negative, and more non-responders had a negative

PD-L1 status. However, since 30% of subjects in the combined dataset did not have PD-L1 status available, this finding may still be subject to bias.

Table 6: Apparent Effect of PD-L1 Status on Objective Response Rate			
	Confirmed Objective Response Number (%)		
	PD-L1 Positive	PD-L1 Negative	PD-L1 Unknown
Non-Responder	41 (56.2)	65 (81.3)	45 (66.2)
Responder	32 (43.8)	15 (18.8)	23 (33.8)
Total	73	80	68
Source: Figure 16 of sponsor's response to FDA clinical pharmacology information request submitted on 21 October 2014.			

1.1.5 Was systemic administration of corticosteroids a covariate of the efficacy?

It remains inconclusive whether systemic administration of corticosteroids affects the efficacy of nivolumab. Apparently, patients with systemic corticosteroid use showed lower ORR rate (**Table 7**). However, only steroid use prior to the achievement of OR was included in this analysis. Therefore, subjects who did not achieve an OR may have a higher percent of steroid use as there was no cut-off date for their steroid use.

Table 7: Apparent Effect of Systemic Steroid Use on Objective Response Rate		
	Confirmed Objective Response Number (%)	
	No Systemic Steroid Use	Systemic Steroid Use
Non-Responder	103 (63.2)	48 (82.8)
Responder	60 (36.8)	10 (17.2)
Total	163	58
Source: Table 1 of sponsor's response, submitted on 21 October 2014, to FDA clinical pharmacology information request.		

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 metastatic melanoma was conducted in conjunction with advice from regulatory agencies in the US and the EU. An administrative split of IND 115,195 from the existing parent IND 100,052 for the indication of melanoma occurred on 13-Jun-2012.

A Chemistry Manufacturing and Controls (CMC) only meeting was held to discuss plans to support studies and licensure on 7-Feb-2012. An End-of Phase I/pre-Phase 3 meeting was held on 17-Jul-2012 to discuss the proposed clinical development plan for second-line

metastatic melanoma (CA209037) and to discuss the potential for accelerated approval. The FDA agreed with the study design change for CA209037, which included the decoupling of ORR from OS, and the evaluation of ORR based on a non-comparative single-arm analysis to seek accelerated approval while maintaining the comparative OS endpoint to convert to regular approval.

Fast Track Designation was granted on 4-Oct-2012 for patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in OS over available therapies. A CMC only meeting was held to obtain feedback on the comparability of (b) (4) to (b) (4) and assignment of the shelf life of a new 40 mg presentation on 12-Dec-2012. Orphan designation has also been granted 23-Jan-2013 for the treatment of Stage IIb to IV melanoma. A Type B pre-BLA CMC meeting was held on 18-Apr-2014 to discuss and obtain FDA concurrence for CMC plans for registrational package to support the potential accelerated approval of nivolumab for the treatment of patients with advanced or metastatic squamous cell NSCLC. A Pre-BLA meeting was held 9-Jul-2014 to gain feedback from the FDA on the submission plan for the planned BLA and the potential for accelerated approval based on ORR in CA209037.

An automated PD-L1 IHC assay for use as an in vitro companion diagnostic is being developed in collaboration with Dako North America Inc (Dako) for the evaluation of a potential predictive biomarker for nivolumab. Following interactions with the Agency, including Center for Devices and Radiological Health (CDRH), a Modular Premarket Approval Application (PMA) has been submitted.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 PIVOTAL TRIAL (STUDY CA209037)

Study (CA209037) was a global, randomized (1:1), open-label Phase 3 trial of nivolumab versus investigator's choice in the treatment of advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 therapy. The primary objective was to evaluate the ORR and the overall survival (OS) of nivolumab versus investigator's choice. The secondary objectives were to evaluate PFS (time to disease progression), HRQoL (Health Related Quality of Life), PD-L1 expression as the covariate of efficacy. And the exploratory objectives were to assess the overall safety, tolerability, PK, exposure-response relationship, and immunogenicity of nivolumab.

The IRRC-assessed confirmed ORR in the treated subjects among the ORR population (primary objective population) for the nivolumab group was 31.7% (38/120) (95% CI: 23.5%, 40.8%). In the reference arm (investigator's choice), the IRRC-assessed confirmed ORR was 10.6% (5/47) (95% CI: 3.5%, 23.1%). Nivolumab treatment led to objective responses independent of age, gender, region, or ECOG performance status, PD-L1 status, BRAF status, prior anti-CTLA-

4 benefit, M stage at study entry, history of brain metastases, smoking status, baseline LDH, or AJCC stage. Numerically higher response rates for nivolumab were observed in the following subgroups: subjects with BRAF wildtype, no prior anti-CTLA-4 benefit, M1B, 65 years old, females, US region, ECOG 0, no history of brain metastases, positive smoking history, LDH ULN, LDH 2*ULN, Stage IV, and PD-L1 positive by IVRS (verified assay). Objective responses with nivolumab were durable.

The descriptive analysis of PFS as assessed by the IRRC demonstrated a median PFS of 4.7 months (95% CI: 2.3, 6.5) and a 6-month PFS rate of 48% (95% CI: 38, 56) in the nivolumab group. In the investigators' choice group, the median PFS was 4.2 months (95% CI: 2.1, 6.3) and the 6-month PFS rate was 34% (95% CI: 18, 51).

No deaths were due to study drug toxicity. Grade 3-4 drug-related AEs were reported in 9.0% and 31.4% of subjects in the nivolumab and investigator's choice groups, respectively. The frequency of subjects with 1 or more drug-related SAEs in the nivolumab vs. investigator's choice group was 6.3% vs. 9.8%, of which 4.5% vs. 8.8% were Grade 3-4, respectively. Drug-related AEs leading to discontinuation of study drug were reported in 2.2% and 7.8% of subjects in the nivolumab and investigator's choice groups, respectively. No drug-related AEs leading to discontinuation of study drug were reported in more than 1 subject in either treatment group.

During treatment, anti-nivolumab ADAs were not detected in 168/180 (93.3%) subjects with evaluable ADA data at baseline and post-baseline, and were detected in 12/180 (6.7%) subjects with evaluable ADA data at baseline and post baseline, of whom 2 (1.1%) subjects were persistent positive. Out of the 12 ADA positive subjects, 2 subjects (1 persistent positive, 1 other positive) each had 1 ADA positive sample with neutralizing antibodies detected. The immunogenicity of nivolumab appeared 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_{min1} 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.

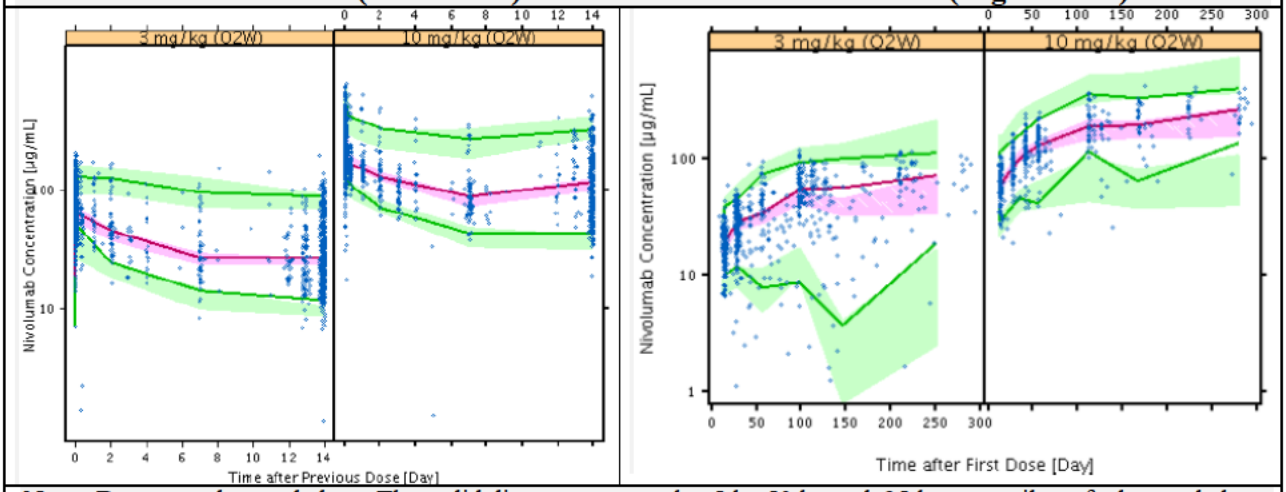
Exposure-Safety Response Analysis: Grade 3+ DR-AEs and AEs leading to DC/D: The E-R of safety analyses (Grade 3+ DR-AEs and AEs leading to DC) was characterized by two separate semi- parametric Cox Proportional-Hazards (CPH) models. The CPH models were developed in 3 stages. First, the relationship between 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_{minss} 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 8**. 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 melanoma (**Table 9**) in study CA209037. The final model was evaluated by visual predictive check with respect C_{min1} and baseline tumor burden (**Figure 5**). The only predictor variable with a significant effect on the odds of OR is baseline tumor burden (95% CI of effect does not include 1). The 95% CI of all the other predictor variables evaluated extended well over the value of 1, indicating a lack of evidence for the effect of these variables on Pr(OR).

Exposure-Safety Response Analysis: Grade 3+ DR-AEs and AEs leading to DC/D: 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 CA209037. The hazard of Grade 3+ DRAEs and AEs leading to DC/D increased by 0.997-fold and 0.979-fold for every 1 µg/mL increase of $C_{avg,ss}$, respectively (**Table 10**, **Table 11**). Baseline LDH was not a significant predictor of the AE risk.

Table 8: Parameter Estimates of PPK Final Model

Parameter[a] [Units]	Estimate[b]	95% Confidence Interval[c]
Structural Model Parameters		
CL_{REF} [L/h]	0.00866	0.00826 - 0.00905
VC_{REF} [L]	3.87	3.75 - 3.99
Q_{REF} [L/h]	0.0296	0.0267 - 0.0329
VP_{REF} [L]	3.80	3.6 - 4.04
CL_{BW} *(REF=80 [kg])*	0.700	0.576 - 0.809
CL_{eGFR}, *(REF=80 mL/min/1.73m^2)*	0.172	0.067 - 0.276
CL_{ECOG} *(REF= 0)*	0.174	0.113 - 0.235
VC_{BW} *(REF=80 [kg])*	0.534	0.463 - 0.607
VC_{sex}, *REF=Female*	0.130	0.0937 - 0.167
Inter-Individual Variability Model Parameters		
ω^2CL	0.188 (0.434)	0.16 - 0.218
ω^2VC	0.0488 (0.221)	0.0403 - 0.0577
ω^2_{VP} [-]	0.294 (0.542)	0.227 - 0.371
ω_{CL}:ω_{VC}	0.0438 (0.457)	0.0335 - 0.0551
Residual Error Model Parameters		
Proportional error [-]	0.207	0.197 - 0.218

[a] Eta shrinkage: ETA_CL: 9.92, ETA_VC: 17.8, ETA_VP: 28.5 and Eps shrinkage (%): 10.9.

[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 (1897 successful out of a total of 2000)

Source: Page 4 of sponsor's population pharmacokinetics and exposure-response report.

Table 9: Parameter Estimates of E-R OR Final Model

Predictor[a]	Estimate	SE[b]	RSE%[c]	Odds Ratio Coefficient (95% CI)
log(BTSIZE)	-0.856	0.305	35.7	0.425 (0.233, 0.773)
log(Cmin1)	-0.494	0.783	158	0.61 (0.132, 2.83)

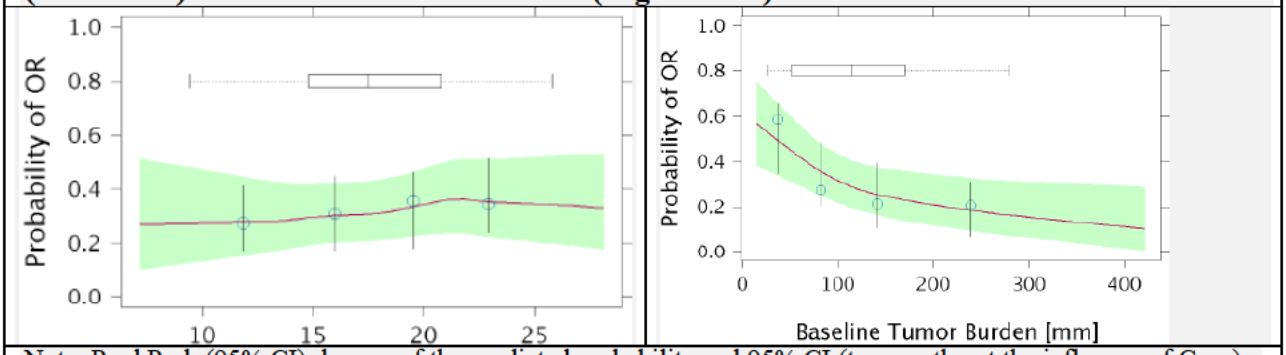
[a] Units of Cmin1 are µg/mL; Baseline Tumor Burden (BTSIZE) are mm

[b] SE: Standard Error

[c] RSE: Relative Standard Error (100* SE/Estimate)

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} (Left Panel) and Baseline Tumor Burden (Right Panel)



Note: Pred Prob (95% CI): lowess of the predicted probability and 95% CI (to smooth out the influence of C_{min1}); Obs: Open symbols representing the observed proportion of OR responders for each quartile of baseline tumor burden, plotted at the median of the quartile; Pred Proportion (90% PI): Vertical bars representing the 90% prediction intervals corresponding to the observed proportion of OR. The horizontal boxplot shows the median, interquartile range, and 5th/95th percentiles of baseline tumor burden.

Source: Pages 110-111 of sponsor's population pharmacokinetics and exposure-response report.

Table 10: Parameter Estimates of E-R (Grade 3+ DR-AEs) Final Model

Predictor	Estimate	SE	RSE%	Hazard Ratio Coefficient[a] (95% CI)
Cavgss [μg/mL]	-0.00345	0.00794	-230	0.997 (0.981, 1.01)

[a] increase in hazard for every unit increase in continuous predictor variables

Source: Page 6 of sponsor's population pharmacokinetics and exposure-response report.

Table 11: Parameter Estimates of E-R (AEs Leading to DC/D) Final Model

Predictor	Estimate	SE	RSE%	Hazard Ratio Coefficient[a] (95% CI)
Cavgss [μg/mL]	-0.0212	0.00942	-44.5	0.979 (0.961, 0.997)

[a] increase in hazard for every unit increase in continuous predictor variables

Source: Page 6 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 exposure is similar between melanoma and NSCLC patients.
- Nivolumab CL and VC increases with increasing BW.
- Body weight normalized (mg/kg) dosing produced approximately uniform exposures ($C_{avg,ss}$ and C_{min1}) over the studied range of body weights.
- Although sex, ECOG status and baseline eGFR were retained in the final model, the effect magnitude were less than 20% and unlikely to be clinically relevant.
- Age, race, baseline LDH, mild hepatic impairment, tumor type, tumor burden, and PD-L1 expression did not have clinically relevant (<20%) effects on nivolumab CL.
- There was a trend of increase in nivolumab clearance in patients with anti-drug antibodies. However, the effect of ADA was unlikely to be clinically relevant as the effect magnitude on CL was < 20%.

Exposure-OR

- C_{min1} produced by 3 mg/kg nivolumab was not a significant predictor of probability of OR in post anti-CTLA4 advanced melanoma patients.
- Higher baseline tumor burden in melanoma was associated with lower probability of OR.

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

- Risk of Grade 3+ DR-AEs and AEs leading to DC/D in post anti-CTLA4 advanced melanoma patients did not increase with $C_{avg,ss}$ produced by dose of 3 mg/kg nivolumab.

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, including uveitis, antoimmune neuropathy, facial paresis, vith nerve paralysis, ALT increased, AST increased, infusion related reaction, blood alkaline phosphatase increased, liver function abnormal, colitis, hyperglycaemia, amylase increase, lipase increase, tubulointerstitial nephritis, hypotension, pneumonitis, hypoxia, diarrhea, fatigue, herpes zoster, post herpetic neuralgia, lymphopenia, rash, arthritis, pancreatitis, ventricular arrhythmia, demyelination, abdominal pain upper, vomiting, and lymphocyte count decreased.

4.2 METHODS

4.2.1 Data Sets

Data sets used are summarized in Table 12.

Table 12: Analysis Datasets for FDA Reviewer's Analysis		
Study Number	Name	Link to EDR
CA209037	aedata.xpt	\\cdsesub1\evsprod\bla125554\0000\m5\datasets\population-pk-melanoma\analysis\datasets\
CA209037	adae.xpt	\\cdsesub1\evsprod\bla125554\0000\m5\datasets\ca209037\analysis\adam\datasets\

4.2.2 Software

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

4.3 RESULTS

The distributions of different grades of all AEs (including drug-related AEs and not-drug-related AEs) of Study CA209037 are presented in **Figure 3**. As shown in the left panel, the distributions were not different between Grade 1-2 AE patients (N=104) and Grade 3+ AE patients (N=123).

High exposure (Quartile 4 of $C_{avg,ss}$) was associated with 9 types of drug related Grade 3+ adverse events, including amylase increase, lipase increase, pancreatitis, colitis, pneumonitis, autoimmune neuropathy, rash, hyperglycaemia, and ventricular arrhythmia. These AEs did not occur with Quartile 1 or 2 although a few occurred in Q3 (**Table 2**). **Table 13** and **Table 14** list drug related Grade 3+ AEs for nivolumab and investigator's choice, respectively.

Overall, efficacy and safety data of Study CA209037 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 high nivolumab exposure groups, potentially indicating signal for safety risk. This observation needs to be supported with more clinical data.

5 APPENDIX

Table 13: Nivolumab Related Grade3+ Adverse Events

USUBJID	Adverse Event	Grade	Cavg,ss (µg/ml)	Quartile	Discontinue Flag
CA209037-101-37645	FACIAL PARESIS	3		NA	
CA209037-101-37645	VITH NERVE PARALYSIS	3		NA	
CA209037-10-37254	UVEITIS	3	59.4	Q1	Y
CA209037-10-37276	AUTOIMMUNE NEUROPATHY	3	105.6	Q4	Y
CA209037-105-37439	ALANINE AMINOTRANSFERASE INCREASED	3	87.4	Q3	
CA209037-105-37439	ASPARTATE AMINOTRANSFERASE INCREASED	3	87.4	Q3	
CA209037-13-37161	INFUSION RELATED REACTION	3	51.1	Q1	
CA209037-13-37161	ALANINE AMINOTRANSFERASE INCREASED	3	51.1	Q1	
CA209037-13-37161	BLOOD ALKALINE PHOSPHATASE INCREASED	3	51.1	Q1	
CA209037-13-37161	LIVER FUNCTION TEST ABNORMAL	3	51.1	Q1	
CA209037-15-37264	COLITIS	3	97.3	Q4	
CA209037-16-37063	HYPERGLYCAEMIA	3	82	Q3	
CA209037-17-37259	AMYLASE INCREASED	3	100.7	Q4	
CA209037-17-37259	LIPASE INCREASED	3	100.7	Q4	
CA209037-17-37259	LIPASE INCREASED	4	100.7	Q4	
CA209037-20-37003	TUBULOINTERSTITIAL NEPHRITIS	3	60.2	Q1	
CA209037-25-37223	HYPOTENSION	3	58.8	Q1	
CA209037-27-37152	COLITIS	3	95.8	Q4	Y
CA209037-27-37152	PNEUMONITIS	3	95.8	Q4	
CA209037-28-37407	HYPOXIA	5		NA	
CA209037-39-37563	DIARRHOEA	3	69.2	Q2	
CA209037-40-37323	FATIGUE	3	90.6	Q3	
CA209037-40-37323	HERPES ZOSTER	3	90.6	Q3	
CA209037-40-37323	POST HERPTIC NEURALGIA	3	90.6	Q3	
CA209037-43-37123	LYMPHOPENIA	3	96	Q3	
CA209037-43-37151	RASH	3	101.4	Q4	
CA209037-43-37159	ANAEMIA	3	49.2	Q1	
CA209037-43-37159	LYMPHOPENIA	3	49.2	Q1	
CA209037-43-37159	ARTHRITIS	3	49.2	Q1	
CA209037-43-37239	PANCREATITIS	3	119.1	Q4	
CA209037-43-37239	AMYLASE INCREASED	3	119.1	Q4	
CA209037-43-37239	LIPASE INCREASED	4	119.1	Q4	
CA209037-43-37239	LIPASE INCREASED	3	119.1	Q4	

CA209037-49-37120	FATIGUE	3		NA	
CA209037-50-37008	VENTRICULAR ARRHYTHMIA	3	109.8	Q4	
CA209037-59-37230	DEMYELINATION	3	59.6	Q1	Y
CA209037-66-37483	ABDOMINAL PAIN UPPER	3	53.1	Q1	
CA209037-66-37483	VOMITING	3	53.1	Q1	
CA209037-67-37526	LYMPHOCYTE COUNT DECREASED	3	41.9	Q1	
CA209037-72-37643	HYPERGLYCAEMIA	3	96	Q4	
CA209037-77-37142	LIPASE INCREASED	3	99.7	Q4	Y
CA209037-77-37142	LIPASE INCREASED	4	99.7	Q4	
CA209037-89-37538	ANAEMIA	3		NA	

Source: FDA reviewer's analysis based on adae.xpt and aedata.xpt for Study CA209037

Table 14: Investigator's Choice Related Grade3+ Adverse Events

USUBJID	Adverse Event	Grade	Discontinuation
CA209037-10-37192	NEUTROPENIA	3	
CA209037-10-37192	INFECTION	3	
CA209037-10-37192	NEUTROPENIC SEPSIS	3	
CA209037-13-37289	NAUSEA	3	
CA209037-13-37289	VOMITING	3	
CA209037-13-37289	FATIGUE	3	
CA209037-15-37205	ANAEMIA	3	
CA209037-16-37305	PLATELET COUNT DECREASED	3	
CA209037-28-37030	THROMBOCYTOPENIA	3	
CA209037-30-37477	NEUTROPENIA	3	
CA209037-36-37349	THROMBOCYTOPENIA	3	Y
CA209037-36-37609	NEUTROPENIA	4	
CA209037-40-37344	NEUTROPENIA	4	
CA209037-43-37263	NEUTROPHIL COUNT DECREASED	3	
CA209037-47-37175	NEUTROPENIA	3	
CA209037-47-37454	NEUTROPHIL COUNT DECREASED	3	
CA209037-48-37359	ANAEMIA	3	
CA209037-48-37359	NAUSEA	3	
CA209037-48-37359	VOMITING	3	
CA209037-49-37326	ANAEMIA	3	
CA209037-49-37326	LYMPHOCYTE COUNT DECREASED	3	
CA209037-49-37326	NEUTROPHIL COUNT DECREASED	4	
CA209037-49-37326	PLATELET COUNT DECREASED	3	
CA209037-49-37326	WHITE BLOOD CELL COUNT DECREASED	3	

CA209037-50-37143	NEUTROPENIA	4	
CA209037-50-37143	FATIGUE	3	
CA209037-50-37143	ARTHRALGIA	3	Y
CA209037-50-37143	NEUROPATHY PERIPHERAL	3	
CA209037-50-37150	ANAEMIA	3	
CA209037-51-37035	NEUTROPENIA	3	
CA209037-57-37445	LEUKOPENIA	3	Y
CA209037-57-37445	NEUTROPENIA	3	
CA209037-57-37445	NEUTROPENIA	4	Y
CA209037-57-37445	ALANINE AMINOTRANSFERASE INCREASED	4	
CA209037-57-37445	ASPARTATE AMINOTRANSFERASE INCREASED	4	
CA209037-60-37322	LIPASE INCREASED	3	
CA209037-60-37396	NEUTROPENIA	3	
CA209037-61-37210	THROMBOCYTOPENIA	3	
CA209037-62-37167	NEUTROPENIA	3	
CA209037-62-37224	NEUTROPENIA	4	
CA209037-63-37650	INFLUENZA LIKE ILLNESS	3	
CA209037-63-37650	PYREXIA	3	
CA209037-76-37511	FATIGUE	3	
CA209037-76-37511	PERIPHERAL SENSORY NEUROPATHY	3	
CA209037-77-37132	THROMBOCYTOPENIA	3	
CA209037-77-37132	HYPERTENSION	3	
CA209037-77-37148	LEUKOPENIA	3	
CA209037-77-37148	LYMPHOPENIA	3	
CA209037-77-37148	NEUTROPENIA	3	
CA209037-77-37148	NEUTROPENIA	4	
CA209037-77-37148	CONSTIPATION	3	
CA209037-77-37201	FATIGUE	3	
CA209037-77-37542	LEUKOPENIA	3	
CA209037-77-37542	NEUTROPENIA	3	
CA209037-8-37075	DIARRHOEA	3	
CA209037-8-37075	GASTROINTESTINAL DISORDER	3	
CA209037-86-37198	HYPOGLYCAEMIA	3	
CA209037-86-37198	HYPOTENSION	3	Y
CA209037-90-37565	NEUTROPENIA	3	
CA209037-90-37565	THROMBOCYTOPENIA	3	
CA209037-90-37625	ANAEMIA	3	
CA209037-90-37625	FEBRILE NEUTROPENIA	3	
CA209037-90-37625	NEUTROPENIA	4	
CA209037-90-37625	NEUTROPENIA	3	

CA209037-90-37625	THROMBOCYTOPENIA	3
CA209037-90-37625	THROMBOCYTOPENIA	4
CA209037-90-37625	DIARRHOEA	3
CA209037-90-37625	ASPARTATE AMINOTRANSFERASE INCREASED	3

Source: FDA reviewer's analysis based on adae.xpt for Study CA209037

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
12/05/2014

LIANG ZHAO
12/05/2014

HONG ZHAO
12/05/2014
I concur.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR BLA 125554

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125554/0	**Brand Name**	OPDIVO
OCP Division (I, II, III, IV, V)	OCP Division V	**Generic Name**	Nivolumab, BMS-936558
Medical Division	DOP2	**Drug Class**	Fully human IgG_4 monoclonal antibody
OCP Reviewer	Xianhua(Walt) Cao, Ph D.	**Indication(s)**	Advanced melanoma
OCP Team Leader	Ruby Leong, Pharm.D. (CP, Acting); 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	7/30/14	**Route of Administration**	Intravenous (IV) over one hour
Estimated Due Date of OCP Review	12/5/14	**Sponsor**	Bristol-Myers Squibb
Medical Division Due Date	12/12/14	**Priority Classification**	Priority, Expedited
PDUFA Due Date	3/30/14		

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)
multiple dose:	**x**	**1**		Study MDX1106-03 (CA209003)
Dose proportionality -				
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:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR BLA 125554

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
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**x**	**3**		MDX1106-01 MDX1106-03 Ono-4538-01 (CA209005)
Data sparse:	**x**	**4**		CA209010 CA209037 CA209063 Ono-4538-02 (CA209051)
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
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**8**		

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

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 [redacted] (b) (4) to-be-marketed) and [redacted] (b) (4) (used in clinical trials).

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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
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, 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?	x			

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	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: CA209037 E-R for safety: MDX1106-03 and CA209037
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	Granted orphan drug designation
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Granted orphan drug designation
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	

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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

x

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	September 15, 2014
Reviewing Clinical Pharmacologist	Date
Ruby Leong	September 15, 2014
Acting 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
09/19/2014

HONGSHAN LI
09/19/2014

LIANG ZHAO
09/19/2014

RUBY LEONG
09/19/2014