CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125377Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA	125377-0
Submission Date	June 25, 2010
PDUFA Date	March 26, 2011 (3 months extension due to a major amendment)
Brand Name	Yervoy™
Product Name	Ipilimumab
Submission Type; Code	Original BLA; NME, Priority Review
Formulation/Strength	50 mg/10 mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL) single-use vials
Dosing regimen	3 mg/kg Q3W for 4 doses as a 90-min IV infusion (b) (4)
Indication	Advanced melanoma in previously treated patients
Sponsor	Bristol Myers Squibb
OND Division	Division of Biologic Oncology Products
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1. EXECUTIVE SUMMARY

Ipilimumab, submitted under BLA 125377, is a new molecular entity developed by Bristol Myers Squibb for the treatment of patients with advanced melanoma. One phase III registration trial and several phase II trials were conducted to support the approval of the proposed indication with (b) (4) dose of 3 mg/kg as a 90-min IV infusion once every three weeks for 4 doses.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed BLA 125377 and has found that the submitted clinical pharmacology data support the proposed dose regimen and indication.

1.2 Phase IV Requirements and Commitments

The Office of Clinical Pharmacology in conjunction with the Office of Biotechnology Products recommends three post-marketing requirements. In addition there are two post-marketing commitments for the sponsor along with several additional comments from the Office of Clinical Pharmacology.

1.2.1 Post-marketing Requirements (PMRs)

1. To develop a validated, sensitive, and accurate assay for the detection of an immune response (binding antibodies) to ipilimumab, including procedures for accurate detection of antibodies to ipilimumab in the presence of ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

2. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ipilimumab, including procedures for accurate detection of neutralizing antibodies to ipilimumab in the presence of ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling. In the event such an assay can not be developed, evidence of due diligence in attempting to develop the assay will be provided.

3. To conduct an assessment of anti-drug antibody (ADA) response to ipilimumab with a validated assay (required in PMR 1) capable of sensitively detecting ADA responses in the presence of ipilimumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 ipilimumab-treated patients enrolled in the required post-marketing study comparing 3 mg/kg versus 10 mg/kg of ipilimumab monotherapy. The final report will include information on the level of ipilimumab in each patient's test sample at each sampling time point.

1.2.2 Post-marketing Commitments (PMC)

1. To identify genetic determinants of immune related adverse reactions caused by ipilimumab, you will obtain $\geq$ 95% complete DNA sample acquisition from the required post-marketing study comparing 3 mg/kg vs 10 mg/kg ipilimumab monotherapy and then conduct genome-wide association analyses and specific

candidate gene (CD86, HLA family) analyses on these samples. You will provide a Final Report specific for this PMC including electronic data sets that address the identification and association of genetic determinants with adjudicated cases of immune related adverse reactions.

2. To perform pharmacogenomic reanalysis of your dataset from Study MDX010-20 using the adjudicated cases based on the FDA agreed upon case definitions of immune-related adverse reactions.

1.2.3 Additional Comments

1. Given the serious nature of ipilimumab irAEs, the genetic determinants of irAEs should be elucidated. Given the uncertain mechanism of these irAEs, a hypothesis-free approach (e.g. genome wide association analyses of phase 2 samples) is recommended.
2. To increase the power and provide replication cohorts, all subsequent ipilimumab studies should include a high DNA sample acquisition rate and objectively-defined and adjudicated irAE cases.
3. Conduct pharmacogenetic analyses across different ipilimumab doses in subsequent studies.
4. For future development programs, collect sparse pharmacokinetic data from all patients to explore exposure-response relationships for efficacy and safety endpoints to support dosing recommendations and dose adjustments.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Efficacy: Ipilimumab is a monoclonal antibody which targets CTLA-4. The proposed indication is for the treatment of advanced melanoma in patients who have received prior therapy. A single registration trial (MDX010-20) was submitted to support the proposed indication. This randomized trial included three treatment arms: 3 mg/kg of ipilimumab, 3 mg/kg of ipilimumab + gp100 (vaccine), and gp100 alone. Ipilimumab demonstrated a statistically significant improvement in overall survival (OS) compared to the gp100 arm (median: 10.1 months vs. 6.4 months). Top-line results from an on-going phase III trial (CA184024) show that ipilimumab at 10 mg/kg in combination with dacarbazine also demonstrates a survival benefit compared to the active control, dacarbazine.

Proposed Dose Regimen: The proposed dose regimen for (b) (4) is 3 mg/kg ipilimumab administered intravenously over a 90-minute infusion every 3 weeks for a total of 4 doses. (b) (4)

Pharmacokinetics: Rich pharmacokinetic (PK) data is available from 84 patients enrolled into 3 clinical trials and sparse PK data is available from 499 patients across 4 clinical trials. Ipilimumab exhibited linear PK over a dose range of 0.3 to 10 mg/kg with a mean elimination half-life of 15 days. The inter-individual variability for clearance was approximately 35%.

Exposure-Response: The exploratory exposure-response (E-R) analyses revealed an increase in OS with increasing drug exposures at 0.3, 3, and 10 mg/kg doses in Phase II trials. Steady state trough concentration of ipilimumab was found to be an independent predictor of OS using a stepwise Cox proportional hazard model after correcting for confounding risk factors including ECOG performance status and baseline lactate dehydrogenase. This positive E-R relationship provides supportive evidence of the effectiveness of ipilimumab and suggests that there might be an increased survival benefit at the higher dose of 10 mg/kg.

Immunogenicity: Approximately 1.1% of the patients treated with ipilimumab were positive for binding anti-ipilimumab antibodies, none had neutralizing activity. However, the presence of ipilimumab in patient samples interfered with the detection of anti-ipilimumab antibodies. Thus, a more sensitive assay for anti-ipilimumab antibody detection and evaluation of response is requested to accurately assess the incidence of immunogenicity.

QTc Evaluation: Ipilimumab did not prolong the QT interval at doses of 3 or 10 mg/kg and an exposure-response analysis did not show any concentration-dependent QT prolongation.

Pediatric Studies: Since the proposed indication for ipilimumab has been granted orphan indication status, no pediatric studies are required under the Pediatric Research Equity Act (PREA).

Safety: Ipilimumab treatment was associated with immune-related adverse events (irAEs) including skin and subcutaneous tissue, gastrointestinal, endocrine, and hepatobiliary disorders. An increase in irAEs was seen with increasing exposure. Pharmacogenomic analyses showed that a missense mutation in CD86 (rs2681417) was associated with increased risk of immune-related gastrointestinal adverse events in the Phase II trials. Other associations between immune-related gene variants and skin, hepatobiliary, and gastrointestinal events were also seen. However, methodological limitations precluded definitive conclusions regarding the strength of the associations.

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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?

Ipilimumab is a fully human monoclonal immunoglobulin (IgG1κ) antibody produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. Ipilimumab is a soluble protein that consists of (b) (4) Ipilimumab has an approximate molecular weight of 148 kilodaltons based on its amino acid sequence derived from the complimentary deoxyribonucleic acid (cDNA) sequence and confirmed by liquid chromatography-mass spectrometry (LC-MS/MS).

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

Ipilimumab acts as a T-cell potentiator. The proposed mechanism of action for ipilimumab is interference with the interaction of CTLA-4 (cytotoxic T lymphocyte antigenγ4; CD152) with the B7 molecules (CD80/CD86) on antigen-presenting cells (APCs). This interference results in subsequent blockade of the inhibitory modulation of T cell activation and potentiation of the immune system.

As shown in Figure 1, tumor antigen released by cancer cells is taken up by dendritic cells (DC) and APCs, and is presented to naive T cells to activate them specifically against the antigen-bearing cancer cells. Within a complex cascade of events, 2 of the key signals between DCs and T cells that are required for activation are: 1) The tumor-specific antigen is presented (as a peptide on major histocompatibility complex [MHC] molecules) to the T cell-receptor, and 2) a B7-costimulatory signal to the CD28 receptor. This leads to proliferation of activated T cells with the capacity to attack and disrupt antigen-bearing tumor cells. Subsequently, as part of a negative feedback loop, CTLA-4, a high-affinity inhibitory receptor, is expressed on activated T cells and blocks the B7-costimulatory signal, which disrupts the integrity of the immunological synapse, reduces cytokine production, and slows T-cell proliferation.

With CTLA-4 blockade by ipilimumab, the negative feedback loop is interrupted and tumor-specific T-cell activation and proliferation is potentiated.

Figure 1. T-cell potentiation via CTLA-4 blockade (Egen JG, et. al. 2002)

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

The proposed (b) (4) regimen is 3 mg/kg ipilimumab administered intravenously (IV) over a 90-minute period every 3 weeks for a total of 4 doses. (b) (4)

Ipilimumab injection is prepared as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow, preservative free, isotonic aqueous solution at pH 7.0 for IV administration. Ipilimumab injection is available as 50 mg/10 mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL) single-use vials.

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?

A summary of completed clinical trials with ipilimumab to support the BLA application is shown in Table 1.

Table 1. Summary of Completed Clinical Studies with Ipilimumab to Support the BLA Application

Study Number	Primary Study Objective	Study Type	No. of Treated Subjects	Treatment Regimen
Phase II				
MDX101-08	Determine the safety and activity profile of multiple doses and determine whether the addition of cyotoxic chemotherapy would augment the effects of ipilimumab	Efficacy/Safety/PK (randomized, open-label, multicenter)	74	Ipi 3 mg/kg Q4Wx4 doses with or without dacarbazine
MDX010-15	Assess the safety and PK of single and multiple doses of ipilimumab derived from a transfectoma or a hybridoma cell line	Safety/PK (open-label, multicenter)	88	Ipi 2.8, 3.0, or 5.0 mg/kg Q8Wx3 Ipi 7.5, 10.0, 15.0, or 10.0 mg/kg single dose Ipi 10.0 mg/kg Q3Wx4
MDX010-28	Collect disease status and OS information for subjects who were alive at the time they completed participation in study MDX010-02, MDX010-08, or MDX010-15	Outcome (multicenter, follow-up)	181	No investigational treatments were administered in this study
CA184004	Correlate pretreatment characteristics of patient and/or tumor w/ clinical tumor response to identify candidate markers predictive of response and/or serious toxicity	Efficacy/Safety/PK (exploratory, randomized, double-blind)	82	Induct: Ipi 3 or 10mg/kg IV Q3Wx4 doses *Main: Ipi 3 or 10mg/kg IV Q12W
CA184007	Estimate rate of Grade ≥ 2 diarrhea when given with either prophylactic oral budesonide or placebo	Efficacy/Safety/PK (randomized, double-blind, placebo-controlled, multicenter)	115	Induct: Ipi 10mg/kg IV Q3Wx4 doses; budesonide 9 mg QD until Wk12; 6 mg QD until Wk14; 3 mg QD until WK 16 *Main: ipi 10mg/kg IV Q12W
CA184008	Evaluate the best overall response rate ad defined by the modified WHO criteria	Efficacy/Safety/PK (open-label, single arm, multicenter)	155	Induct: Ipi 10mg/kg IV Q3Wx4 doses *Main: Ipi 10mg/kg IV Q12W
CA184022	Estimate the best overall response rate ad defined by the modified WHO criteria	Efficacy/Safety/PK (randomized, double-blind, multicenter)	214	Induct: Ipi 0.3, 3, or 10 mg/kg IV Q3Wx4doses *Main: Ipi 0.3, 3, or 10 mg/kg IV Q12W
Phase III				
MDX010-20	Determine the efficacy as measured by OS and BORR and safety	Efficacy/Safety/Quality of Life (randomized, double-blind, multicenter)	643	Randomization 1:3:1 Arm A: Placebo + GP100 (Q3Wx4) Arm B: Ipi (3mg/kg Q3Wx4 doses) + GP100 (Q3Wx4) Arm C: Ipi (3mg/kg Q3Wx4) + placebo

*Maintenance dosing: administration of ipilimumab Q12W until disease progression, toxicity requiring study drug discontinuation, withdrawal of consent or study closure

2.2.1.1 Registration Clinical Trial(s)

The efficacy and safety of ipilimumab for metastatic melanoma are based on results from a single registration trial, MDX010-20, entitled, "*A Randomized, Double-blind, Multicenter Study Comparing MDX-010 Monotherapy, MDX-010 in Combination with a Melanoma Peptide Vaccine, and Melanoma Vaccine Monotherapy in HLA-A*0201-Positive Patients with Previously Treated Unresectable Stage III or IV Melanoma.*"

MDX010-20 was a randomized, double-blind, multi-center trial where HLA-A2*0201 patients with pre-treated metastatic melanoma were randomized 3:1:1 to the following treatment arms:

- Ipilimumab (3 mg/kg) + gp100 (1 mg Peptide A, 1 mg Peptide B)
- Ipilimumab (3 mg/kg) + placebo
- gp100 (1 mg Peptide A, 1 mg Peptide B) + placebo

Patients were stratified for M-stage and prior aldesleukin (IL-2) treatment and received treatment once every three weeks for four doses (Q3Wx4). Patients with stable disease or a better response at week 12 were re-staged at week 16 and again at week 24, if response was maintained. Patients who experience disease progression after initial objective response to the first cycle of therapy and patients who progressed following stable disease lasting more than three months after the first evaluation at week12 were eligible for blinded re-treatment.

Trial MDX010-20 (b) (4) . Gp100 is an investigational synthetic peptide cancer vaccine containing several amino acids of the glycoprotein 100 (gp100) melanoma antigen. There is a methionine substitution at position 210 designed to improve immunogenicity. (b) (4) Ipilimumab also potentiates T-cells. Theoretically, ipilimumab and gp100 would work together in a synergistic manner. Only HLA-A2*0201 patients were enrolled in trial MDX010-20 since use of gp100 is only relevant in this patient population.

As mentioned above, gp100 consists of 2 separate peptide components: Peptide A, a peptide with sequence YLEPGPVTV (gp100: (b) (4)) and Peptide B, a peptide with the sequence IMDQVPFSV (gp100: (b) (4)). One dose of gp100 consists of Peptide A, (b) (4) and Peptide B, (b) (4). The vaccine placebo consists of sterile 0.9% sodium chloride.

Overall survival (OS) was the primary efficacy endpoint of trial MDX010-20. The ipilimumab + placebo arm demonstrated a median survival benefit of 3.7 months over the gp100 + placebo arm (Figure 2 and Table 2).

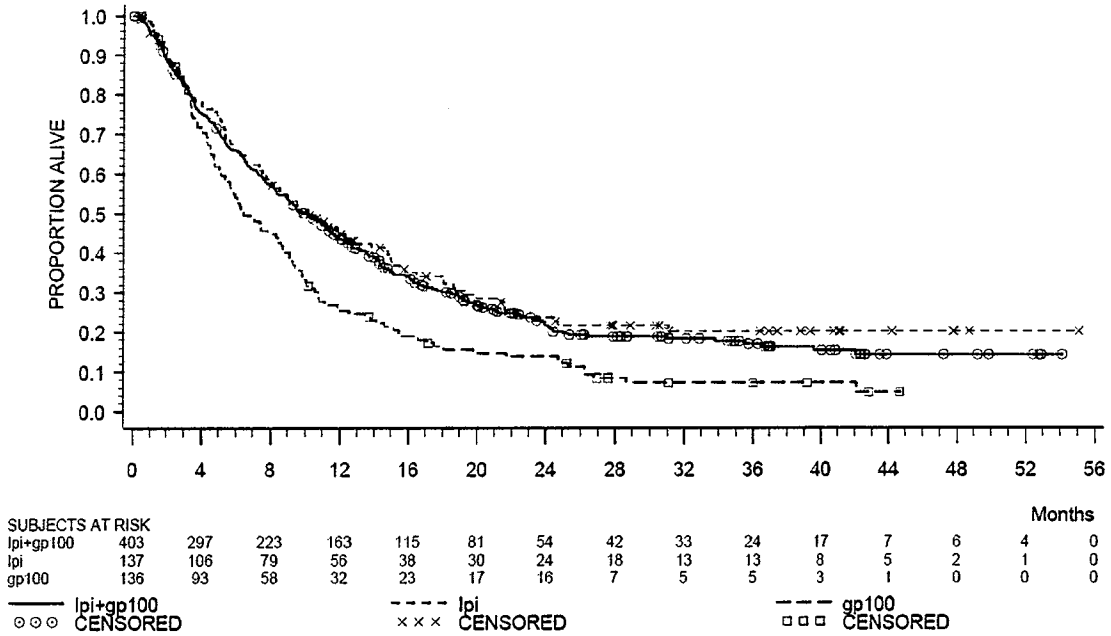

Figure 2. Overall survival by treatment (intention-to-treat population) in Trial MDX010-20

Table 2. Overall Survival Analysis in Trial MDX010-20

	Primary Comparison	**Ipilimumab + gp100**	**gp100**
Overall Survival	N	403	136
p-value = 0.0004	Number of deaths	306	119
	Number censored	97	17
	Hazard ratio (95% CI)	0.68 (0.55, 0.85)	
	Median OS, months (95% CI)	9.95 (8.48, 11.50)	6.44 (5.49, 8.71)
	Secondary Comparisons	**Ipilimumab**	**gp100**
Overall Survival	N	137	136
p-value = 0.0026	Number of deaths	100	119
	Number censored	37	17
	Hazard ratio (95% CI)	0.66 (0.51, 0.87)	
	Median OS, months (95% CI)	10.12 (8.02, 13.80)	6.44 (5.49, 8.71)
		Ipilimumab + gp100	**Ipilimumab**
Overall Survival	N	403	137
p-value = 0.7575	Number of deaths	306	100
	Number censored	97	37
	Hazard ratio (95% CI)	1.04 (0.83, 1.30)	
	Median OS, months (95% CI)	9.95 (8.48, 11.50)	10.12 (8.02, 13.80)

(Source: Sponsor's Table 4.1.1A in the Clinical Overview Report)

2.2.1.2 Clinical Pharmacology Study

Data on the pharmacokinetics (PK) of ipilimumab is available from phase I and II clinical trials (Table 1). No PK data was collected in the registration trial (MDX010-20). Using non-compartmental analysis (NCA), PK parameters were derived from intensive PK sample collection in patients with advanced melanoma treated with 2.8, 3 or 10 mg/kg ipilimumab during the induction period. Population PK analyses were performed for the sparse PK data from 499 patients in trials CA184004, CA184007, CA184008, and CA184022. No studies were performed in healthy volunteers.

Ipilimumab plasma concentrations from Medarex studies (MDX010-08 and MDX010-28) were measured by a separate bioanalytical method which was different from the method used for the BMS sponsored studies. In the two Medarex studies, PK parameters were derived using NCA from intensive PK sampling data following 2.8 to 20 mg/kg single and multiple doses of ipilimumab.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints and how are they measured in clinical pharmacology and clinical studies?

The original primary endpoint of trial MDX010-20 was BORR (best overall response rate). This endpoint was agreed upon through an SPA (special protocol agreement) in 2005 but was later changed by the sponsor to OS.

The original primary efficacy parameter of BORR up to week 24 relied on the primary comparison between combination therapy to vaccine alone and then between combination therapy to ipilimumab alone. The later revised protocol with an endpoint of OS included a primary comparison between combination therapy and vaccine alone and the secondary comparisons were between combination therapy and ipilimumab and between ipilimumab and vaccine alone in a closed testing procedure.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Two different bioanalytical methods were used to determine the concentrations of ipilimumab, one measuring ipilimumab in plasma and the other in serum. In the phase II trials sponsored by BMS (CA184004, CA184007, CA184008, and CA184022), ipilimumab concentrations were measured using a serum ELISA method. An earlier ELISA method, STM1693, was used in the Medarex sponsored trials, MDX010-08 and MDX010-15.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicated the time to

the onset and offset of the desirable pharmacological response or clinical endpoint.

An exploratory exposure-response (E-R) relationship for OS in patients with unresectable stage III or IV melanoma based on the results from phase II studies has been performed. PK data was not collected in the registration trial (MDX010-20). Exposure-efficacy analyses were conducted using pooled data from 498 patients from studies CA184004, -007, -008 and -022 in which sparse PK samples were collected. These studies utilized doses of 0.3, 3 and 10 mg/kg. Predicted steady-state trough concentrations (C_{min}) of ipilimumab from the sponsor's final population pharmacokinetic (PopPK) model were used for the analysis. Steady state C_{min} is an appropriate measure of exposure because upon multiple dose administration, steady state concentrations of ipilimumab were reached by the third dose in 9 weeks. Details of the PopPK and E-R analyses can be found in Appendix 4.2

A time-to-event analysis for OS was performed with patients stratified into four groups according to their C_{min} (0.61–19.4, 19.5–43.7, 44–65.3, >65.3–155.3 **μg/ml) and the** results are shown in Figure 3. A clear separation between the survival curves of patients in different C_{min}-quartile groups is observed, indicating an E-R relationship. An increase in survival is observed with increasing exposures.

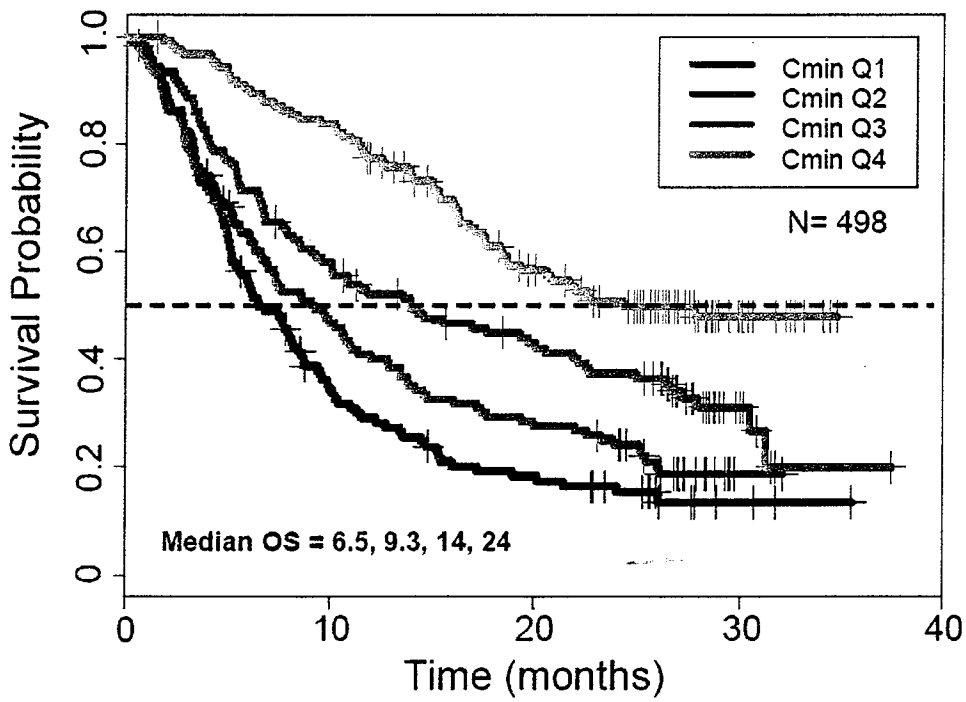

Figure 3. The exposure-response relationship for ipilimumab in pooled phase II studies. Overall survival by steady state trough concentrations (C_{min}) of ipilimumab. Data were pooled from studies CA184004, -007, -008 and -022.

Table 3 shows the median survival in different C_{min}-quartile groups. The difference in median survival between the quartiles is not only due to low drug concentrations, but also due to confounding risk factors in these groups (described below).

Table 3. Median Survival for Patients in Different C_{min} Groups in Phase II and III Trials

Group	Median Survival (months)	95% CI
Cmin Q1 (N=125)	6.51	5.19 – 8.67
Cmin Q2(N=124)	9.26	6.87 – 12.0
Cmin Q3 (N=124)	14.0	9.56 – 22.1
Cmin Q4 (N=125)	24.3	18.7 – NA
gp100 (N=136) *	6.44	5.49 – 8.71
Ipilimumab (3 mg/kg) (N=137) *	10.1	8.02 –13.8

Source: Table 4.4.1A in sponsor's clinical overview

A stepwise Cox proportional hazard model identified C_{min} as a significant independent predictor of OS. In addition, baseline level of lactate dehydrogenase (LDH) and ECOG status (0 vs. 1) were identified as risk factors for OS. Increasing levels of baseline LDH increased the hazard ratio; the hazard ratio was lower in patients with ECOG status of 0 compared to patients with an ECOG status of 1. This analysis excluded two patients who had an ECOG status of 2. Table 4 shows the distribution of risk factors (LDH, ECOG status) in the C_{min}-quartile groups. The highest quartile had patients with lower levels of baseline LDH compared to the lower quartiles. The proportion of patients with ECOG status of 1 was lower in the highest quartile compared to the lower quartiles. These factors along with higher C_{min} in the highest quartile account for an increased median survival.

Table 4. Distribution of Risk Factors (LDH, ECOG status) in Different C_{min} Groups

Group	Median C_{min} (μg/ml)	Median LDH (IU/L)	Number of patients with ECOG status = 0 (%)	Number of patients with ECOG status = 1 (%)
C_{min} Q1* (N=125)	8.52	219	65 (52 %)	59 (47.2 %)
C_{min} Q2 (N=124)	31.6	241	79 (63.7 %)	45 (36.3 %)
C_{min} Q3* (N=124)	54.5	219	83 (66.9 %)	40 (32.3 %)
C_{min} Q4 (N=125)	82.1	180	95 (76 %)	30 (24 %)

* C_{min} Q1 and C_{min} Q3 each had 1 patient with an ECOG status of 2

A Cox proportional hazard model was used for the E-R analysis because it accounted for imbalances of such risk factors. The model predicted that, for a 10 μg/ml increase in exposure, the hazard would decrease by 10%. The p-value was less than 0.0001 and the confidence interval of the hazard ratio excluded 1. This is likely to improve survival significantly because the median C_{min} ranged from 8.5 μg/ml to 82 μg/ml from the lowest to the highest quartile. Similar results were obtained using observed C_{min} after the second dose instead of model predicted C_{min}.

A sub-group analysis was performed by excluding study CA184007 and patients who were administered 0.3 mg/kg of ipilimumab. Study CA184007 was removed because at the studied dose of 10 mg/kg of ipilimumab, the median survival was 19.3 months which was higher than the median survival observed for ipilimumab in other phase II studies. Thus, any potential bias due to study CA184007 was removed. The 0.3 mg/kg dose group was removed for confirming that the E-R relationship is not biased by the low dose group

with very low exposures. Similar to the results obtained using all subjects, C_{min} was found to be a significant predictor of OS and the point estimate (CI) for the hazard ratio was 0.9 (0.86–0.95).

Study CA184022: An E-R analysis was conducted using data from 160 patients from study CA184022 alone because this phase II study included all three dose levels of 0.3, 3 and 10 mg/kg. Consistent with other results, separation between the survival curves of patients in the lower and highest C_{min}-quartile groups was observed. C_{min} was found to be a significant predictor of OS and the point estimate with CI for the hazard ratio was 0.91 (0.85–0.98). The Cox proportional hazard model suggests that the E-R relationship is non-linear and there is likely to be a saturation phase where increasing exposures might not significantly increase survival. At the proposed dose of 3 mg/kg, the E-R relationship is significant which suggests that increasing exposures would result in increased survival.

2.2.4.2 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.

There is an increased incidence of Grade 2/3/4 and Grade 3/4 immune-related adverse events (irAEs) with increasing exposures in patients with unresectable stage III or IV melanoma in phase II studies (Figure 4). Data were pooled from studies CA184004, -007, -008 and -022. The irAEs involved the gastro-intestinal tract (e.g., diarrhea and colitis), skin (e.g., pruritus and rash), endocrine glands (e.g., hypothyroidism), liver (e.g., transaminase elevations) and nervous system (e.g., motor neuropathy). Logistic regression models were used by the sponsor to explore the relationship between steady state C_{min} predicted by the PopPK model and observed irAEs. Data from 498 patients were used in the analysis. The model predicts that at median C_{min} of 3 and 10 mg/kg doses, Grade 2/3/4 irAEs were approximately 33% and 51%, and Grade 3/4 irAEs were 13% and 24%, respectively. The model predictions are consistent with observed data where an increase in irAEs was observed with increasing doses (Table 5).

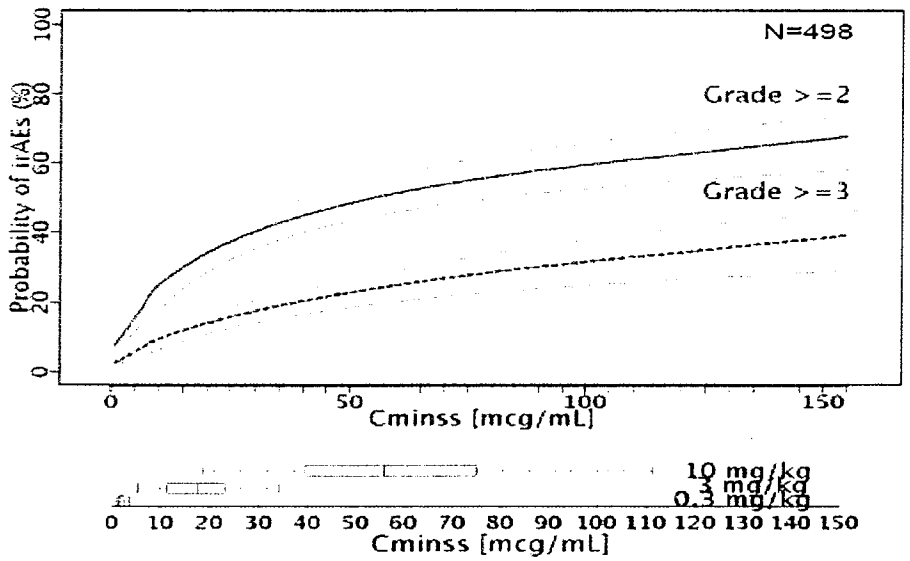

Figure 4: The probability of patients with irAEs in Phase II studies

The solid blue and dashed red lines represent the mean logistic regression prediction for Grade 2/3/4 and Grade 3/4 adverse events, respectively. The shaded area represents the 95% confidence interval of the prediction. The horizontal box plots represent the distributions of steady-state C_{min} at each dose group. Data were pooled from studies CA184004, -007, -008 and -022. Source: Sponsor's Figure 5.5.1.3 Population PK Report.

Table 5. Immune Related AEs (irAE) during the Induction Phase

	% of Subjects				
	Phase 3 Study (MDX010-20)			Phase 2 Studies	
	3 mg/kg Ipi (N = 131)	3 mg/kg Ipi + gp100 (N = 380)	gp100 (N = 132)	Pooled 3 mg/kg (N = 111)	Pooled 10 mg/kg (N = 325)
Any irAE	59.5	56.8	31.8	61.3	72.0
Grade 3-4	13.0	10.0	3.0	6.3	24.3
Grade 5	0.8	1.1[a]	0	0.9	0.9[b]

(Source: Sponsor's Table 5.3.1.1 in the Clinical Overview Report)

2.2.4.3 Does this drug prolong the QT/QTc interval?

The FDA QT Interdisciplinary Review Team (QT-IRT) concluded that no large QT prolongation effects of ipilimumab (3 mg/kg and 10 mg/kg) were detected in patients with advanced melanoma. Additionally, an exposure-response analysis did not show any concentration-dependent prolongation in QT.

ECGs in the melanoma patients population treated with ipilimumab were collected in study CA184004 (n=82). Triplicate, serial ECGs were collected at screening, baseline, Day 1 and Day 64 (prior to ipilimumab infusion, 90 minutes and 150 minutes after

starting infusion); a limited number of patients had ECGs collected at Week 24. The point estimates and the 90% confidence intervals corresponding to the largest upper bounds for ipilimumab (3 mg/kg and 10 mg/kg) for Day 1 and Day 64 were determined (Table 6). The ΔQTcF exceeded the regulatory threshold on Day 64 with the 3 mg/kg dose; however this was attributed to the variability in the patient population and was not considered to be suggestive of a positive signal for a QT prolongation.

Table 6: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Ipilimumab (3 mg/kg and 10 mg/kg) for Day 1 and Day 64 (FDA Analysis)

Treatment	Day	Time (hour)	ΔQTcF (ms)	90% CI (ms)
Ipilimumab 3 mg/kg	1	2.5	0.4	(-3.4, 4.2)
Ipilimumab 3 mg/kg	64	2.5	3.9	(-3.6, 11.4)
Ipilimumab 10 mg/kg	1	1.5	3.8	(0.3, 7.3)
Ipilimumab 10 mg/kg	64	1.5	4.8	(0.0, 9.6)

Adverse events which could potentially be clinical manifestations of torsades de pointes or QT prolongation were summarized across all completed studies in melanoma patients. Overall, there did not appear to be a signification concern regarding the adverse events possibly related to QT prolongation in this population. For a full review of the potential of ipilimumab to prolong the QT interval, refer to the QT-IRT review (Appendix 4.3).

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues.

The proposed dose of 3 mg/kg is acceptable based on a 3.6-month survival benefit that was observed in the ipilimumab arm at the 3 mg/kg dose over the control (gp100 vaccine) arm in the registration trial (MDX010-20). However, the E-R analysis with the data from Phase II studies suggests that increasing exposures might increase survival in advanced melanoma patients. The Kaplan-Meier plot of OS for patients in different C_{min}-quartile groups from phase II studies is shown in Figure 5. The survival curves for the vaccine (gp-100; gray curve) and the ipilimumab (green curve) arms from trial (MDX010-20) have been included to serve as a reference. The OS in lowest quartile (C_{min} Q1) is comparable with that in the vaccine (gp-100) arm. The second quartile (C_{min} Q2) is comparable with the ipilimumab arm at the proposed dose from the registration trial. The median survival is different in the different arms. The lowest quartile has a median survival of 6.5 months which is comparable to the median survival of 6.4 months observed for the vaccine arm (see Table 3).

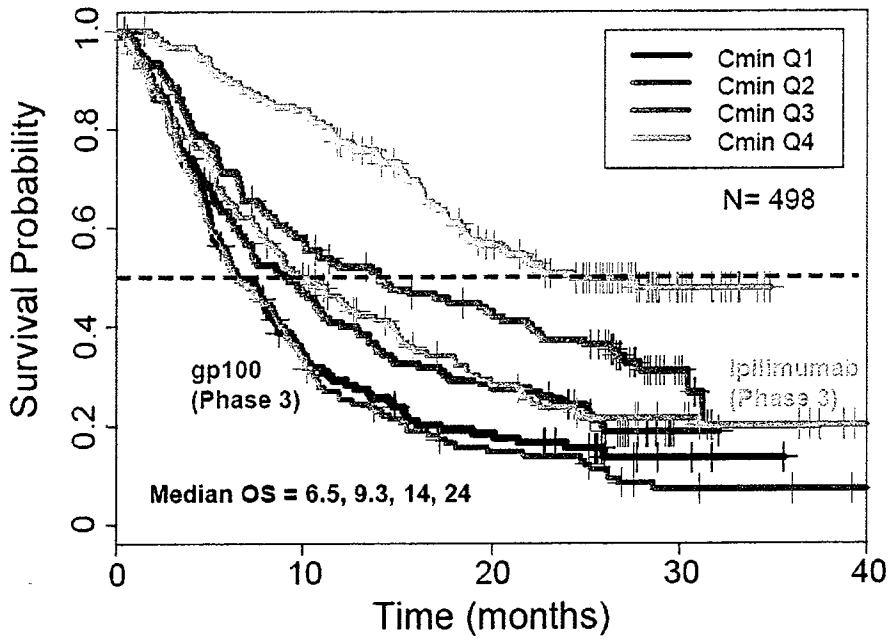

Figure 5. The exposure-response relationship for ipilimumab in Phase II studies. Overall survival by steady state trough concentrations (C_{min}) of ipilimumab.
Data were pooled from studies CA184-004, -007, -008 and -022. The Kaplan-Meier curves for the vaccine (gp100; gray) and the ipilimumab (green) arms from study MDX010-20 have been superimposed to serve as a reference. Source: PM Review

PK data are available from 98 patients at the 3 mg/kg dose. Among these, 41% of the patients were in the second quartile which is comparable to the ipilimumab arm in the registration trial. However, 56% of the patients were in the lowest quartile which was comparable to the vaccine arm. The E-R analysis shows that increasing exposures as observed in 3rd and 4th quartiles (C_{min} Q3 and C_{min} Q4) will result in improved survival benefit. While 70% of the patients who received the 10 mg/kg dose were in the 3rd and 4th quartiles, only 3% of the patients in the 3 mg/kg dose group were in these quartiles, this E-R analysis suggests that from the perspective of effectiveness of the drug, 3 mg/kg might not be an optimal dose.

The median survival for patients in various dose groups is shown in Table 7. While the curves overlap at early time points, there is separation between the groups at later time points. There is a trend towards an increase in survival with increasing doses. This supports the overall conclusion from the E-R analysis that 3 mg/kg might not be an optimal dose in terms of efficacy. Similar trend for increased survival with increasing doses was observed in study CA184022 which included all three dose levels.

Table 7. Median Survival for Patients in Different Dose Groups in Phase II Studies

Dose Group	Median Survival (months)	95% CI
0.3 mg/kg (N=72)	8.67	7.72 – 13.4
3 mg/kg (N=111)	9.66	8.18 – 13.5
10 mg/kg (N=383)	13.5	10.3 – 16.3

The dose response is not as pronounced as E-R is because there is significant overlap in the steady-state trough concentration levels achieved within various dose groups. Even at

the high dose of 10 mg/kg, 30% of the patients had exposures in the lower two quartiles that were comparable to the exposures observed at the lower doses. This is because of significant unexplained variability in the PK of the drug. The inter-individual variability on clearance from the sponsor's PopPK model was 34%.

Top line data from a controlled on-going trial (CA184024) also suggests that there may be an improved survival benefit at higher dose of ipilimumab (see section 2.4.3 for further information). Overall, the E-R analysis from phase II studies along with top line data from CA184024 suggests that from the perspective of effectiveness, 3 mg/kg may not be an optimal dose and that increasing exposures may improve survival.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

Ipilimumab exhibits linear PK over the dose range of 0.3 mg/kg to 10 mg/kg. It has a mean half-life of approximately 15 days and steady state concentrations are reached by the third dose upon Q3W administration. The answers to the following questions describe PK data from clinical trials which contributed to the PK analysis of ipilimumab in melanoma patients.

2.2.5.1 What are the single dose and multiple dose PK parameters?

MDX010-15

In study MDX010-15, a phase I trial, 89 patients received either single or multiple doses of ipilimumab. Intensive PK samples were collected from 35 patients who received 2.8 to 5 mg/kg of ipilimumab for three doses (Group A), 30 patients who received only a single dose between 7.5 and 20 mg/kg (Group A), and 24 patients who received 10 mg/kg Q3W for 4 doses (Group B). The objectives of this study involved assessing the PK and safety profiles of single and multiple doses of ipilimumab and determining the PK comparability between Process A and Process B ipilimumab products. Only Process B ipilimumab product was used in the registration trial (MDX010-20), PK comparability results are summarized in section 2.5.2. The patients that received Process A ipilimumab in MDX010-15 are those treated at the 3.0 mg/kg dose, the remainder of the patients received Process B.

Table 8. Summary Statistics for Single-Dose PK Parameters of Ipilimumab in MDX010-15[a]

PK Parameters (units)	Day 1 of Multiple Dose			Single Dose			
	2.8 mg/kg (N=13)	3.0[b] mg/kg (N=12)	5.0 mg/kg (N=10)	7.5 mg/kg (N=6)	10 mg/kg (N=7)	15 mg/kg (N=6)	20 mg/kg (N=11)
C_{max} (μg/mL)	79.9 (24%)	84.5 (38%)	162 (28%)	292 (23%)	300 (24%)	440 (7.5%)	533 (33%)
T_{max} (hr)	2.5 (1.5,5.5)	1.75 (1.5, 4)	3.5 (1.5,5.5)	2.0 (1.48,2.5)	2.0 (1.5,7.0)	3.25 (1.5,22)	3.0 (1.42,5.5)
$AUC_{0\text{-}21d}$ (μg·hr/mL)	12081 (44%)	12383 (32%)	26875 (23%)	44853 (22%)	37706 (24%)	67107 (11%)	64808 (23%)
AUC_{inf} (μg·hr/mL)	19583 (74%)	19596 (68%)	42337 (32%)	70847 (19%)	60099 (43%)	98325 (23%)	78258 (46%)

Terminal $t_{1/2}$ (days)	16.0 (9.5)	17.3 (11.0)	16.0 (10.9)	16.1 (6.7)	15.3 (8.3)	16.5 (6.0)	12.4 (8.3)
CL (mL/hr)	12.8 (6.8)	13.8 (8.1)	11.6 (5.2)	8.9 (2.1)	15.7 (6.2)	13.6 (2.2)	21.9 (11.5)
V_{ss} (L)	5.50 (2.07)	5.88 (1.61)	5.38 (1.86)	4.66 (1.10)	6.66 (2.31)	6.15 (1.93)	6.08 (1.84)

[a]AUC and C_{max} are expressed as geometric mean (CV%), T_{max} as in median (min, max), all the other parameters are expressed as arithmetic mean (SD)
[b]Represents patients who received Process A (hybridoma-derived) ipilimumab

Intensive PK sampling took place at the following time points on Days 1, 57, and 85 for the 2.8, 3.0, and 5.0 mg/kg doses of ipilimumab: pre-dose, end of infusion, 2, 2.5, 3, 4, 5.5, 24, 72, 168, 336, and 504 hours after the end of infusion; samples were collected on Days 92, 99, 106, 113, 141, 169, 253, and 381 for patients who continued treatment. For the 7.5, 10, 15, and 20 mg/kg doses, intensive sampling was only performed after the first dose. For the multiple 10 mg/kg (Q3Wx4) dose administration, sampling took place at the above time points only after the dose on Day 64, otherwise samples were collected on Days 22, 43, 71, 78, 85, 92 and 106; samples were collected every 50 days for patients who continued treatment.

Ipilimumab exposure measurements, C_{max}, AUC_{inf}, and $AUC_{0\text{-}21d}$ appeared less than dose proportional (Table 8). Other PK parameters, $t_{1/2}$, CL and V_{ss} were comparable across the dose range of ~3 to 20 mg/kg. The $t_{1/2}$ for the single doses ranged from 12.4 to 16.5 days, which was slightly longer than that observed in studies CA184007 (Table 10) and CA184008 (data not shown). The sponsor states that this is most likely due to the extended PK sampling beyond 21 days post-dose in MDX010-15 compared to only up to 21 days post-dose in the other two studies.

Table 9. Summary Statistics for Multiple-Dose PK Parameters of Ipilimumab in MDX010-15[a]

	Group A			Group B
Time and Dose Number of Sampling	Day 57 (Dose 2)	Day 57 (Dose 2)	Day 85 (Dose 3)	Day 64 (Dose 4)
PK Parameters (units)	2.8 mg/kg (N=7)	3.0 mg/kg (N=5)	5.0 mg/kg (N=3)	10 mg/kg (N=13)
C_{max} (μg/mL)	108 (38%)	103 (68%)	237 (32%)	441 (36%)
T_{max} (hr)	2.5 (1.33, 4.0)	3 (1.5, 24)	2.5 (1.58, 5.5)	2.5 (1.25, 48)
$AUC_{0\text{-}21d}$ (μg·hr/mL)	15206 (30%)	18396 (33%)	37670 (30%)	55433 (35%)
Terminal $t_{1/2}$ (days)	11 (3)	13 (9)	N/A	15 (9)

[a] AUC and C_{max} are expressed as geometric mean (CV%), T_{max} as in median (min, max), all the other parameters are expressed as mean (SD). All the dates are when the last available data is collected.

Group A included patients who received 3 mg/kg ipilimumab QWx3, the sponsor's proposed clinical dose. However, patients who received the 3 mg/kg dose were given Process A (hybridoma-derived) ipilimumab, not the to-be-marketed Process B (transfectoma-derived) ipilimumab.

The single 10 mg/kg dose was used to compare single- (Table 8) and multiple-dose (Table 9) PK for ipilimumab. The median T_{max} following multiple 10 mg/kg doses was 2.5 hours versus 2.0 hours for the single dose. And the mean C_{max} value following

multiple 10 mg/kg dose administration was 461 μg/mL versus 307 μg/mL for the single dose. The $AUC_{0\text{-}21d}$ was higher for the multiple dose, but the $t_{1/2}$ was similar between the two dosing regimens, 359 hr versus 366 hr for multiple and single doses, respectively.

Overall, the mean $t_{1/2}$ was 15 days with a T_{max} occurring at 2.5 hours (Table 9). There was a large range for the T_{max} values at the 3.0, 10, and 15 mg/kg doses. Comparing the mean $AUC_{0\text{-}21d}$ for the last dose (Table 9) to Dose 1 (Table 8), accumulation indices were 1.26, 1.48, 1.40, and 1.47 for the 2.8, 3.0, 5.0 and 10 mg/kg cohorts, respectively. The drug accumulation is consistent with the estimated $t_{1/2}$ of approximately two weeks.

CA184007

In study CA184007, ipilimumab (manufactured by Process B- (b) (4)) was administered as 10 mg/kg. Patients were also randomized to receive oral budesonide (Entocort® EC) or placebo administered at 9 mg QD until Week 12, then tapered to 6 mg QD until Week 14, and finally to 3 mg QD until Week 16. Intensive PK sample collection (pre-dose, end of infusion [90 minutes], 24, 72, 168, 336, and 504 hrs) took place in a subset of patients after the first dose (Week 1) and after the third dose (Week 7). A total of 116 patients were treated in this study with 12 patients having intensive PK samples available, and 112 patients having sparse PK samples available. Table 10 shows the summary statistics of the PK parameters generated by NCA in the patients receiving ipilimumab + placebo who had intensive sampling. The PK of ipilimumab + placebo and ipilimumab + budesonide were compared in the PopPK analysis.

Table 10. Summary Statistics for PK Parameters in CA184007

PK Parameters (units)	First Dose (N=11)		Third Dose (N=12)	
	Mean (CV%)[a]	Range	Mean (CV%)[a]	Range
Cmax (μg/mL)	206 (21%)	136-265	215 (24%)	141-347
Tmax (hr)	1.58	1.50-1.75	1.58	1.45-24.5
$AUC_{0\text{-}21d}$ (μg·hr/mL)	33498 (18%)	17707-41649	47722 (27%)	17254-68518
AUC_{inf} (μg·hr/mL)	42844 (23%)	19063-55463	N/A	N/A
Terminal $t_{1/2}$ (days)	9.62 (3.46)	5.96-17.5	15.2 (7.05)	7.93-28.8
CL (mL/hr)	19.1 (6.56)	10.8-35.7	N/A	N/A
Vss (L)	6.04 (1.89)	2.43-9.07	N/A	N/A

[a]All values are expressed as arithmetic means (SD), except for AUC and C_{max}, which are expressed as geometric means (CV%), T_{max} is expressed in median (range).

CA184008

In study CA184008, 16 patients received ipilimumab (Process B- (b) (4)) 10 mg/kg as 90-minute IV infusions at Weeks 1, 4, 7 and 10 (Induction Period). Intensive PK sampling (pre-dose, end of infusion [90 minutes], 24, 72, 168, 336, and 504 hrs) was conducted in 4 patients after the first dose (Week 1) and after the third dose (Week 7). A total of 148 patients were evaluable for sparse PK. Since only 4 patients had intensive PK data for which NCA was performed, the PK parameters are not presented. Overall, the PK of the four patients was similar to the PK in the ipilimumab + placebo arm in study CA184007

(Table 10). The mean systemic total CL and V_{ss} were approximately 20% lower compared to CA184007, but the $t_{1/2}$ and AUC were similar.

CA184004, CA184022, and MDX010-08

Sparse PK samples were collected from CA184022 and CA184004, two phase II studies with ipilimumab monotherapy. No intensive sampling was performed in either of these studies. The data collected from CA184022 was used in the PopPK analysis. The PK data collected from CA184004 was used in the validation dataset for PopPK analysis but not in the model building dataset. Thus the exposure-response and covariate analyses do not include data from study CA184004, but do include data from CA184007, -008, and -022.

Study MDX010-08 used Process A ipilimumab material and only had intensive PK collection in four patients, hence the PK results from this study are not included in this review.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable. Ipilimumab has not been administered to healthy volunteers because of its safety profile.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable. Ipilimumab is administered as an IV infusion.

2.2.5.4 What are the characteristics of drug distribution?
The mean Vss across studies was 6.0 L ranging from 5.5 to 6.7 (pooled data). The small Vss value indicates that ipilimumab is confined primarily to the extracellular fluid volume consistent with its large molecular weight. This value was also consistent with the Vss estimated from the PopPK model.

No radiolabeled tissue distribution studies for ipilimumab have been performed. It is not characteristic to have tissue distribution studies for biological agents.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Not applicable. No radiolabeled mass balance study of ipilimumab has been performed in man to determine the proportion of administered dose cleared through specific mechanisms. Ipilimumab is a biological product. Mass balance studies are not generally performed for biological products because they are proteins which are degraded into amino acids that are then recycled into other proteins.

2.2.5.6 What are the characteristics of drug metabolism?

Not applicable. No metabolism study has been conducted for ipilimumab. Ipilimumab is a biological product. Metabolism studies are not generally performed for biological products because these products are proteins that are degraded into amino acids which are then recycled into other proteins.

2.2.5.7 What are the characteristics of drug excretion?
The mean CL was 15.2 ml/hr ranging from 12.8-18.3 ml/min across studies (pooled data). This mean CL was consistent with the mean CL obtained in the PopPK model.

No radiolabeled mass balance study of ipilimumab has been performed in man to determine the proportion of administered dose cleared through specific mechanisms.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The results of the PopPK analysis of the pooled phase II data from three BMS trials (CA184007, CA184008, CA184022) indicated that the PK of ipilimumab was linear in the dose range of 0.3 to 10 mg/kg. Results from study MDX010-15 showed a less than dose proportional relationship since AUC and C_{max} decreased with increasing dose. However, the assay used for MDX010-15 (STM1693) was not validated according to ICH Guidelines and did not perform as well as the assay used in the BMS studies.

Dose linearity was examined in the PopPK analysis by testing the effect of dose on CL, and 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 ipilimumab were 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. Figure 6 shows box plots of the maximum posteriori (MAP) Bayesian estimates of individual CL by dose.

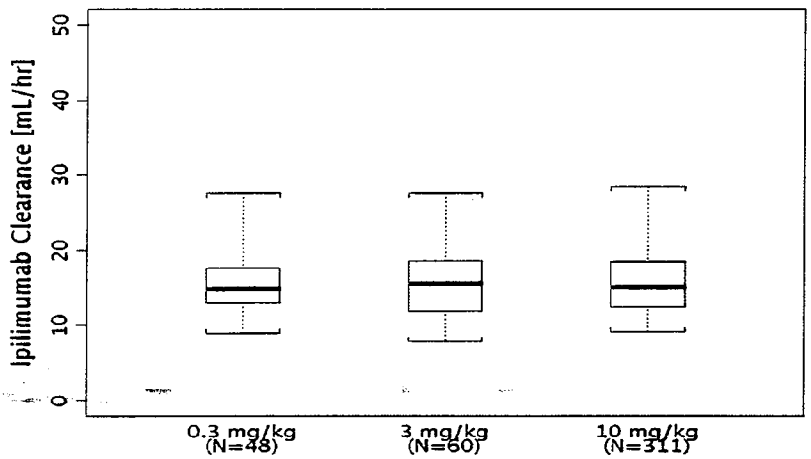

Figure 6. Box plots of individual ipilimumab clearance by dose (mg/kg) (CA184007, CA184008, CA184022)[a]

[a] Boxes (25th, 50th, and 75th percentiles) and whiskers (5th and 95th percentiles)

Additional box plots of ipilimumab AUC and C_{max} were made comparing the data across 0.3, 3, and 10 mg/kg. Both the AUC and C_{max} were found to increase in a dose proportional manner suggesting linearity (Figure 7).

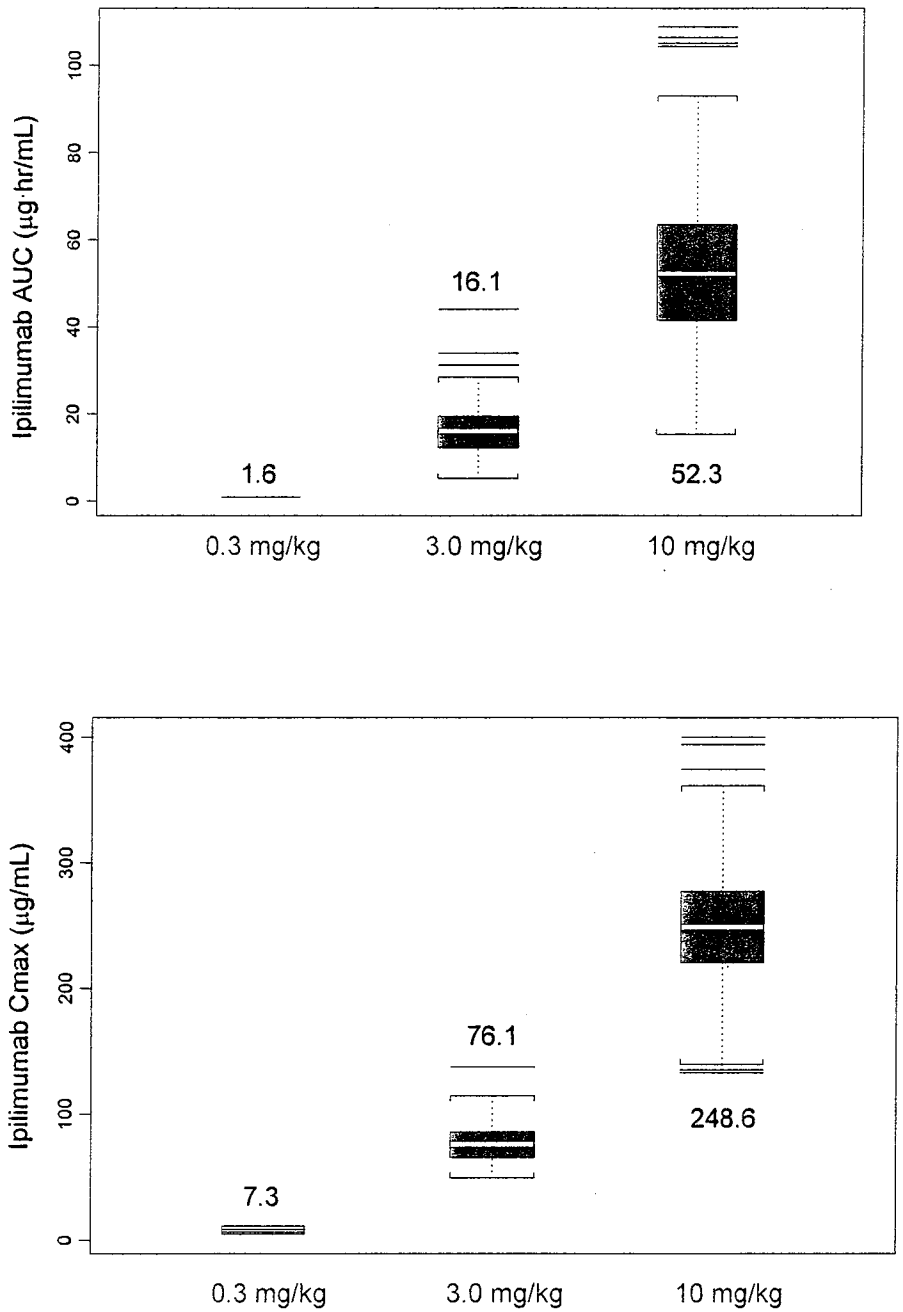

Figure 7. Box plots of individual ipilimumab AUC and C_{max} by dose (mg/kg) (CA184007, CA184008, CA184022)[a]

[a] Boxes (25th, 50th, and 75th percentiles) and whiskers (5th and 95th percentiles). Values shown above or below each individual box plot represent the median for that group.

2.2.5.9 How do the PK parameters change with time following chronic dosing?
At 10 mg/kg dosed every 21 days, the average ratio of C_{max} for Dose 3 relative to Dose 1 was 1.1 for BMS studies (pooled data) and 1.47 in Medarex study MDX010-15, indicating minimal accumulation. An accumulation index of 1.4 (range: 0.96 - 1.81) was calculated from the ratio of $AUC_{0\text{-}21d}$ following Dose 3 to that for Dose 1 for BMS studies. These results are consistent with an accumulation index of 1.5 calculated for ipilimumab based on the AUC ratios.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-individual variability on CL was 34%. Body weight was identified as a covariate for central volume (V_C) because inclusion of weight as a covariate on V_C in the reviewer's PopPK analysis reduced the objective function value by 131 from the sponsor's base model. The inter-individual variability on V_C reduced from 22.9% to 16.6%. Body weight and baseline levels of LDH were identified as covariates for CL by the sponsor. These covariates identified in the final model by the sponsor are likely not to be significant because reviewer's analysis showed that the inclusion weight alone as a covariate for CL resulted in the reduction in the objective function value by 3.54 from the sponsor's base model. The inter-individual variability on CL was reduced from 39.5% to 38.3%. Consistent with the sponsor's analysis, inclusion of baseline LDH as a covariate resulted in the reduction in the objective function value by 13.3 from the base model. The inter-individual variability on CL was reduced from 39.5% to 37.4%. Inclusion of all covariates in the model resulted in reduction of inter-individual variability on CL from 39.5% to 34.4%.

There were no clear trends identified between the PK parameters obtained from the model and age, gender, renal function, hepatic function concomitant budesonide, ECOG performance status, prior systemic anti-cancer therapy, HLA.A2*201 genotype status, and immunogenicity (HAHA status) (see section 2.3.2 for details).

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 effect of age, gender, body weight, baseline lactate dehydrogenase, immunogenicity status, HLA status, ECOG status, renal function, hepatic function, concomitant use of budesonide and prior anti-cancer therapy on exposure was evaluated using the PopPK analysis. No clinically meaningful effect of these covariates was identified using data from 420 patients in Phase II studies (see section 2.3.2 for details).

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific

populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dose regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly Patients

The PopPK analysis shows that age does not significantly affect the PK of ipilimumab. Figure 8 shows that the inter-individual variability in CL cannot be explained by age. The median CL in the elderly (≥65 years of age) and non-elderly groups were 0.0148 and 0.0153 L/h, respectively.

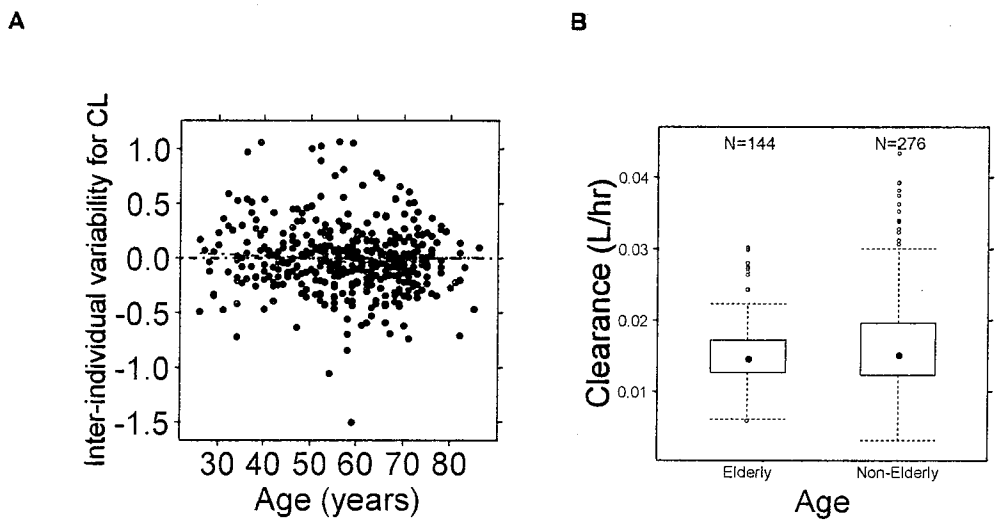

Figure 8. A) Inter-individual variability on clearance and B) Clearance vs. age.

2.3.2.2 Pediatric Patients

The safety and effectiveness of ipilimumab in the pediatric patient population has not been studied. Since the proposed indication has been granted as an orphan indication for ipilimumab, no pediatric studies are required under the Pediatric Research Equity Act (PREA).

2.3.2.3 Gender

Gender does not significantly affect the PK of ipilimumab based on the PopPK analysis. Box plot of the inter-individual variability on CL shows that there is no systematic trend between males and females as evidenced by a median of zero (Figure 9). The median CL was 0.0161 and 0.0133 L/hr in men and women, respectively.

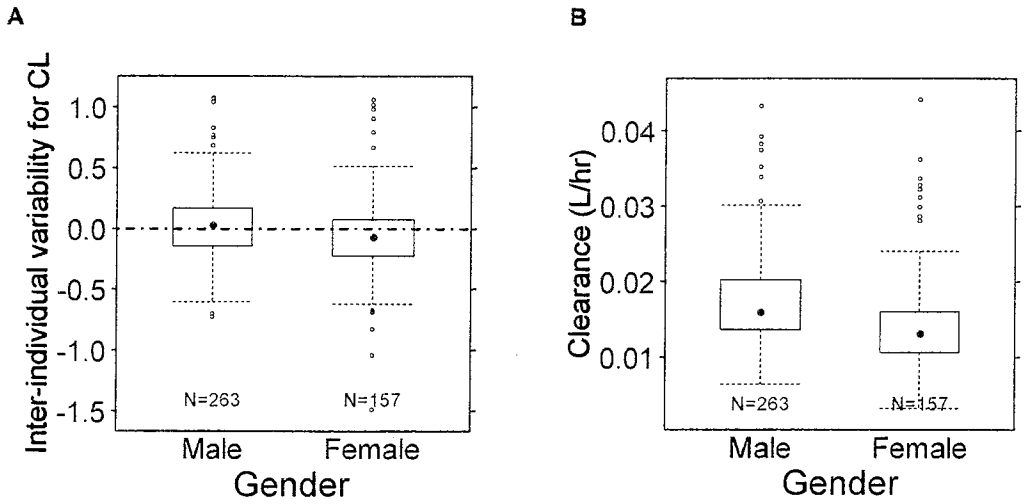

Figure 9. A) Inter-individual variability on clearance and B) Clearance vs. Gender.

2.3.2.4 Race

The effect of race on the PK of ipilimumab could not be evaluated because there was insufficient number of patients in the non-Caucasian ethnic groups. Among the 420 patients included in the PopPK analysis, 412 (98%) were Caucasians.

2.3.2.5 Renal Impairment

The PopPK analysis suggests that there is no effect of renal impairment on the PK of ipilimumab. Figure 10 shows that the inter-individual variability in CL cannot be explained by renal function. There is no trend between inter-individual variability on CL and glomerular filtration rate (GFR) for patients with mild and moderate renal impairment. There were only 4 patients with severe renal impairment. Median CL in various renal function groups were similar (Table 11). Similar results were obtained using creatinine CL as a measure of renal function (Figure 11).

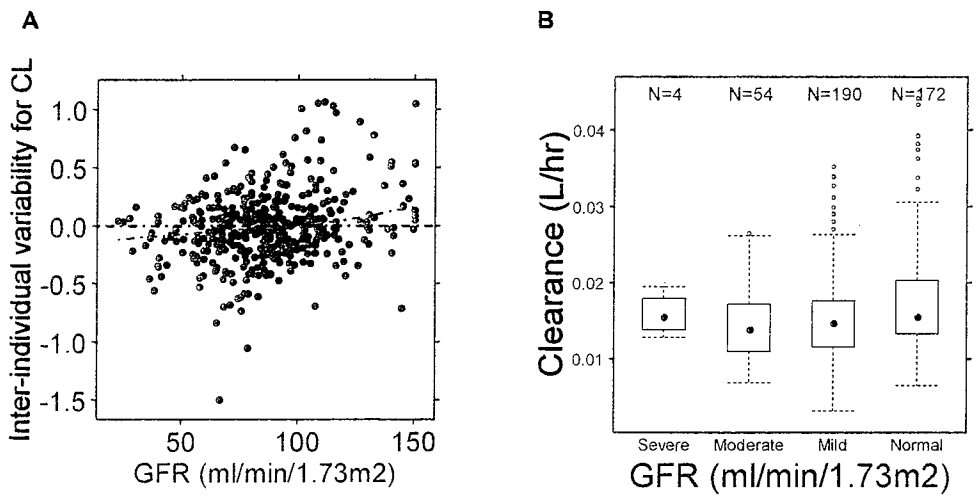

Figure 10. A) Inter-individual variability on clearance and B) Clearance vs. glomerular filtration rate (GFR).
Renal function was classified as normal (≥90 mL/min/1.73m^2), mild impairment (60 to <90 mL/min/1.73m^2), moderate impairment (30 to <60 mL/min/1.73m^2), and severe impairment (<30 mL/min/1.73m^2).

Table 11. Clearance by Renal Function Status

Renal function group based on GFR	Median Clearance (L/hr) – stratified by GFR	Median Clearance (L/hr) – stratified by CRCL
Normal	0.0157	0.0157
Mild	0.0148	0.0147
Moderate	0.0140	0.0132
Severe	0.0157	0.0149

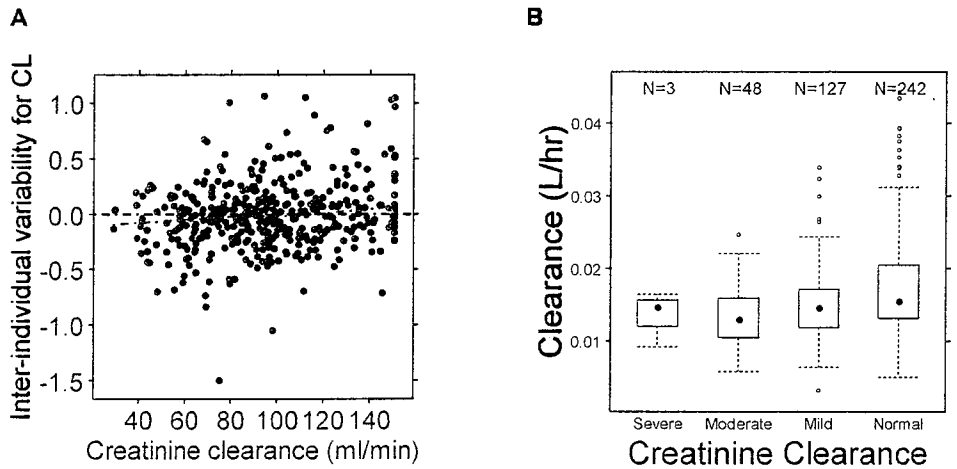

Figure 11. A) Inter-individual variability on clearance and B) Clearance vs. Creatinine clearance.
Renal function was classified as normal (≥ 90), mild impairment (60 to <90), moderate impairment (30 to <60), and severe impairment (< 30).

2.3.2.6 Hepatic Impairment

The PopPK analysis shows that there is no clinically meaningful effect of hepatic impairment on the PK of ipilimumab. There is a trend for increase in inter-individual variability for CL with baseline levels of alkaline phosphatase (ALP) as shown in Figure 12. This is likely not to be significant because a categorical analysis showed that patients with high baseline ALP (> 115 IU/L) had 1.14-fold higher CL than patients with normal levels of ALP (≤ 115 IU/L). There was no clear trend for inter-individual variability for CL and baseline aspartate aminotransferase (AST), total bilirubin, and alanine aminotransferase (ALT) as shown in Figure 13 and Figure 14. A slight increase in CL (1.17-fold) was observed for patients with low levels albumin compared to normal patients. There was limited information from 31 patients in the low albumin group because only 1 patient had albumin level less than 2.5 g/dL. The median albumin level in the low group was 3.4 g/dL which is close to normal.

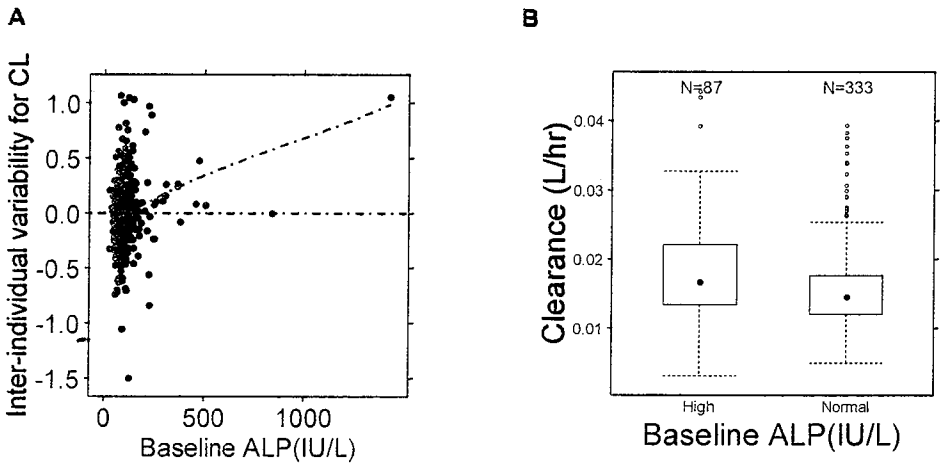

Figure 12. A) Inter-individual variability on clearance and B) Clearance vs. baseline alkaline phosphatase (ALP).
ALP level ≤ 115 IU/L was considered normal. Median values of clearance in the high and normal groups are 0.0169 and 0.0148 L/h, respectively. Median values of ALP in the high and normal groups are 142 and 79 IU/L, respectively.

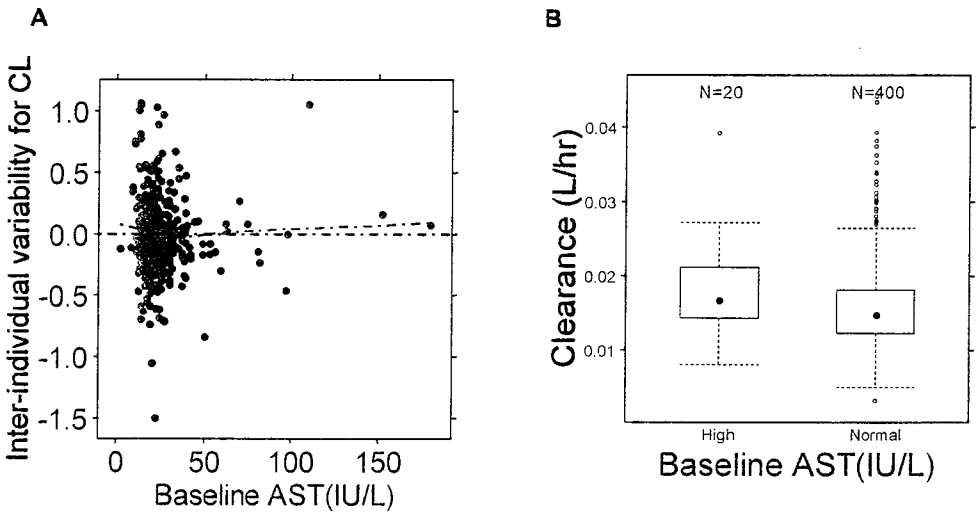

Figure 13. A) Inter-individual variability on clearance and B) Clearance vs. baseline aspartate aminotransferase (AST).
AST level ≤ 43 IU/L was considered normal. Median values of clearance in the high and normal groups are 0.0168 and 0.0150 L/h, respectively. Median values of albumin in the high and normal groups are 62.5 and 20 IU/L, respectively.

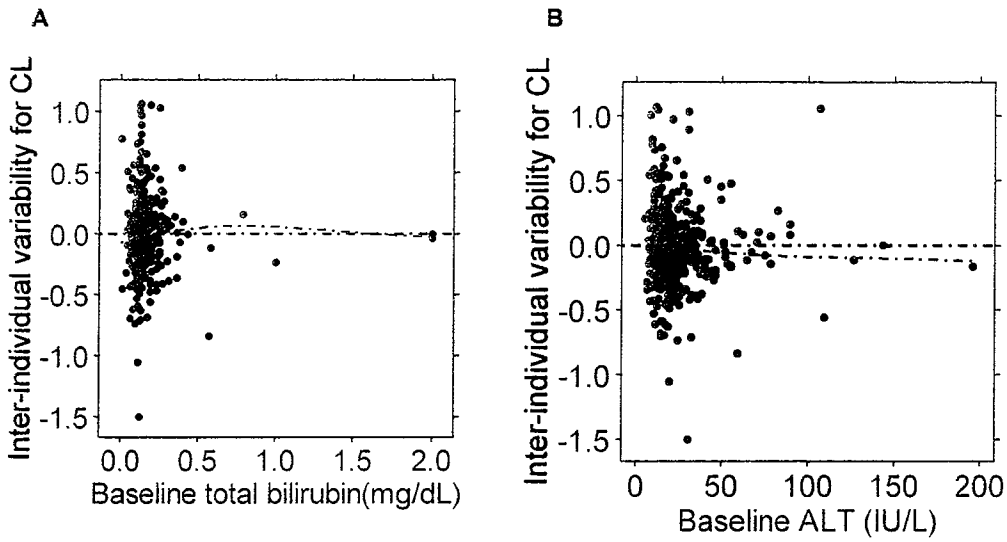

Figure 14. Inter-individual variability on clearance vs. A) baseline total bilirubin and B) baseline alkaline transaminoferase (ALT).

2.3.2.7 What pharmacogenetics information is in the application and is it important or not?

DNA was collected in four phase II studies (CA184004, -007, -008, -022) and associations between variants in immune-related genes with worst grade (≥2) irAEs including hepatobiliary, gastrointestinal (GI), and dermatological manifestations were assessed. Consistent with the sponsor's analyses, a missense mutation in CD86 (rs2681417) was associated with increased risk of GI irAEs in patients receiving ipilimumab. Other associations with skin, hepatobiliary, and GI events were also seen. However, several limitations preclude definitive conclusions regarding the strength of the associations, including 1) lack of uniform DNA sample acquisition from analyzed phase II studies; 2) no DNA collection in the pivotal phase III trial; 3) lack of justification for candidate gene/SNP selection; 4) limited numbers of patients treated with doses other than 10 mg/kg; and 4) questionable irAE definition. No definitive label modifications are warranted at this time. For more detailed information regarding pharmacogenomics assessment of this BLA refer to the separate Genomics Group review (Appendix 4.1).

2.3.2.8 What pregnancy and lactation use information is in the application?

Animal reproduction studies have not been conducted with ipilimumab. It is not known whether ipilimumab can cause fetal harm when administered to a pregnant woman or can

affect reproduction capacity. Since human IgG1 is known to cross the placental barrier, ipilimumab has the potential to be transmitted from the mother to the developing fetus. The product label recommends that ipilimumab should not be given to pregnant women unless clearly needed.

No study has been conducted to determine whether ipilimumab is secreted into breast milk. Because, human IgG1 is known to be secreted into human breast milk, there is a potential for ipilimumab to be passed from mother to nursing child. The product label recommends that women who are taking ipilimumab should not breast-feed.

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?

The incidence of anti-product (ipilimumab) antibody (APA) formation is approximately 1.1% (11 out of 1024 patients) across 7 clinical studies in patients with advanced melanoma. This result represents pooled data of evaluable melanoma patients who received ipilimumab and had positive APA titers post-baseline. The results are presented according to the assay type. The same serum ECL assay was used for the studies CA184004, -007, -008, and -022 (Table 12). Serum samples were collected prior to Dose 1 (baseline) and prior to all subsequent ipilimumab doses at trough drug concentrations as well as between 70-85 days after the last dose. Twenty-six out of 560 (26/560, 4.6%) patients in the four phase II studies tested positive for anti-ipilimumab antibodies at any time point during the studies, and 11/513 (2.1%) were positive post-baseline. Pre-existing baseline APAs were observed in 15 patients. Six of the 15 patients (6/15) had Ig-specific APAs both pre- and post-dose. None of the binding antibodies were found to have neutralizing capacity.

Table 12. Number (%) of Unresectable Stage III or IV Melanoma Patients with Anti-Ipilimumab Responses (Serum ECL Assay)

Study	Dose (mg/kg)	Positive at Any Time point	Positive Post-Baseline
		No. Positive/ No. Evaluated (%)	
CA184004	3	3/40 (7.5)	0/36 (0)
	10	1/42 (2.4)	1/40 (2.5)
CA184007	10	2/115 (1.7)	1/108 (0.9)
CA184008	10	4/154 (2.6)	1/142 (0.7)
CA184022	0.3	6/71 (8.5)	4/58 (6.9)
	3	5/69 (7.2)	3/66 (4.5)
	10	5/69 (7.2)	1/63 (1.6)
Cumulative		26/560 (4.6)	11/513 (2.1)

Table 13. Number (%) of Subjects with Anti-Ipilimumab Responses (Plasma ECL Assay)

Study	Treatment Groups (Ipilimumab dose mg/kg)	Anti-Ipilimumab Response	Maximum Titer
MDX010-20	Ipilimumab (3 mg/kg)	0/131 (0%)	-

	Ipilimumab (3 mg/kg) + gp100	0/380 (0%)	-
	gp100	0/312 (0%)	-
Cumulative		0/643 (0%)	
MDX010-08	Metastatic melanoma	2/76 (2.6%)	8-fold
MDX010-15	Stage III, IV melanoma	5/88 (5.7%)	Positive
Cumulative (screening assay only)		7/164 (4.3%)	

Immunogenicity testing was performed in MDX010-20, the registration trial. Samples were obtained prior to Dose 1, at the first follow-up visit, and every 12 weeks thereafter. A total of 1569 samples from 643 patients were analyzed using a plasma ECL method. Of the total samples, 66 (4.2%) were determined to be potential positives. Of these 66 samples, 18 were determined to be positive pre-dose, without a corresponding post-dose positive sample. The remaining 48 potential positives were determined to be negative based on post-dose to pre-dose titer ratios. Accordingly, all samples tested in study MDX010-20 were found to be negative for APAs (Table 13). No samples were tested for neutralizing capacity since none were found to be positive for APAs.

Immunogenicity testing was also performed in two phase I studies in patients with melanoma: MDX010-08 and MDX010-15. Between the two studies, 7 out of 164 (4.3%) patients were positive for APAs using a screening assay. Confirmatory assays were not available at the time of reporting for these two studies, thus only the 7 baselines samples were considered to be APA positive.

It appeared that APA incidence decreased with increasing dose of ipilimumab. Patients receiving 10 mg/kg ipilimumab had about a 6% lower APA incidence rate than those receiving 0.3 mg/kg (Table 14). However, the 90% CI for each of the three doses is very large. Interference from the ipilimumab in patient samples may have masked any positive APA titers at the higher ipilimumab dose (see CMC review for further details). The sponsor will need to develop a more sensitive assay allowing for the accurate detection of APAs in the presence of ipilimumab (see sections 2.4.3 and 2.6.6.1 for further details). Overall, the incidence of APA in all patients across 7 melanoma studies is 1.1%.

Table 14. Immunogenicity Summary by Ipilimumab Dose[1]

Treatment	Positive at any Timepoint	Positive Post-Baseline[2]	
	No. positive/ No. evaluated (%)	No. positive/ No. evaluated (%)	90% CI
0.3 mg/kg	6/71 (8.5%)	4/58 (6.9%)	(2.4%, 15.1%)
3.0 mg/kg	8/109 (7.3%)	3/102 (2.9%)	(0.8%, 7.4%)
10 mg/kg	12/380 (3.2%)	4/353 (1.1%)	(0.4%, 2.6%)
Total	26/560 (4.6%)	11/513 (2.1%)	(1.2%, 3.5%)

[1]Includes anti-ipilimumab, anti-Ig, or both types of antibodies confirmed by an immunodepletion assay
[2]Denominator includes patients with both a baseline and a post-baseline measurement

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

Based on the PopPK analysis, immunogenicity status has no effect on ipilimumab PK (Figure 15). Inter-individual variability on CL cannot be explained by immunogenicity status.

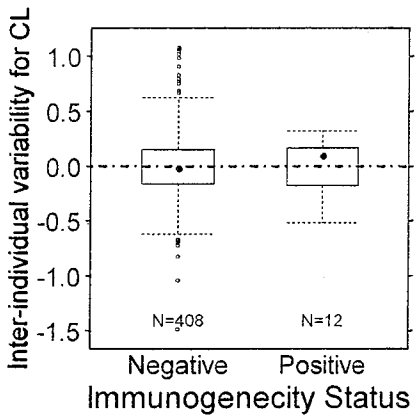

Figure 15. Inter-individual variability on clearance vs. immunogenicity status.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

Samples confirmed positive for APAs to ipilimumab were tested for the presence of neutralizing antibody with a competition ECL immunoassay. Detection of neutralizing anti-ipilimumab antibodies was based on the ability of the APAs to prevent the binding of ipilimumab to the CTLA-4 receptor.

As stated in section 2.3.3.1 above, APAs were not tested for neutralizing capacity in studies MDX010-08, MDX010-15, and MDX010-20. APAs were tested for neutralizing capacity in the 4 phase II studies. However, no neutralizing antibody activity was detected.

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

It is unclear whether immunogenicity has any effect on clinical efficacy because the available data does not allow for this evaluation.

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 sponsor states that the impact of immunogenicity on the safety of ipilimumab was evaluated in patients who had at least one positive APA response at any time point. The APA incidence was noted especially as it related to the frequency and type of irAE, anaphylaxis, hypersensitivity, and overall AEs (serious and non-serious), and those that led to study discontinuation.

Twenty-six (26) patients across the 4 phase II trials had at least one positive HAHA at any time point (Table 14). Of these patients, the majority had a low positive titer (i.e. titer of 10), except for three patients who had titers of 50. However, none of the APA-positive patients had any infusion-related or peri-infusional hypersensitivity or anaphylactic reactions.

Five patients in MDX010-15 were positive for APAs; of these, three patients had Grade 1 rash or pruritis. None had any infusion related reactions. Additionally, there were no clinically relevant infusion related reactions in the two patients from study MDX010-08 who tested positive for APAs.

Overall, the available data does not suggest that immunogenicity status has an impact on ipilimumab safety.

2.4 Extrinsic Factors

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

2.4.2 Drug-drug interactions

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

No. Ipilimumab is a biological product which is not metabolized by liver cytochrome P450 enzymes or other drug metabolizing enzymes. Ipilimumab as a monoclonal antibody targeting CTLA-4 is unlikely to have an effect on CYPs or other drug metabolizing enzymes in terms of inhibition or induction.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No. See response to 2.4.2.1.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

No. See response to 2.4.2.1.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No. See response to 2.4.2.1.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

No. See response to 2.4.2.1.

2.4.2.6 Does the label specify co-administration of another drug (e.g. combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No. The proposed regimen for ipilimumab is as a monotherapy. Ipilimumab in combination with budesonide (Entocort) was studied in trial CA184007 and ipilimumab in combination with dacarbazine (DTIC) was studied in trial MDX010-08. PopPK analysis results showed that neither of these agents had an effect on ipilimumab PK.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

The current proposed use of ipilimumab is as a monotherapy. Additional medications may be given concomitantly to alleviate symptoms arising from AEs. In general, drugs affecting the immune system, such as immunosuppressants should be avoided since they could interfere with the pharmacodynamic activity of ipilimumab.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No. The combination of budesonide with ipilimumab was not found to alter ipilimumab PK. Based on the PopPK analysis, there is no effect on ipilimumab PK due to concomitant use of budesonide and prior anti-cancer therapy (Figure 16).

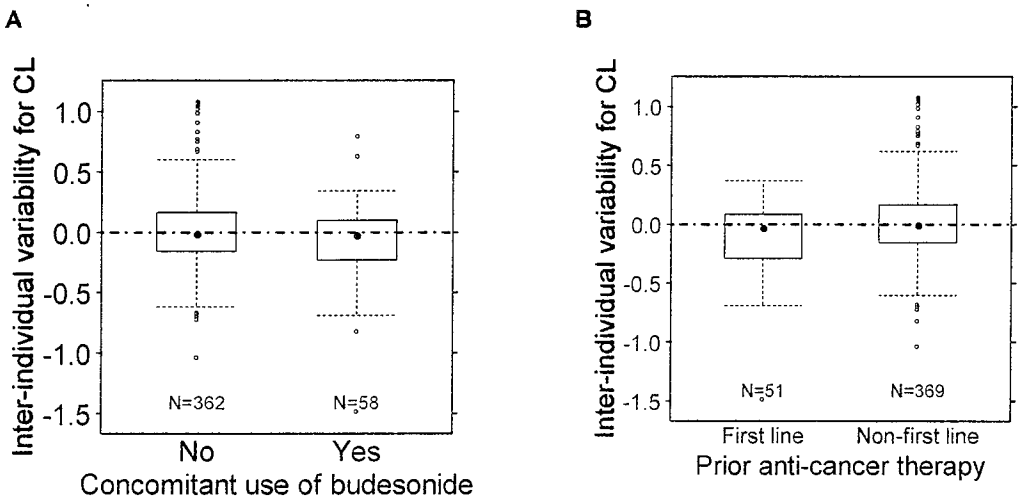

Figure 16. Inter-individual variability on clearance vs. A) Concomitant use of budesonide and B) Prior anti-cancer therapy.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Top line results from an on-going phase III trial (CA184024) show a survival benefit in patients with untreated Stage 3 or 4 melanoma receiving 10 mg/kg ipilimumab + dacarbazine (250 patients) compared to placebo + dacarbazine (252 patients). The median survival for the ipilimumab treated group at the 10 mg/kg dose is higher than the median survival (10.1 months) observed at the 3 mg/kg dose of ipilimumab in study MDX010-20. This increased survival might be due to one or many factors such as the combined effect of ipilimumab and dacarbazine, a higher 10 mg/kg dose of ipilimumab, or differences in the patient population (chemotherapy naïve versus a pre-treated population). In light of these topline results and toxicity profile as well as the E-R analysis which shows that 10 mg/kg ipilimumab may provide additional survival benefit compared to 3 mg/kg ipilimumab, the FDA has requested that the sponsor conduct a head-to-head comparative trial of 3 mg/kg versus 10 mg/kg ipilimumab in melanoma patients.

The immunogenicity results indicate that the presence of ipilimumab interferes with the detection of anti-ipilimumab antibodies at higher doses of ipilimumab (3 and 10 mg/kg). Thus, the FDA has requested the sponsor to develop and validate a more sensitive assay for APA detection and to evaluate APA response in at least 300 patients.

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 have been used in the development of the ipilimumab drug substance, Processes A, B, and C. This review focuses only on Processes A and B, since these two comprise the ipilimumab substances used in the clinical trials for marketing approval. Process A involved the manufacture of ipilimumab using a hybridoma cell line. Process B, refers to the manufacturing process using a recombinant Chinese hamster ovary (CHO) cell line. (b) (4) The Process B (b) (4) ipilimumab substance is the to-be-marketed form of the drug. The key differences between Process A and the two Process B substances are shown in Table 15. The two trials, MDX010-15 and MDX010-20 (registration study) used the product manufactured from two different processes.

(b) (4)

Table 15. Manufacturing Processes for Ipilimumab

Key Features	Process A	Process B (b) (4)	Process B (b) (4) (b) (4)
(b) (4)	Hybridoma (b) (4) (b) (4)	Recombinant CHO cell line (b) (4)	Recombinant CHO cell line (b) (4) (b) (4)
Clinical trials in which process was used	MDX010-08 MDX010-15 (3mg/kg only)	MDX010-15 MDX010-20	MDX010-20 CA184004 CA184007 CA184008 CA184022

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?

The proposed to-be-marketed ipilimumab product is manufactured using Process B. Process B material was used in all the phase II studies as well as the registration study (Table 15). Process A material was used in study MDX010-08 and only at the 3 mg/kg dose level in study MDX010-15.

As part of study MDX010-15, the comparability between Process A and B drug products was assessed using equimolar doses of ipilimumab Process A (3 mg/kg, N=12) and Process B (2.8 mg/kg; N=13) (Figure 17). While the ratios for Cmax and AUC (point estimate) were close to 100%, the 90% CIs were outside the 80-125% limits for comparability (Table 16). From a CMC perspective, however, the two manufacturing processes were found to be comparable (see CMC review for further details).

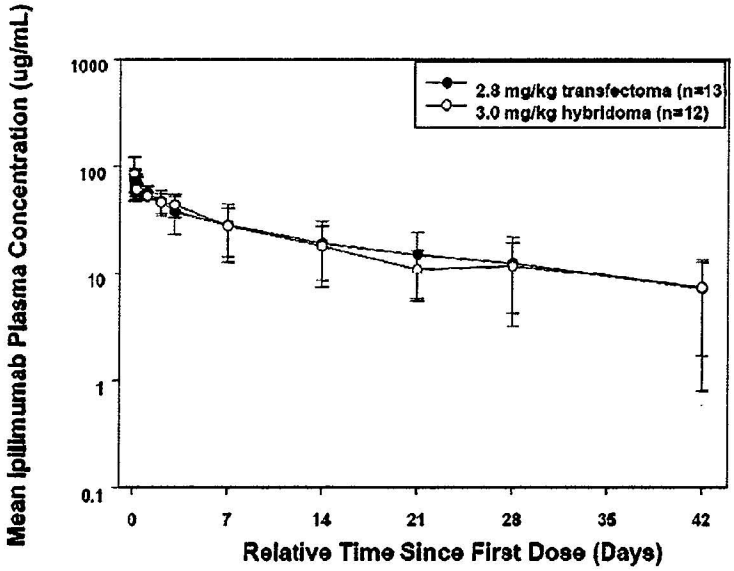

Figure 17. Mean (SD) plasma concentrations versus time profiles of ipilimumab in melanoma subjects dosed with either Process A (3.0 mg/kg) or Process B (b) (4) (2.8 mg/kg) ipilimumab.

Table 16. Statistical Analysis for PK Parameters in Study MDX010-15

PK Parameters	Process	Geometric Means	Point Estimate (%)	90% Confidence Limits
C_{max} (μg/mL)	B	79.9	94.5	(79.1, 112.9)
	A	84.5		
$AUC_{0\text{-}504h}$ (μg·hr/mL)	B	12801	97.6	(75.4, 126.3)
	A	12384		
AUC_{inf} (μg·hr/mL)	B	19583	99.9	(67.7, 147.5)
	A	19597		

The ratio (point estimate) presented represents Process B (b) (4) versus Process A.

Both MDX010-08 and MDX010-15 were phase II studies conducted by Medarex prior to the BMS sponsored phase II trials. The comparability data for Process A versus Process B was not previously submitted to the FDA for review.

A bioanalytical comparability exercise was also carried out for Process B (b) (4) and Process B (b) (4). In study MDX010-20, of the 511 patients who received ipilimumab, 463 (90.6%) patients received product supplied from Process B (b) (4), 42 (8.2%) patients received product supplied from Process B (b) (4), and 6 (1.2%) patients received product supplied from (b) (4). From a CMC perspective, the two manufacturing processes were found to be comparable (see CMC review for further details).

To evaluate the PK of ipilimumab produced by Process B (b) (4) and Process B (b) (4), a cross-study comparison was performed in 29 patients who received 10 mg/kg dose of Process B (b) (4) (n=13) in MDX010-15 or Process B (b) (4) in CA184007 (n=12) and CA184008 (n=4). PK data from CA184007 and CA184008 were combined (n=16) for this assessment. The PK parameters for (b) (4) were summarized (Table 17) but no comparative statistical analysis was performed.

Table 17. Summary of PK Parameters of Process (b) (4) and Process B (b) (4) for Ipilimumab in Melanoma Patients

Study[a]	Process	Dose[b]	Sample size (n)	Mean (CV%) PK Parameters[c]					
				C_{max} (μg/mL)	T_{max} (hr) (range)	AUC_{0-21d} (μg·hr/mL)	$t_{1/2}$ (day)	CL (mL/hr)	Vss (L)
MDX010-15	(b) (4)	#1	7	300 (24%)	2 (1.5-7)	37706 (24%)	15 (8.3)	15.7 (6.2)	6.7 (2.3)
MDX010-15	(b) (4)	#4	13	441 (36%)	2.5 (1.3-48)	55433 (35%)	15 (9.4)	N/A[d]	N/A[d]
CA184007 & CA184008	(b) (4)	#1	15	205 (19%)	1.6 (1.5-1.8)	34176 (19%)	9.5 (3.2)	18.3 (5.9)	5.8 (1.7)
CA184007 & CA184008	(b) (4)	#3	16	223 (24%)	1.6 (1.5-24)	48924 (24%)	15.6 (6.9)	N/A[d]	N/A[d]

[a]Ipilimumab concentrations were measured in plasma in study MDX010-15 and in serum in studies CA184007 and CA184008
[b]All patients received a dose of 10 mg/kg ipilimumab
[c]Arithmetic means (SD) except Cmax and AUC which are expressed as geometric means (CV%), and Tmax as median (range)
[d]CL and Vs in the third/fourth dose are not calculated (not available, N/A)

$AUC_{(0-21d)}$, T-half, CL, and Vss values are similar for the 2 drug substance manufacturing processes. Cmax appears higher, and half-life longer after single dose in MDX010-15. The sponsor states that this was likely due to more extensive PK samplings around the Tmax in MDX010-15, and longer PK sampling beyond 21 days which allowed to fully characterize the half-life in MDX010-15. The variability (CV%) in the PK parameter estimates for the Process B (b) (4) appears slightly higher than Process B (b) (4). This may be due to the different ELISA methods used in the analysis of study samples, and differences in study conduct. However, these changes should have a minimal impact on safety and efficacy.

2.6 Analytical

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Two different bioanalytical methods were used to determine the concentration of ipilimumab (human serum ELISA and human plasma STM1693). In the phase II trials sponsored by BMS (CA184004, CA184007, CA184008, and CA184022), ipilimumab concentrations were measured using an ELISA method. An earlier ELISA method, STM1693, was used in the Medarex sponsored trials, MDX010-08 and MDX010-15.

2.6.2 Which metabolites have been selected for analysis and why?

Ipilimumab is a biological product which is degraded into amino acids that are then recycled into other proteins. No metabolites of ipilimumab could be measured, thus only the parent compound was analyzed.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total ipilimumab concentrations were measured in all cases.

2.6.4 What bioanalytical methods are used to assess therapeutic protein concentrations?

Two different analytical methods were used to determined ipilimumab concentrations. The first method, STM1693, was used for Medarex trails (MDX010-08, MDX010-15) and assessed ipilimumab concentrations in human plasma. The second method, BMS human serum ELISA, was used for BMS trials and assessed ipilimumab concentrations in human serum. Each method has been described separately.

Medarex Method- STM1693
Medarex Method STM1693 was not validated according to current industry standards. (b) (4)

(b) (4)

of .

Between years 2000 and 2005, STM1693 went through a number of method modifications: Versions 1 through 5. These modifications involved analyzing standards (b) (4) Two validation reports were provided, 4656 (dated July 15, 2004) and 4657 (dated August 23, 2005). Results from the more recent validation report, 4657, have been reviewed.

BMS Human Serum ELISA Method
A second ELISA method was developed based on STM1693 and was used to support four BMS sponsored clinical trials (CA148004, CA184007, CA184008, and CA184022). (b) (4) . In general, the BMS human

serum ELISA method used the same basic reagents and format as STM1693, but was validated according to current industry standards.

The ELISA method employed (b) (4)

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

Medarex Method- STM1693

(b) (4)

BMS Human Serum ELISA Method

(b) (4)

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

Medarex Method- STM1693
STM1693 was shown to be precise, accurate, and linear with a working range of 0.001 μg/mL (LLOQ) to 0.1 μg/mL (ULOQ) ipilimumab.

BMS Human Serum ELISA Method
Forty-one out of forty-eight of the QC samples at the LLOQ of 0.4 μg/mL had their calculated concentrations within ± 20% of the nominal value. All dilution QC samples at a (b) (4) dilution had calculated concentrations within ± 20% of their nominal values.

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

Medarex Method- STM1693
The mean recovery of QC samples was within the acceptance criteria of 25% of nominal since intra-assay variability ranged from 1.5-20.6% CV. Inter-assay precision was

calculated from all individual QC sample results from all plates over all days (n=108) and ranged from 4.2-18% CV.

A mean % recovery, minimum % recovery, and maximum % recovery were calculated for each QC sample on each plate (n=12). The overall % recovery over all QC samples ranged from 53-155% and the mean overall accuracy was 96%, 80%, 86% for the (b) (4) QC samples, respectively. There were QC samples that did not meet the acceptance criteria for accuracy (≤ 25% of nominal value) but these values were included in the analysis to summarize and present the true accuracy and precision of the assay.

BMS Human Serum ELISA Method
The inter-assay precision was within 6.8% CV and the intra-assay precision was within 5.2% CV. The assay accuracy was within ± 9.0% of their nominal values. At the LLOQ of 0.4 μg/mL, the intra-assay precision was 9.4% CV and inter-assay precision was 10.5% CV; the assay accuracy was within ± 9.9% of the nominal value. For the dilution QC at 500 μg/mL, the intra-assay precision was 4.5% CV and inter-assay precision was 3.9% CV; the assay accuracy was within ± 9.5% of the nominal value.

The intra-assay and inter-assay precision based on the QC samples accompanying individual runs across the four Phase II studies were within ± 18.9% and the assay accuracy was within ± 7.1% of their nominal concentrations. The coefficient of determination (r^2) values for the standard curves from all runs was = 0.999. The individual parameters for assessment of method performance from each study are presented in Table 18.

Table 18. BMS Human Serum ELISA Method Performance across Phase II Clinical Trials

Study No.	# of Runs	Accuracy	Precision		Coefficient of Determination
			Intra-assay	Inter-assay	
CA184004	(b) (4)	± 6.7 [a]	≤ 18.9% [a]	≤ 13.3%	0.9994
CA184007		± 5.2	≤ 14.3% [b]	≤ 10.1%	0.9994
CA184008		± 7.1	≤ 14.3%	≤ 12.2%	0.9995
CA184022		± 6.6	≤ 14.3%	≤ 8.5%	0.9993

[a] Excludes two outlier values from run (b) (4) using Dixon (rank) outlier test. With these removed, intra-assay precision met the pre-specified acceptance criteria.
[b] Excludes an outlier value from run (b) (4). With this removed, intra-assay precision met the pre-specified acceptance criteria.

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

Medarex Method- STM1693
Robustness experiments showed that ipilimumab can be recovered from test samples stored at 2-8°C for (b) (4) and samples can be freeze-thawed (b) (4) additional cycles following initial analysis without detrimental effect on ipilimumab detection.

BMS Human Serum ELISA Method
BMS-734016 is stable at room temperature for (b) (4) and (b) (4) freeze/thaw cycles. Short-term stability of ipilimumab in human serum was evaluated at -70°C or below.

Ipilimumab was stable for up to [redacted] (b) (4) at -70°C or below. Ipilimumab was stable in human whole blood at room temperature and on ice for at least [redacted] (b) (4). The concentration of ipilimumab can be accurately determined following serial dilution of the sample.

2.6.4.5 What is the QC sample plan?

Medarex Method- STM1693

[redacted] (b) (4)

BMS Human Serum ELISA Method

[redacted] (b) (4)

2.6.6 *What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.*

Seven clinical studies in patients with advanced melanoma included immunogenicity analysis. Three of these studies were sponsored by Medarex and used three different human plasma ECL immunogenicity assays (studies MDX010-08, -15, and -20). The remaining four studies were sponsored by BMS and used a human serum ECL immunogenicity assay (studies CA184004, CA184007, CA184008, and CA184022). The bioanalytical methods and assay performance are described in detail below.

Medarex Method- STM1699

Assay STM1699, a sandwich ELISA, was employed in study MDX010-08. In this assay, [redacted] (b) (4)

Medarex Method- STM3022

Assay STM3022, a bridge ELISA method, was employed in study MDX010-15. [redacted] (b) (4)

Human Serum ECL Immunogenicity Assay

An ECL (electrochemiluminescent) immunoassay (human serum ECL immunogenicity assay) was used in four phase II studies (CA184004, CA184007, CA184008, and CA184022). This assay has enhanced sensitivity and drug tolerance compared to the other two ELISA methods used. Detection of APAs was achieved by [redacted] (b) (4)

(b) (4)

(b) (4)

Human Plasma ECL Immunogenicity Assay
The fourth immunogenicity assay was used to support study MDX010-20 and utilized the same format, reagents, and positive controls as the human serum ECL assay, but was validated for use in human heparinized plasma and is thus referred to as the human plasma ECL assay. The screening cut-point for this assay was determined using plasma samples from normal healthy volunteers, whereas cut-point determination in the human serum ECL assay was made using serum samples from melanoma ipilimumab-naïve patients.

2.6.6.1 What is the performance of the binding assay(s)?

Medarex Method- STM1699
Assay STM1699, a sandwich ELISA, was employed in study MDX010-08. Since MDX010-08 used only ipilimumab manufactured by Process A, which is not the to-be marketed process, details of this trial have not been included in this review.

Medarex Method- STM3022
Assay STM3022, a bridge ELISA method, was employed in study MDX010-15. (b) (4)

The CV for both intra- and inter-assay precision was below the pre-set acceptance criteria of 35%. The test for intra-assay precision had a maximum CV of 23% and 9% for inter-assay precision. The stability analyses indicated that samples are stable when stored at - (b) (4). Additionally, samples were considered to be stable for up to (b) (4) (3 and 6 month stability data was not available).

Human Serum ECL Immunogenicity Assay

The human serum ECL immunogenicity assay was used in four BMS-sponsored phase II studies. (b) (4)

(b) (4)

Study CA184022 was the only study in which immunogenicity was assessed at 0.3, 3, and 10 mg/kg of ipilimumab. Trough samples were collected at Weeks 7 and 10. Table 19 shows the number (%) of patients with APA assessment and concurrent ipilimumab serum trough concentrations <5, 5-10, and >10 μg/mL. The distribution of the trough concentrations by dose group indicates that a majority of the patients in the 0.3 mg/kg dose had ipilimumab serum trough concentrations <5 μg/mL, whereas the majority of patients treated at 3 and 10 mg/kg had ipilimumab serum trough concentrations >10 μg/mL.

Table 19. Number (%) of Patients with Concurrent Ipilimumab Serum Trough Concentrations and APA Assessments in Study CA184022

Concentration Category	Number (%) of Patients	
(μg/mL)	Week 7 n = 126	Week 10 n = 98
< 5	40 (31.7)	30 (30.6)
5 – 10	11 (8.7)	6 (6.1)
> 10	75 (59.5)	62 (63.3)

Patients treated at the lowest dose (0.3 mg/kg) of ipilimumab had the highest rate of APA formation (Table 14). This indicates that concurrent ipilimumab levels in serum may be interfering with the ability of the assay to detect ADAs against ipilimumab.

Human Plasma ECL Immunogenicity Assay

The human plasma ECL immunogenicity assay was used in study MDX010-20. (b) (4)

(b) (4) .

PC samples were stable at room temperature for up to (b) (4) prior to analysis with no significant change in response and were stable for up to (b) (4) freeze/thaw cycles. The assay cutpoint was calculated to be (b) (4) response units and the mean cutpoint factor was determined to be (b) (4). The assay sensitivity was found to be (b) (4). Since MDX-010 may interfere with the ability to detect anti-MDX-010 antibodies, interference was tested. The assay demonstrated the ability to detect a positive immunogenicity response in the presence of up to (b) (4) MDX-010. The intra-assay and inter-assay precision were **≤5.01% CV and ≤28.6% CV for the** negative and positive controls, respectively. The assay was considered to be robust since the variation between the analyses for the NC and PC were 13.4% and 7.9%, respectively.

2.6.6.2 What is the performance of the neutralizing assay(s)?

Samples that were confirmed positive and specific for anti-ipilimumab antibody with the previously described ECL assays were further tested for the presence of neutralizing antibody with a separate competition ECL immunoassay. Detection of neutralizing anti-ipilimumab antibodies in this assay was based on the ability of anti-ipilimumab antibodies to prevent the binding of ipilimumab to the CTLA-4 receptor. There were no clinical samples that were positive for binding anti-product antibodies tested positive using this neutralizing assay.

The ECL assay was validated and the lowest concentration of anti-ipilimumab neutralizing antibody that was reproducibly detected above the assay cut-point of (b) (4) was (b) (4) and was selected as the relative assay detection limit. The intra-assay precision (%CV) was determined to be 13.9% for the positive QC and 15.2% for the negative QC. The inter-plate precision was 14.8% for the positive QC and 16.4% for the negative QC. In an assessment of product interference, (b) (4) of anti-ipilimumab antibodies can be detected above the cut-point in the presence of (b) (4) ipilimumab. Samples were found to be stable for (b) (4) freeze/thaw cycles, at room temperature for up to (b) (4) and up to (b) (4) prior to analysis at 2-8°C.

3. DETALIED LABELING RECOMMENDATIONS

The following is the sponsor's original proposed language for the clinical pharmacology related sections of the label. (June 25, 2010)

(b) (4)

[redacted]

(b) (4)

The following is the FDA recommended language for clinical pharmacology related sections of the label. (February 11, 2011)

6.2 Immunogenicity

In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralizing antibodies against ipilimumab detected.

Because trough levels of ipilimumab interfere with the ECL assay results, a subset analysis was performed. In this analysis it was observed that 6.9% of 58 evaluable patients, who were treated with 0.3 mg/kg dose, tested positive for binding antibodies against ipilimumab.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to YERVOY with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted with YERVOY.

8.6 Renal Impairment

No formal studies of YERVOY in patients with renal impairment have been conducted *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No formal studies of YERVOY in patients with hepatic impairment have been conducted *[see Clinical Pharmacology (12.3)]*.

(b) (4)

12.3 Pharmacokinetics

The pharmacokinetics of ipilimumab was studied in 499 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg administered once every 3 weeks for four doses. Peak concentration (C_{max}), trough concentrations (C_{min}), and area under the curve (AUC) of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of YERVOY administered every 3 weeks, ipilimumab clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index of 1.5-fold or less. Ipilimumab steady-state concentration was reached by the third dose. The following mean (percent coefficient of variation) parameters were generated through population pharmacokinetic analysis: terminal half-life of 14.7 days (30.1%); systemic clearance (CL) of 15.3 mL/h (38.5%); and volume of distribution at steady-state (Vss) of 7.21 L (10.5%). The mean (±SD) ipilimumab Cmin achieved at steady-state with the 3 mg/kg regimen was 21.8 mcg/mL (±11.2).

Specific Populations: Cross-study analyses were performed on data from patients with a variety of conditions, including 420 patients with melanoma who received single or multiple infusions of YERVOY at doses of 0.3, 3.0, or 10 mg/kg. The effects of various covariates on ipilimumab pharmacokinetics were assessed in population pharmacokinetic analyses.

Ipilimumab CL increased with increasing body weight; however, no dose adjustment of YERVOY is required for body weight after administration on a mg/kg basis. The following factors had no clinically meaningful effect on the CL of ipilimumab: age

(range 26 to 86 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, positive anti-ipilimumab antibody status, prior use of systemic anticancer therapy, or baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined as there were insufficient numbers of patients in non-Caucasian ethnic groups.

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ipilimumab pharmacokinetics in patients with calculated creatinine clearance values of 29 mL/min or greater.

Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels did not have a clinically important effect on ipilimumab pharmacokinetics in patients with various degrees of hepatic impairment.

The following is the sponsor's response to the FDA recommended language for clinical pharmacology related sections of the label (February 18, 2011). Only sections with changes have been included below.

6.2 Immunogenicity

In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralizing antibodies against ipilimumab detected.

Because trough levels of ipilimumab interfere with the ECL assay results, a subset analysis was performed. In this analysis it was observed that 6.9% of 58 evaluable patients, who were treated with 0.3 mg/kg dose, tested positive for binding antibodies against ipilimumab.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to YERVOY with the incidences of antibodies to other products may be misleading.

8.7 Hepatic Impairment

No formal studies of YERVOY in patients with hepatic impairment have been conducted *[see Clinical Pharmacology (12.3)]*. (b) (4)

4. APPENDICIES

Appendix 4.1

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	125377
Submission Date	6/25/10
Applicant Name	Bristol-Myers Squibb
Generic Name	Ipilimumab
Proposed Indication	Advanced Melanoma
Primary Reviewer	Christian Grimstein, Ph.D.
Secondary Reviewer	Issam Zineh, Pharm.D., MPH

1 Background

Ipilimumab is a fully human monoclonal immunoglobulin (IgG1κ) specific for human cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T cells. The proposed mechanism of action for ipilimumab is T-cell potentiation through interference of the interaction of CTLA-4 with B7 molecules on antigen presenting cells, with subsequent blockade of the immune system inhibitory function of CTLA-4. T-cell potentiation is expected to result in active immune response to cancer cells. The applicant included analysis of several single nucleotide polymorphisms (SNPs) in immune-related genes with respect to safety from four Phase 2 studies. DNA was not collected in the Phase 3 study. No pharmacogenetic labeling language was proposed by the applicant. On 30 July 2010, the agency requested individual genotype data for subjects who provided DNA samples in the Phase 2 studies to perform independent pharmacogenetic safety analyses. Data were received on 10 Sept 2010.

This review evaluates if variants in immune-related genes are associated with worst grade (≥2) immune-related adverse events (irAE) including hepatobiliary, gastrointestinal, and dermatological manifestations.

2 Submission Contents Related to Genomics

Phase 2 studies with pharmacogenomic samples (Table 1) and a list of the sponsor's candidate gene variants (Table 2) are shown below. The sponsor did not describe specific criteria for candidate selection.

Table 1: Ipilimumab phase 2 studies with DNA collection as part of the ipilimumab development program

Study	Objective	Subjects (w/DNA for SNP analysis)	Design	Ipilimumab Dose	Endpoints	Genotyping (# polymorphisms)	Data Submitted
CA184004	Predictive Biomarker, Efficacy, Safety	N=82 (76; 93%)	R, DB, MC	3mg/kg; 10mg/kg	Safety, Efficacy, PD	22	Yes
CA184007	Safety, Efficacy	N=115 (94; 82%)	R, DB, PC	10mg/kg	Safety	18	Yes
CA184008	Efficacy, Safety	N=155 (37 24%)	OL, SA, MC	10mg/kg	Efficacy	18	Yes
CA184022	Efficacy, Safety	N=214 (18; 8%)	R, DB, MC	0.3mg/kg; 3mg/kg; 10mg/kg	Efficacy	18	Yes

DB, double-blind; MC, multi-center; OL, open-label; R, randomized; SA, single arm

Table 2: Candidate genes/variants assessed in pharmacogenetic studies

Gene	Polymorphism
BTNL2	rs2076530
CCR5	Δ32, rs28897671
CD86	rs1129055, rs2681417
CTLA4	rs11571317, rs1863800, rs231775, rs3087243, rs4553808
IFNAR1	rs2257167
IFNAR2	rs7279064
INFG	rs2069705, rs2430561
IL23R	rs1004819, rs11209026, rs2201841, rs7517847
NOD2	rs2066844, rs2066845, rs5743293
PTPN22	rs2476601

3 Key Questions and Summary of Findings

3.1 Are variations in immune-related genes associated with immune-related adverse events (irAE) of ipilimumab therapy?

Sponsor analysis:

The sponsor evaluated 22 polymorphisms in immune related genes for associations with increased risk of irAEs in four phase 2 studies. Immune-related adverse events were defined in a generally consistent way as adverse events causally related to drug exposure and consistent with an immune-mediated adverse event. Criteria by which causality was established were not described. The majority of patients in these studies received ipilimumab 10 mg/kg (Table 3).

Table 3: Number of patients receiving different ipilimumab doses among studies

Study	0.3 mg/kg	3 mg/kg	10 mg/kg
CA184004	0	40	42
CA184007	0	0	115
CA184008	0	0	155
CA184022	72	71	71
Total	72	111	383

The odds of worst grade irAE ≥ 2 by genotype groups were calculated for each irAE class (skin, hepatobiliary and gastrointestinal). The sponsor combined data from studies CA184007, CA184008 and CA 184022 for analyses. The sponsor did not explain why study CA184004 was analyzed separately. Also, in study CA184004 data from patients in two dosing groups (3mg/kg and 10mg/kg) were combined presumably to increase power, whereas in the other studies associations were tested only in the 10 mg/kg group. irAEs seem to be associated with higher doses of ipilimumab according to the pharmacometrics review (Appendix 4.2).

The sponsor calculated odds ratios (OR) comparing heterozygote minor allele (genotype 1/2) vs. wildtype (genotype 1/1), and homozygous minor allele (genotype 2/2) vs. 1/1 using appropriate methods. The sponsor concluded no specific polymorphism was convincingly associated with increased risk of specific irAEs. However, based on combined analysis of patients receiving 10 mg/kg ipilimumab in studies CA184007, CA184008 and CA184022, the sponsor showed minor allele heterozygotes for rs2681417 in the CD86 gene had almost 4-fold higher risk of GI irAEs compared with wild-type homozygotes (OR (95% CI): 3.95 (1.32, 11.83); p=0.011) This observation did not replicate in the CA184004 study, potentially due to limited number of heterozygotes (5/76). There were no homozygous minor allele carriers for rs2681417 in any of the four studies.

Potential associations between presence of HLA-alleles and irAEs in the Phase 2 studies were also evaluated by the sponsor. Associations with HLA-A2 *201 were tested in study CA184004 (N=76), CA184007 (N=87), CA184008 (N=148), and CA184022 (N=205). Other common HLA alleles (present in ≥10% of patients) were also assessed. Associations with common HLA-A alleles were tested in study CA184004 and CA184007; common HLA-B alleles were assessed in study CA184007. According to the sponsor, no associations between irAEs and presence of allele A2*201 or other HLA-A (*01,*02,*03,*11,*24) or HLA-B alleles (*07,*08,*27,*35,*40,*44,*57) were found.

Reviewer analysis:
The sponsor provided individual patient data and irAE categorized as CTCAE 0, 1 and 2+ (worst grade). 225 patients were genotyped in all dose groups and 171 were genotyped in the 10mg/kg dose group. Alternatively to the sponsor's approach, the reviewer 1) combined data from all four phase 2 studies; and 2) analyzed associations with overall irAE risk in addition to specific types of irAEs. Chi-square-test was performed to test for association between genotype and irAEs. Logistic regression

was used to estimate OR. Given that occurrence of irAE seems to be associated with higher doses of ipilimumab, the highest dose given (10 mg/kg) was analyzed separately.

Associations between genotype and irAEs were assessed based on a two-step analysis. In step 1, we assumed a shared mechanism for AEs across tissues, and tested for genetic associations with overall irAE risk at the $p<0.1$ level. If a significant association was observed, associations with specific types of irAEs were evaluated. In step 2, we assumed an independent mechanism of AEs across tissues, and genetic associations with specific types of irAEs assessed at the $p<0.05$ level. Findings were considered potentially informative if: 1) ORs were directionally similar for variant carrier groups, or a gene-dose effect was observed (e.g., increasing protection [or risk] with increasing numbers of variant alleles); 2) associations were consistent across different classes of irAEs.

No variants were associated with overall irAE based on separate analyses considering 1) all doses of ipilimumab and 2) 10mg/kg ipilimumab. Analyses of specific types of irAEs showed replicated the sponsor's findings regarding the CD86 variant and GI irAE risk (Table 4). However, the exact influence of this genetic variant could not be definitively established because of the lack of patients carrying two copies of the minor allele. Of note, CD86 is expressed on antigen presenting cells and provides co-stimulatory signals necessary for T-cell activation and survival and is the ligand for CTLA-4. rs2681417 results in an exon missense mutation (Val>Ile) in CD86 which may provide functional support for the association Analyses did not reveal robust findings for other variants that initially showed a statistical association (Table 4). The findings were inconclusive due to 1) internal inconsistency in the association among specific genotypes (IFNAR2); 2) different direction of effect in minor allele heterozygotes compared to minor allele homozygotes (PTPN22, BTNL2, IL23R); and/or small numbers of minor allele homozygotes (CD86, PTPN22).

Table 4: Pharmacogenetic associations with specific irAEs (10 mg/kg dose)

Gene	Polymorphism	irAE	% data availability (#patients, DNA collected = 171 =100%)	Wald p-value (gene effect)	Within-genotype events (1/1;1/2;2/2; no AE/ worst grade AE)	OR 1/2 vs. 1/1	95% CI	OR 2/2 vs. 1/1	95% CI	OR variant vs. wild type	95% CI	Wald p-value (genotype effect)
CD86	rs2681417	GIAE	99%	0.02	109/43; 8/10; 0/0	3.7	1.2, 8.6	n/a	n/a	3.2	1.2, 8.6	0.02
PTPN22	rs2476601	GIAE	100%	0.14	102/51; 15/1; 1/1	0.13	0.02, 1.0	2	0.12, 33	0.25	0.06, 1.1	0.07
BTNL2	rs2076530	HAE	99%	0.24	52/2;76/11; 29/0	3.8	0.80,17.7	n/a	n/a	2.7	0.58, 12.7	0.20
IFNAR2	rs2257167	HAE	95%	0.01	77/6; 64/2; 9/4	0.40	0.08, 2.1	5.7	1.4, 24	1.1	0.33, 3.4	0.92
IFNAR2	rs2257167	SKAE	95%	0.93	59/24; 45/21; 13/0	1.2	0.57, 2.3	n/a	n/a	0.89	0.44, 1.7	0.74
IL23R	rs7517847	SKAE	76%	0.03	28/10; 42/26; 23/1	1.7	0.73,4.2	0.12	0.01,1.0	1.2	0.50, 2.7	0.73

HAE: hepatobiliary adverse events; GIAE: gastrointestinal adverse events; SKAE: skin adverse events; OR: odds ratio

4 Summary and Conclusions

DNA was collected in four phase 2 studies and associations between immune-related gene variants and irAEs were assessed. Consistent with the sponsor's analyses, a missense mutation in CD86 (rs2681417) was associated with increased risk of GI irAEs in patients receiving ipilimumab. Other associations with skin, hepatobiliary, and GI events were seen. However, several limitations preclude definitive conclusions regarding the strength of the associations, including 1) lack of uniform DNA sample acquisition from analyzed phase 2 studies; 2) no DNA collection in the pivotal phase 3 study; 3) lack of justification for candidate gene/SNP selection; 4) limited numbers of patients treated with doses other than 10 mg/kg; and 5) questionable irAE definition. No definitive label modifications are warranted at this time.

5 Recommendations

The Office of Clinical Pharmacology Genomics Group has reviewed studies CA184004, CA184007, CA184008 and CA184022 as part of the current NDA submission for ipilimumab. The following recommendations should be conveyed to the sponsor:

1. Given the serious nature of ipilimumab irAEs, the genetic determinants of irAEs should be elucidated. Given the uncertain mechanism of these irAEs, a hypothesis-free approach (e.g. genomewide association analyses of phase 2 samples) is recommended.
2. To increase power and provide replication cohorts, all subsequent ipilimumab studies should include a high DNA sample acquisition rate and objectively-defined and adjudicated irAE cases.
3. Conduct pharmacogenetic analyses across different ipilimumab doses in subsequent studies.

5.1 Label Recommendations

N/A

Christian Grimstein, Ph.D.
Reviewer, Genomics Group, OCP

Issam Zineh, Pharm.D., M.P.H.
Associate Director, Genomics Group, OCP

Appendix 4.2

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	BLA 125377
Submission Number (Date)	June 25, 2010
Compound (Dosing regimen)	Ipilimumab ((b) (4) 3 mg/kg IV over a 90-minute period every 3 week for a total of 4 doses. (b) (4))
Clinical Division	DBOP
Primary PM Reviewer	Anshu Marathe, Ph.D.
Secondary PM Reviewer	Christine Garnett, Pharm.D.

1 Summary of Findings

1.1 Key Review Questions

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

1.1.1 Is there evidence of exposure-response for effectiveness?

Yes, there is evidence of exposure-response relationship for overall survival in patients with unresectable stage III or IV melanoma in phase 2 studies.

Pooled Data: Exposure-efficacy analysis was conducted using pooled data from 498 patients from studies CA184-004, -007, -008 and -022 because pharmacokinetic data was not collected in the phase 3 trial (MDX010-20). These studies utilized doses of 0.3, 3 and 10 mg/kg and sparse pharmacokinetic data was collected. A brief description of the studies is provided in Table 9 and Appendix B. Predicted steady state trough concentrations (C_{min}) of ipilimumab from the sponsor's final population pharmacokinetic (PopPK) model were used for the analysis. Steady state C_{min} is an appropriate measure of exposure because upon multiple dose administration, steady state is reached by the third dose in 9 weeks which is lower than the median survival observed in these studies.

A time-to-event analysis for overall survival was performed with patients stratified into four groups according to their Cmin (0.61 – 19.4, 19.5 – 43.7, 44 – 65.3, >65.3 – 155.3 μg/ml) and the results are shown in Figure 1. A clear separation between the survival curves of patients in different Cmin-quartile groups is observed, thus indicating exposure–response relationship. An increase in survival is observed with increasing exposures. Similar results were obtained using observed trough concentrations after the second dose, as the stratification factor in the Kaplan-Meier analysis (Figure 23). Table 1 shows the median survival in different Cmin-quartile groups. The difference in median survival between the quartiles is not only due to low drug concentrations, but also due to confounding risk factors in these groups (described below).

A stepwise Cox proportional hazard model also identified Cmin as a significant independent predictor of overall survival. Baseline level of lactate dehydrogenase (LDH) and ECOG status (0 vs. 1) were also identified as risk factors for overall survival. Increasing levels of baseline LDH increased hazard. The hazard was lower in patients with ECOG status of 0 compared to patients with an ECOG status of 1. This analysis excluded two patients who had an ECOG status of 2. Table 2 shows the distribution of risk factors (LDH, ECOG status) in the C_{min}-quartile groups. The highest quartile had patient with lower levels of baseline LDH compared to the lower quartiles. The proportion of patients with ECOG status of 1 was lower in the highest quartile compared to the lower quartiles. These factors along with higher drug concentrations in the highest quartile account for an increased median survival. A Cox proportional hazard model was used for exposure-response analysis because it accounts for imbalances of such risk factors. The parameters from the Cox model are shown in Table 3. The model predicted that, for a 10 μg/ml increase in exposure, the hazard would decrease by 10%. The p-value was less than 0.0001 and the confidence interval of the hazard ratio excluded 1. This is likely to improve survival significantly because the median drug concentrations ranged from 8.5 μg/ml to 82 μg/ml from the lowest to the highest quartile. Similar results were obtained using observed trough concentrations after the second dose instead of model predicted C_{min} (see Table 15 in section 3.3.2 for details).

A sub-group analysis was performed by excluding study CA184-007 and patients who were administered 0.3 mg/kg of ipilimumab. Study 007 was removed because at the studied dose of 10 mg/kg of ipilimumab, the median survival was 19.3 months which was higher than the median survival observed for ipilimumab in other phase 2 studies (Table 22). Thus, any potential bias due to study 007 was removed. The 0.3 mg/kg dose group was removed because we wanted to confirm that the exposure-response relationship is not biased by the low dose group with very low exposures. Similar to the results obtained using all subjects, C_{min} was found to be significant predictor of overall survival and the point estimate (CI) for the hazard ratio were 0.9 (0.86 – 0.95) (see Table 16 in section 3.3.2 for details).

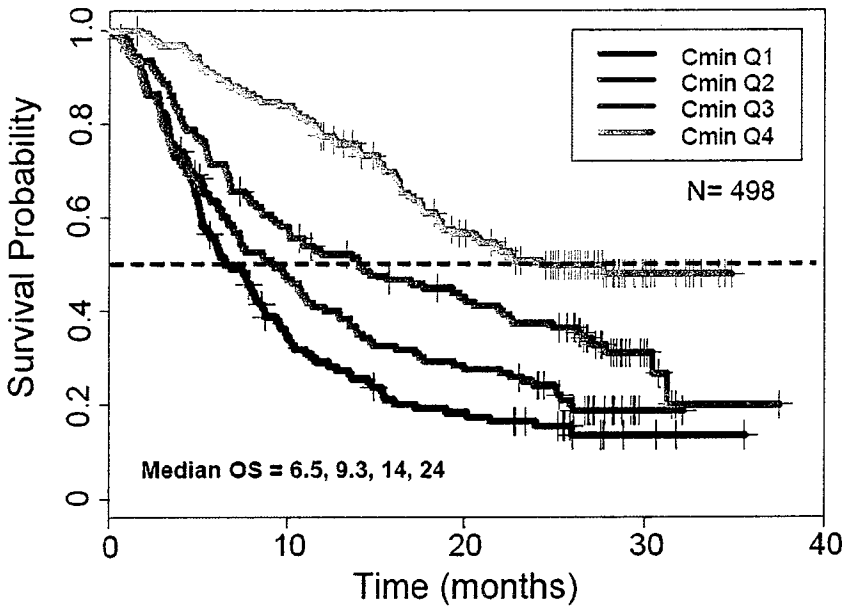

Figure 1: The exposure-response relationship for Ipilimumab in pooled Phase 2 studies. Overall survival by steady state trough concentrations (C_{min}) of ipilimumab. Data were pooled from studies CA184-004, -007, -008 and -022.

Table 1: Median survival for patients in different Cmin groups in phase 2 studies, vaccine and ipilimumab arms in phase 3 studies

Group	Median Survival (months)	95% CI
Cmin Q1 (N=125)	6.51	5.19 – 8.67
Cmin Q2(N=124)	9.26	6.87 – 12.0
Cmin Q3 (N=124)	14.0	9.56 – 22.1
Cmin Q4 (N=125)	24.3	18.7 – NA
gp100 (N=136) *	6.44	5.49 – 8.71
Ipilimumab (3 mg/kg) (N=137) *	10.1	8.02 –13.8

Source: Table 4.4.1A in sponsor's clinical overview

Table 2: Distribution of risk factors (LDH, ECOG status) in different Cmin groups

Group	Median Cmin (µg/ml)	Median LDH (IU/L)	Number of patients with ECOG status = 0 (%)	Number of patients with ECOG status = 1 (%)
Cmin Q1* (N=125)	8.52	219	65 (52 %)	59 (47.2 %)
Cmin Q2 (N=124)	31.6	241	79 (63.7 %)	45 (36.3 %)
Cmin Q3* (N=124)	54.5	219	83 (66.9 %)	40 (32.3 %)
Cmin Q4 (N=125)	82.1	180	95 (76 %)	30 (24 %)

* Cmin Q1 and Cmin Q3 each had 1 patient with an ECOG status of 2

Table 3: Cox model parameter estimates

Predictor	Slope estimate	Std. error on estimate	P-value	Hazard ratio (HR)	95% HR confidence limits
C_{min} per 10 µg/ml	-0.103	0.019	<.0001	0.902	0.87 – 0.936
LDH per 100 IU/L	0.139	0.014	<.0001	1.15	1.12 – 1.18
ECOG (0 vs. 1)	-0.596	0.113	<.0001	0.551	0.441 – 0.688

Study CA184-022: An exposure-response analysis was conducted using data from 160 patients from study CA184-022 alone because this phase 2 study included all three dose levels of 0.3, 3 and 10 mg/kg. Consistent with other results, separation between the survival curves of patients in the lower and highest C_{min}-quartile groups was observed (Figure 25). C_{min} was found to be significant predictor of overall survival and the point estimate (CI) for the hazard ratio were 0.91 (0.85 – 0.98) (see Table 17 in section 3.3.2 for details). Cox proportional hazard model by dose group shows that slope of the exposure-response relationship is steeper for the lower doses compared to the higher dose (Table 18). This suggests that the exposure-response relationship is non-linear and there is likely to be a saturation phase where increasing exposures might not significantly increase survival. At the proposed dose of 3 mg/kg, the exposure-response relationship is significant which suggests that increasing exposures for these patients would result in increased survival.

Overall, an exposure-response relationship was identified for overall survival in study CA184-022 and pooled analysis of phase 2 studies that provides supportive evidence for the effectiveness of the drug.

1.1.2 Is the proposed dose of 3 mg/kg optimal?

The proposed dose of 3 mg/kg is acceptable because a 3.6 month survival benefit was observed in the ipilimumab arm at the 3 mg/kg dose compared to the control (gp100 vaccine) arm in the phase 3 study (MDX010-20). However, exposure-response analysis from Phase 2 studies suggests that increasing exposures might increase survival in advanced melanoma patients. The Kaplan-Meier plot for overall survival for patients in different C_{min}-quartile groups from phase 2 studies is shown in Figure 2. The survival curves for the vaccine (gp-100) and the ipilimumab arms from the phase 3 study (MDX010-20) are superimposed as reference. The lowest quartile (C_{min} Q1) is comparable with the vaccine (gp-100) arm. The second quartile (C_{min} Q2) is comparable with the ipilimumab arm at the proposed dose from the phase 3 study. Table 1 shows the median survival in the different arms. The lowest quartile has a median survival of 6.5 months which is comparable to the median survival of 6.4 months observed for the vaccine arm.

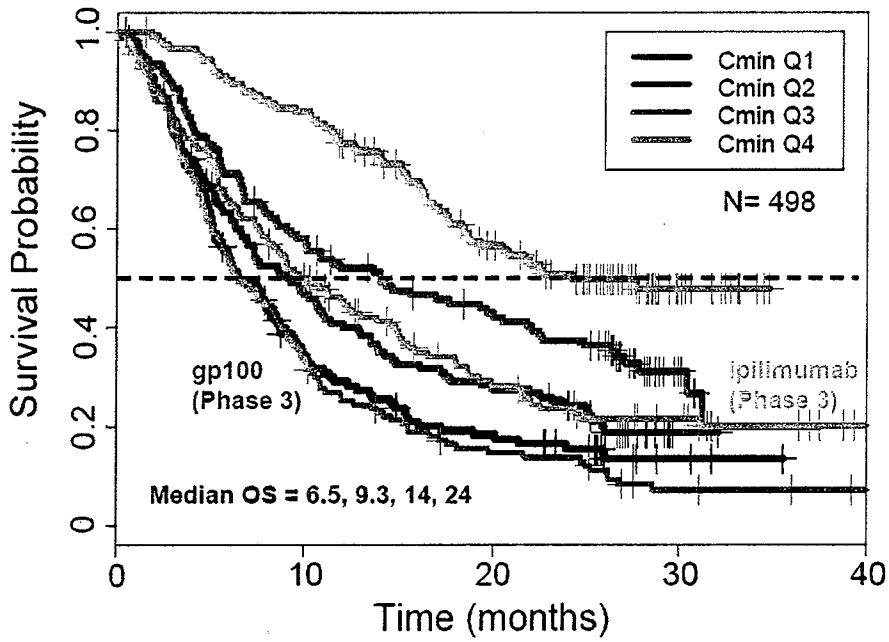

Figure 2: The exposure-response relationship for Ipilimumab in Phase 2 studies. Overall survival by steady state trough concentrations (C_{min}) of ipilimumab. Data were pooled from studies CA184-004, -007, -008 and -022. The Kaplan-Meier curves for the vaccine- gp100 (gray) and the ipilimumab (green) arms from Phase 3 (MDX010-20) study are superimposed as reference.

Exposure-response analysis shows that increasing exposures as observed in 3rd and 4th quartile (Cmin Q3 and Cmin Q4) will result in improved survival benefit. The distribution of patients with different doses of ipilimumab within each C_{min}-quartile are shown in Table 4. There were 124 and 125 subjects with PK data in the 3rd and 4th quartile respectively. Among these, 122 and 124 subjects belonged to the 10 mg/kg dose group in the two quartiles. Thus more than 98% of the patients in 3rd and 4th quartile with increased survival were at the 10 mg/kg dose.

PK data are also available from 98 patients at the 3 mg/kg dose. Among these, 41% of the patients were in the second quartile which is comparable to the Ipilimumab

arm in the phase 3 study. However, 56% of the patients were in the lowest quartile which was comparable to the vaccine arm. Thus, exposure-response suggests that from the perspective of effectiveness of the drug, 3 mg/kg might not be an optimal dose.

Table 4: Number of patients in different dose groups in the C_{min}-quartiles

Cmin group	0.3 mg/kg (%)	3 mg/kg (%)	10 mg/kg (%)
Cmin Q1	48 (100%)	55 (56%)	22 (6%)
Cmin Q2	0 (0%)	40 (41%)	84 (24%)
Cmin Q3	0 (0%)	2 (2%)	122 (35%)
Cmin Q4	0 (0%)	1 (1%)	124 (35%)
Total	48	98	352

The Kaplan-Meier plots by dose groups for patients in the phase 2 studies are shown in Figure 3. The median survival for patients in various dose groups is shown in Table 5. While the curves overlap at early time points, there is separation between the groups at later time points. There is a trend for increase in survival with increasing doses. This supports the overall conclusion from exposure-response analysis that 3 mg/kg might not be an optimal dose in terms of efficacy. Similar trend for increased survival with increasing doses was observed in study CA184-022 which included all three dose levels (Figure 28).

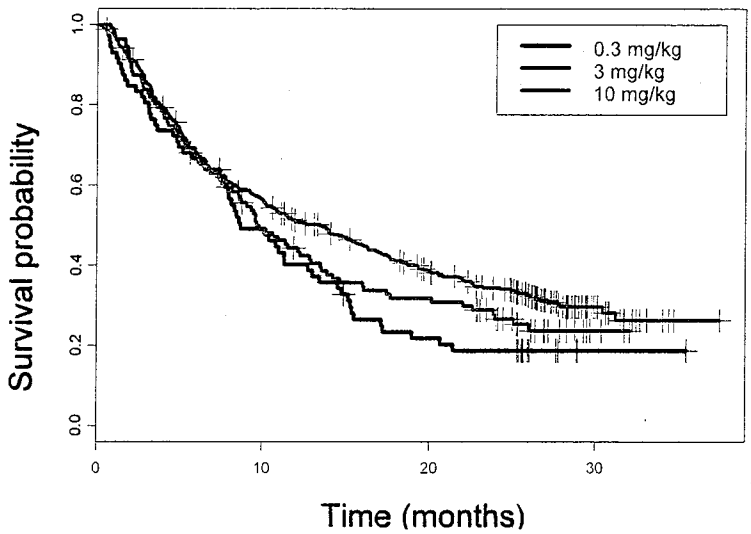

Figure 3: Overall survival by dose groups of ipilimumab. Data were pooled from studies CA184-004, -007, -008 and -022.

Table 5: Median survival for patients in different dose groups in phase 2 studies

Dose Group	Median Survival (months)	95% CI
0.3 mg/kg (N=72)	8.67	7.72 – 13.4
3 mg/kg (N=111)	9.66	8.18 – 13.5
10 mg/kg (N=383)	13.5	10.3 – 16.3

The dose response is not as pronounced as exposure-response because there is significant overlap in the steady-state trough concentration levels achieved within various dose groups. This is visualized by the box plots in Figure 4. As shown in Table 4, even at the high dose of 10 mg/kg, 30% of the patients had exposures in the lower two quartiles that were comparable to the exposures observed at the lower doses. This is because of significant unexplained variability in the PK of the drug. The inter-individual variability on clearance from the sponsor's population PK model was 34%.

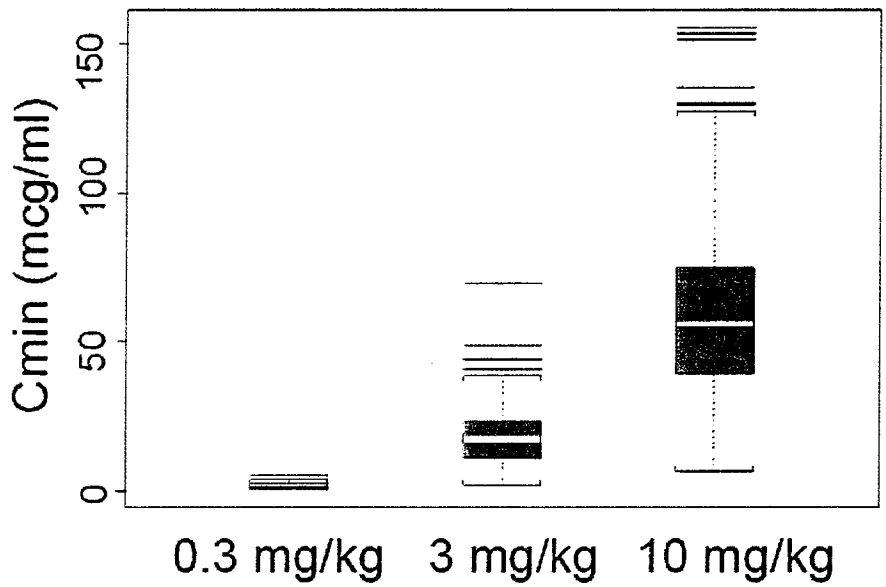

Figure 4: Steady state trough concentrations of ipilimumab by dose groups. Data were pooled from studies CA184-004, -007, -008 and -022.

Top line data from a well controlled ongoing trial CA184-024 also suggests that there would be improved survival benefit at higher dose of iplilimumab. In this study patients were treated with 10 mg/kg of ipilimumab in combination with dacarbazine. The active control arm comprised of patients who were treated with placebo in combination with dacarbazine. Increased survival benefit is observed in the ipilimumab treated group. This increased survival might be due to one or many factors such as the combined effect of ipilimumab and dacarbazine, a higher 10 mg/kg dose of ipilimumab or due to differences in patient population in this study compared to previous studies (chemotherapy naïve versus pretreated population).

Overall, exposure-response analysis from phase 2 studies along with top line data from CA184-024 suggests that from the perspective of effectiveness, 3 mg/kg might not be an optimal dose and increasing exposures might improve survival.

1.1.3 Is there evidence of exposure-response for immune-related adverse events?

Yes, there is a evidence for increased incidence of grade 2/3/4 and grade 3/4 immune-related adverse events (irAEs) with increasing exposures in patients with unresectable stage III or IV melanoma in phase 2 studies (Figure 5). Data were pooled from studies CA184-004, -007, -008 and -022. The irAEs involved gastro-intestinal tract (eg. diarrhea and colitis), skin (eg. pruritus and rash), endocrine glands (eg. hypothyroidism), liver (eg. transaminase elevations) and nervous system (eg. motor neuropathy). Logistic regression models were used by the sponsor to explore the relationship between steady state Cmin predicted by the population PK model and observed irAEs. Data from 498 patients were used in the analysis. The model predicts that at median Cmin for 3 and 10 mg/kg grade 2/3/4 irAEs were approximately 33% and 51%. Grade 3/4 irAEs were 13% and 24%. The model predictions are consistent with observed data where increase in irAEs was observed with increasing doses (Table 6).

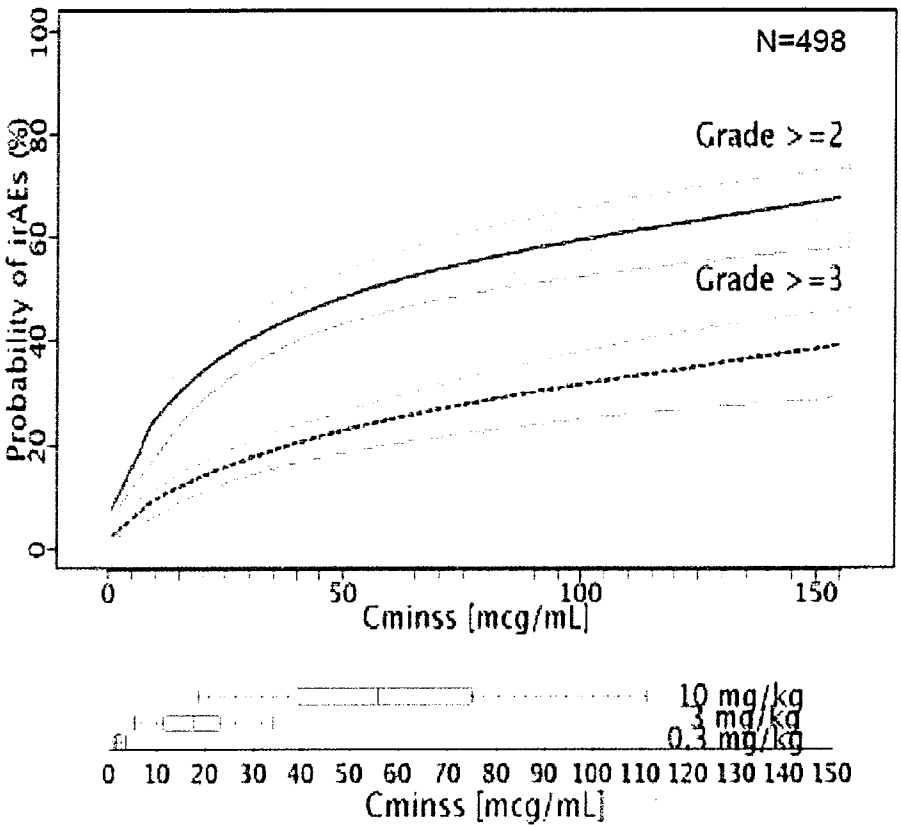

Figure 5: The probability of patients with immune-related adverse events in Phase 2 studies. The solid blue and dashed red lines represent the mean logistic regression prediction for Grade 2/3/4 and Grade 3/4 adverse events. The shaded area represents the 95% confidence interval of the prediction. The horizontal box plots represent the distributions of steady-state Cmin at each dose group. Data were pooled from studies CA184-004, -007, -008 and -022. Source: Sponsor's Figure 5.5.1.3 in the Population PK Report.

Table 6: Immune related AEs during the induction phase

	% of Subjects				
	Phase 3 Study (MDX010-20)			Phase 2 Studies	
	3 mg/kg Ipi (N = 131)	3 mg/kg Ipi + gp100 (N = 380)	gp100 (N = 132)	Pooled 3 mg/kg (N = 111)	Pooled 10 mg/kg (N = 325)
Any irAE	59.5	56.8	31.8	61.3	72.0
Grade 3-4	13.0	10.0	3.0	6.3	24.3
Grade 5	0.8	1.1[a]	0	0.9	0.9[b]

(Source: Sponsor's Table 5.3.1.1 in the Clinical Overview Report)

Potential associations between presence of HLA alleles and irAEs in the Phase 2 studies were also evaluated. No associations between irAEs and HLA status (positive and negative) were found (see Dr. Christian Grimstein's Genomics Review for details).

1.1.4 Is there exposure-response relationship for overall survival in HLA positive and negative patients?

Yes, there is evidence of exposure-response relationship for overall survival in both HLA positive and HLA negative patients in phase 2 studies. Exposure-efficacy analysis was conducted based on HLA subtypes because HLA negative patients were excluded from the Phase 3 trial (MDX010-20) as the activity of the vaccine, gp100 (control arm) was restricted to HLA positive patients. (b) (4) the direct mechanism of action for ipilimumab is not HLA-dependent. The CTLA-4 receptor-ligand interaction is HLA-independent.

Kaplan-Meier curves for overall survival of HLA positive (N=196) and negative patients (N=274) stratified into four groups according to their C_{min} (0.61 – <21, 21 – <41.1, 41.1 – 63.8, >63.8 – 154 μg/ml) are shown in Figure 6. Separation between the survival curves of patients in the lower and highest C_{min}-quartile groups is observed for both HLA positive and negative patients. Stepwise Cox proportional hazard model also identified Cmin as a significant predictor of overall survival in both HLA subtypes (Table 7). The slope of the exposure-response relationship is steeper in HLA negative patients compared to HLA positive patients and for 10 μg/ml increase in exposure, the hazard would decrease by 8% and 12% in HLA positive and negative patients. The survival curves are comparable between HLA positive and negative patients. Overall, an exposure-response relationship was identified for overall survival in both HLA positive and HLA negative patients that provide supportive evidence for the effectiveness of the drug in HLA negative patients.

Results from the exposure-response analysis and comparable survival in HLA positive and negative patients in phase 2 studies, the HLA-independent mechanism of action of the drug and results from the well controlled ongoing trial, CA184-024 that included both HLA positive and negative patients in favor of ipilimumab suggest of effectiveness of ipilimumab in HLA negative patients.

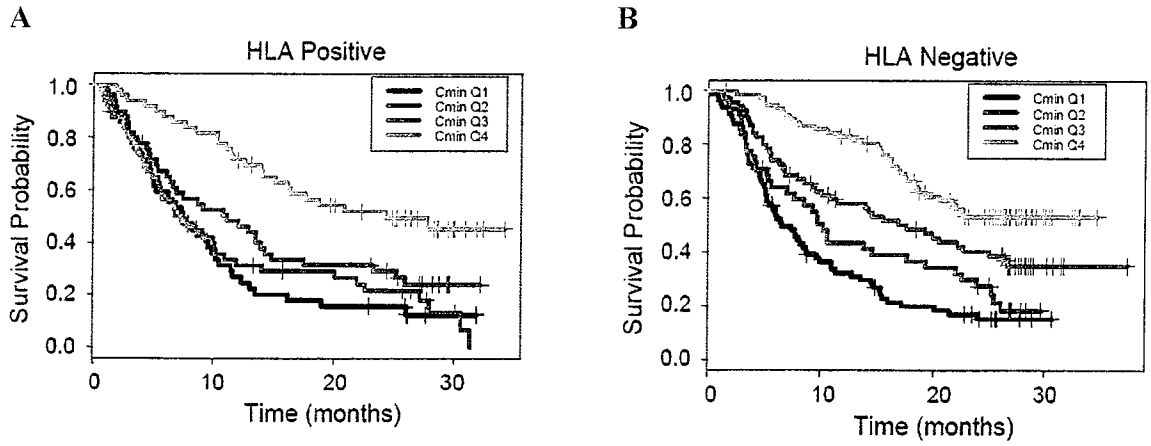

Figure 6: The exposure-response relationship for Ipilimumab in A) HLA positive and B) HLA negative patients from Phase 2 studies. Overall survival by steady state trough concentrations (C_{min}) of ipilimumab. Data were pooled from studies CA184-004, -007, -008 and -022.

Table 7: Cox model parameter estimates by HLA status

Predictor	Slope estimate	Std. error on estimate	P-value	Hazard ratio (HR)	95% HR confidence limits
HLA Positive					
C_{min} per 10 μg/ml	-0.0786	0.0271	0.0038	0.924	0.877 – 0.975
LDH per 100 IU/L	0.152	0.0289	<.0001	1.16	1.1 – 1.23
ECOG (0 vs. 1)	-0.643	0.171	0.0002	0.526	0.376 – 0.736
HLA Negative					
C_{min} per 10 μg/ml	-0.133	0.0271	<.0001	0.876	0.83 – 0.923
LDH per 100 IU/L	0.214	0.0328	<.0001	1.24	1.16 – 1.32
ECOG (0 vs. 1)	-0.415	0.167	0.0129	0.661	0.476 – 0.916

1.2 Recommendations

Division of Pharmacometrics finds the BLA acceptable from a clinical pharmacology perspective and has the following recommendations for the sponsor.

- Based on reviewer's exposure-response analysis, the proposed dose of 3 mg/kg might not be optimal and increasing exposures might improve survival. This analysis supports the comparative trial of 3 mg/kg vs. 10 mg/kg ipilimumab monotherapy

- For future development programs, the sponsor should collect sparse pharmacokinetic data from all subjects. The purpose is to develop exposure response relationship for efficacy and safety endpoints to support proposed dosing recommendations and dose adjustments.

1.3 Label Statements

The labeling recommendations relevant to clinical pharmacology for BLA 125377 are provided in section 3.

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK Analysis

Sponsor performed population PK modeling utilizing data from phase 2 studies in patients with unresectable stage III or IV melanoma. Primary objective of the population PK analysis was to characterize the population pharmacokinetics of ipilimumab and to quantify sources of variability in ipilimumab exposures.

2.1.1 Methods

PK data from a total of 499 patients (2095 observations) from four phase 2 studies (Table 8). Description of the studies with other relevant information is provided in Table 9. The PPK model was developed with 1767 observations from 420 subjects enrolled in 3 of the studies (CA184-007, -008 and -022), and data from 79 subjects enrolled in the remaining study (CA184-004) was used for external model validation.

PK data were then fitted using Nonmem software program. Model building and covariate assessments were conducted using standard methods. The final model for the PK database was evaluated for performance using several tests, including evaluation of an internal validation database, numeric predictive check, and visual predictive check (VPC) evaluation.

Table 8: Studies Used for the Population PK Model

Study	Subjects		
	Total	Excluded (%)	Included (%)
CA184004	82	3 (3.66)	79 (96.34)
CA184007	116	4 (3.45)	112 (96.55)
CA184008	155	7 (4.52)	148 (95.49)
CA184022	196	36 (18.37)	160 (81.63)
Total	549	50 (9.11)	499 (90.89)

(Source: Sponsor's Table 3.4.1.2A in the Population PK Report)

Table 9: Studies Used for the Population PK Model

Study #: Title *Study Population*	Ipilimumab Treatment	Planned Sample Size[a]	Nominal PK Sampling Schedule
CA184004: A randomized Phase 2 study to determine potential predictive markers of response to MDX-010 (BMS-734016) in patients with unresectable stage III or IV malignant melanoma *Subjects with advanced Stage III or Stage IV melanoma who were administered a tetanus booster and influenza or pneumococcal vaccine within 10 days prior to receiving ipilimumab*	Induction Period: Dose: 3 and 10 mg/kg Regimen: Once every 3 weeks. (Week 1, 4, 7 and 10) Maintenance Period: Regimen: Once every 12 weeks. (Week 24, 36, 48 etc.)	90	On Day 1 and Day 43, pre-infusion and after 90-minute infusion. Three additional samples were taken between Day 3-7 (post-dose) after week 7 dose, Day 10-15 (post-dose) after week 7 dose and the pre-dose sample on Day 64.
CA184007: A randomized, double-blind, placebo-controlled, Phase 2 study comparing the safety of ipilimumab administered with or without prophylactic oral budesonide (Entocort™ EC) in patients with unresectable stage III or IV malignant melanoma *Subjects with a histologic or cytologic diagnosis of unresectable Stage III or IV malignant melanoma*	Induction Period: Dose: 10 mg/kg Regimen: Once every 3 weeks. (Weeks 1, 4, 7 and 10) Note: Subjects were randomized to 1:1 ratio for oral budesonide and placebo. Budesonide was administrated at 9 mg once daily until Week 12, tapered to 6mg once daily until Week 14, and finally to 3mg once daily until Week 16. Maintenance Period: Regimen: Once every 12 weeks. (Weeks 24, 36, 48 etc.)	110	Schedule A: On Day 1 and Day 43, pre-infusion and after 90-minute infusion. Three additional samples were taken between Day 45-49, Day 52-57, and the pre-dose sample on Day 64. Schedule B: on day 1 and 43, pre-dose and after 90-minute infusion, 24, 72 hr post-infusion, day 8 (± 27 hours), day 15 (±48 hours); two additional pre-dose samples were taken on day 22 and day 64.
CA184008: A multi-center, single arm Phase 2 study of MDX-010 (BMS-734016) monotherapy in patients with previously treated unresectable stage III or IV melanoma *Subjects with previously treated unresectable Stage III or IV melanoma*	Induction Period: Dose: 10 mg/kg Regimen: Once every 3 weeks. (Week 1, 4, 7 and 10) Maintenance Period: Regimen: Once every 12 weeks. (Week 24, 36, 48 etc.)	144	Schedule A: On Day 1 and Day 43, pre-infusion and after 90-minute infusion. Three additional samples were taken between Day 3-7 after week 7 dose, Day 10-15 after week 7 dose and the pre-dose sample on Day 64. Schedule B: on day 1 and 43, pre-dose and after 90-minute infusion, 24, 72 hr post-infusion, day 8 (± 27 hours), day 15 (±48 hours); two additional pre-dose samples were taken on day 22 and day 64.
CA184022: A randomized, double-blind, multi-center, Phase 2 fixed dose study of multiple doses of Ipilimumab (MDX-010) monotherapy in patients with previously treated unresectable stage III or IV melanoma *Subjects with advanced Stage III or Stage IV melanoma, who were previously treated with any regimen except a CD-137 agonist or a CTLA4 inhibitor or agonist.*	Induction Period: Dose: 0.3, 3, 10 mg/kg Regimen: Once every 3 weeks. (Week 1, 4, 7 and 10) Maintenance Period: Regimen: Once every 12 weeks. (Week 24, 36, 48 etc.)	210	On Day 1 and Day 43, pre-infusion and after 90-minute infusion. Three additional samples were taken between Day 3-7 (post-dose) after week 7 dose, Day 10-15 (post-dose) after week 7 dose and the pre-dose sample on Day 64.

(Source: Sponsor's Table 3.1 in the Population PK Report)

2.1.2 Conclusions

- Covariate analysis showed that clearance and central volume increases with increasing body weight. Clearance of ipilimumab also increases with increasing baseline LDH.
- The following baseline covariates were found to not have clinically significant effects on the PK of ipilimumab, given the available data: age, gender, renal function, hepatic function, concomitant budesonide, ECOG performace status,

prior systemic anti-cancer therapy, HLA.A2*201 genotype status, and immunogenicity (HAHA status).

- Parameter estimates for fixed effect and random effects with standard errors are presented in Table 19 in the Appendix. Basic goodness of fit plots from the sponsor's final model is presented in Figure 26 in the Appendix.

Reviewer's comments on Sponsor's Population PK Analysis:

- *Sponsor's population PK analysis is generally adequate and acceptable.*
- *Body weight was identified as a covariate for central volume (V_C) which is acceptable because reviewer's analysis showed that inclusion of weight as a covariate on V_C alone reduced the objective function value by 131 from the sponsor's base model. The inter-individual variability on V_C reduced from 22.9% to 16.6%.*
- *Body weight and baseline levels of LDH were identified as covariates for clearance. These covariates that were identified in the final model are likely not to be significant because reviewer's analysis showed that the inclusion weight alone as a covariate for clearance resulted in the reduction in the objective function value by 3.54 from the sponsor's base model. The inter-individual variability on clearance (CL) was reduced from 39.5% to 38.3%. Consistent, with the sponsor's analysis inclusion of baseline LDH as a covariate resulted in the reduction in the objective function value by 13.3 from the base model. The inter-individual variability on clearance (CL) was reduced from 39.5% to 37.4%. Inclusion of all covariates in the model resulted in reduction of inter-individual variability on clearance (CL) from 39.5% to 34.4%.*
- *Consistent with the sponsor. no clear trends were identified between the PK parameters obtained from the model and age, gender, renal function, hepatic function concomitant budesonide, ECOG performace status, prior systemic anti-cancer therapy, , HLA.A2*201 genotype status, and immunogenicity (HAHA status) in reviewer's analysis (see section 3.3).*

2.2 Exposure-Response Analysis for Effectiveness

The objective was to characterize the relationship between Ipilimumab exposures and measures of efficacy (overall survival and best objective response (BOR)).

2.2.1 Methods

Data from 498 patients with PK information from phase 2 studies (CA184-004, -007, -008 and -022) were utilized for a graphical assessment of exposure-response relationship for overall survival and development of semi-parametric Cox proportional hazards (CPH) model that included the effects of covariates on the exposure-response relationship. Logistic regression models were used to explore the relationship between exposures and BOR and irCA. The dataset for these BOR and irCA comprised of 354 and 419 patients from studies CA184-007, -008 and -022. BOR rate was defined as the proportion of subjects with complete response and partial response. Steady-state trough concentrations

of ipilimumab computed from the sponsor's population PK model were used for the analysis. Exposure-response relationship was also conducted for an exploratory composite efficacy endpoint, immune-related clinical acticvity (irCA).

2.2.2 Conclusions

- **Overall Survival:** Kaplan-Meier plot showed an increase in survival with increasing steady state trough concentrations of ipilimumab (Figure 7). More than 90% and 99% of the patients in the 2nd and 3rd tertiles were treated at the 10 mg/kg group (Table 10). The CPH model showed that Cmin, baseline LDH and ECOG status were predictors of overall survival. Hazard increased with increasing baseline LDH and for subjects with ECOG status greater than zero (Table 11).

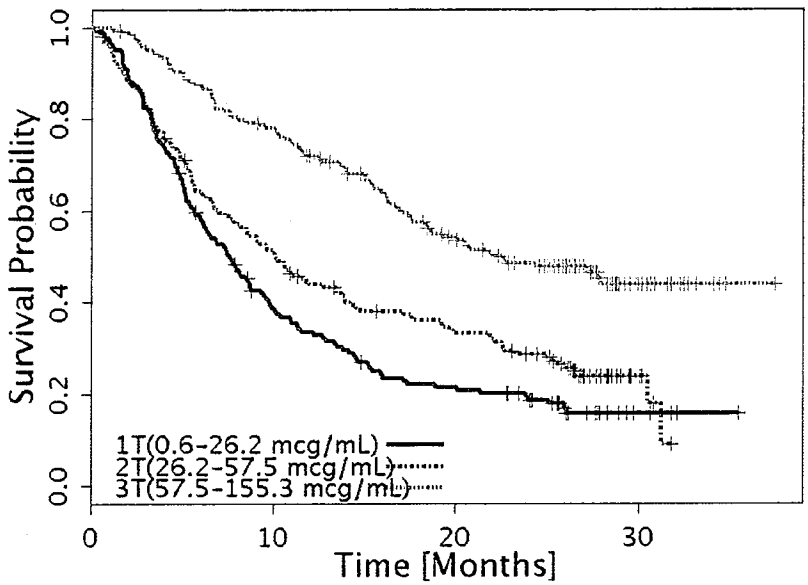

Figure 7: Kaplan-Meier plot of overall survival by Cmin in phase 2 studies. 1T, 2T and 3T refer to the tertiles of Cmin. Data was pooled from studies CA184-004, -007, -008 and -022. Source: Sponsor's Figure 3.5.4.2B in the Population PK Report.

Table 10: Number of patients in different dose groups in the C_{min}-tertiles

Cminss Tertiles (mcg/mL)	Number of Subjects	Number (Percentage) of Subjects		
		0.3 mg/kg	3 mg/kg	10 mg/kg
1T (0.6-26.2)	165	48 (29.09)	81 (49.09)	36 (21.82)
2T (26.2-57.5)	168	0 (0)	16 (9.52)	152 (90.48)
3T (57.5-155.3)	165	0 (0)	1 (0.61)	164 (99.39)

Note: 1T/2T/3T: tertiles of Cminss

(Source: Sponsor's Table 3.5.4.2B in the Population PK Report)

Table 11: Parameter estimates of Cox proportional hazard model

Predictor	Predictor Median (5th-95th Percentile)	Hazard Ratio Coefficient[a] (95% CI)	Hazard Ratio 5th Percentile: Median (95% CI)	Hazard Ratio 95th Percentile: Median (95% CI)
Cminss [mcg/mL]	43.9 (1.75 - 103)	0.990 (0.986, 0.994)	1.52 (1.29, 1.8)	0.552 (0.437, 0.697)
LDH [IU/L][b]	206 (131 - 846)	2.32 (1.91, 2.8)	0.684 (0.628, 0.745)	3.27 (2.5, 4.28)
	Comparator : Reference	**Hazard Ratio Coefficient[c] (95% CI)**		
ECOG Status	>0:=0 (N=176:322)	1.72 (1.37, 2.15)		

[a] Hazard ratio coefficient represents the hazard ratio for one unit of change in the predictor variable.

b The hazard ratio coefficient for LDH corresponds to log transformed LDH (which was employed as the linear predictor, as the distribution of LDH is right-skewed)

[c] Hazard ratio coefficient represents the hazard ratio for comparator relative to reference predictor variable.

(Source: Sponsor's Table 5.4.1.3 in the Population PK Report)

- **Best objective response:** There is an increase in the probability of best objective response with increasing steady state trough concentrations of ipilimumab (Figure 8). Cmin was a significant predictor of BOR with a p-value of <0.01 and an odds ratio that excluded 1 (Table 12). There was also an increase in the probability of immune-related clinical activity with increasing exposures (data not shown).

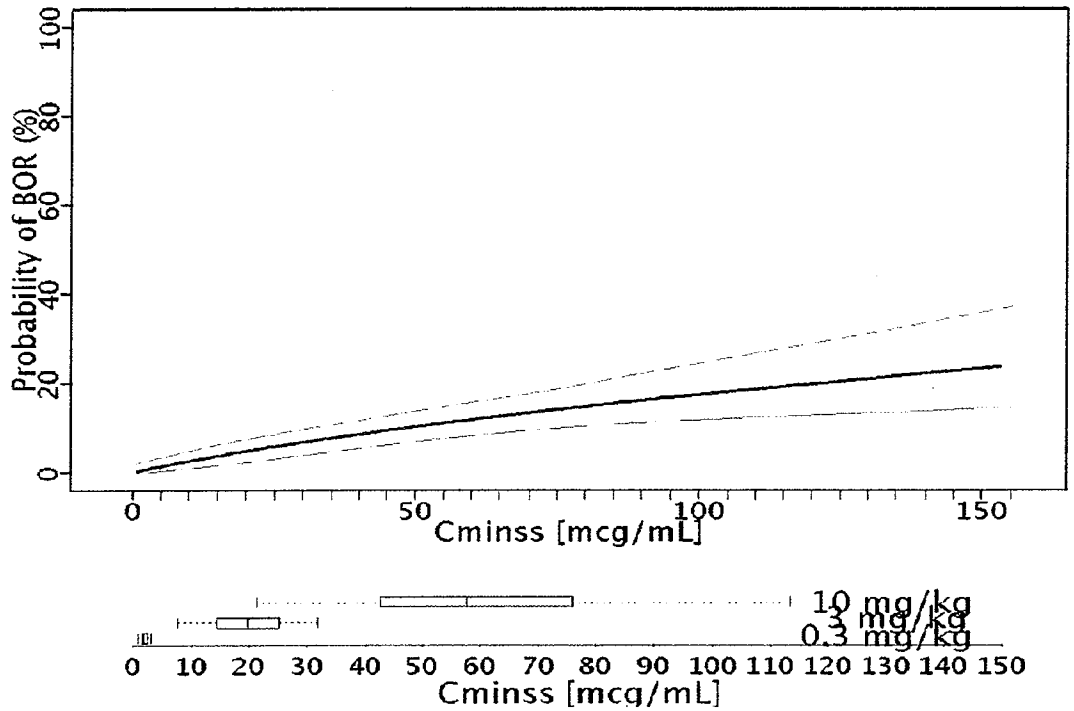

Figure 8: The probability of patients with objective response in Phase 2 studies. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval of the prediction. The horizontal box plots represent the distributions of steady-state Cmin at each dose group. Source: Data were pooled from studies CA184-007, -008 and -022. Sponsor's Figure 5.2.1.3 in the Population PK Report.

Table 12: Summary of logistic regression model for BOR

Predictor	Odds Ratio Coefficient (95%CI)[b]	p-value	Median Cminss (5th, 95th Percentile)	Odds Ratio: 5th Percentile :Median of Cminss (95%CI)	Odds Ratio: 95th Percentile :Median of Cminss (95%CI)
Log(Cminss)[a]	2.41 (1.66, 4.26)	< 0.01	49.3 (1.75 - 110)	0.0531 (0.00742, 0.38)	2.03 (1.26, 3.26)

[a] Cminss was log-transformed. Log(Cminss) increases by one unit for approximately 2.7-fold increase in Cminss.
[b] 95% CI obtained from bootstrap (N=500).

(Source: Sponsor's Table 5.2.1.3 in the Population PK Report)

Reviewer's comments on Sponsor's Exposure-Response Analysis for Effectiveness*: The sponsor's conclusion of increase in overall survival with increasing exposures in phase 2 studies is acceptable. An independent analysis was conducted by the reviewer and the overall results were consistent with the sponsor (see sections 1.1.1and 1.1.2). Similar results were obtained using observed trough concentrations instead of model predicted C_{min} (see section 3). Reviewer's sub-group analyses confirmed that the exposure-response relationship is robust (see section 3).*

2.3 Exposure-Response Analysis for Safety

The objective of this analysis was to characterize the relationship between ipilimumab exposures and probability of immune-related adverse events (irAEs).

2.3.1 Methods

Data from 498 patients with PK information from phase 2 studies (CA184-004, -007, -008 and -022) were utilized for the exposure-response relationship. Logistic regression models were used to explore the relationship between steady state Cmin predicted by the population PK model and observed irAEs. The irAEs involved gastro-intestinal tract (eg. diarrhea and colitis), skin (eg. pruritus and rash), endocrine glands (eg. hypothyroidism), liver (eg. transaminase elevations) and nervous system (eg. motor neuropathy).

2.3.2 Conclusions

- There is increase in the probability of grade 2/3/4 and grade 3/4 irAES with increasing steady state trough concentrations of ipilimumab (Figure 5). The model predicts that at median Cmin for 3 and 10 mg/kg grade 2/3/4 irAEs were approximately 33% and 51%. Grade 3/4 irAEs were 13% and 24%.

Reviewer's comments on Sponsor's Exposure-Response Analysis for Safety: *The sponsor's conclusion that the probability irAEs increases with increasing exposure is acceptable. The model predictions are consistent with observed data where increase in irAEs was observed with increasing doses (Table 6).*

3 RESULTS OF REVIEWER'S ANALYSIS

3.1 Objectives

The reviewer's analysis objectives are:

1. To characterize the exposure-response relationship for overall survival of ipilimumab.
2. To use the results of objective (1) to establish whether proposed dose of 3 mg/kg is optimal.
3. To explore whether the proposed dose of 3 mg/kg is adequate to obtain similar exposures across patients.
4. To compare the exposure-response relationship for overall survival in HLA positive and negative patients.

3.2 Methods

3.2.1 Data Sets

Data sets used are summarized in Table 13.

Table 13: Analysis Data Sets.

Study Number	Name	Link to EDR
Phase 2 CA184-004 CA184-007 CA184-008 CA184-022	os_all.xpt pk_all.xpt	\\cbsap58\m\eCTD_Submissions\STN125377\0004\m5\datasets\pop pk\analysis
Phase 3 MDX010-20	os.xpt	\\cbsap58\m\eCTD_Submissions\STN125377\0014\m5\datasets\mdx 010-20\analysis

3.2.2 Software

SAS, S-PLUS, NONMEM and R were used for the reviewer's analyses.

3.3 Results

3.3.1 Population Pharmacokinetic Analysis

Age/ Body weight: Age does not significantly affect the pharmacokinetics of Ipilimumab. Figure 9 shows that the inter-individual variability in clearance cannot be explained by age.

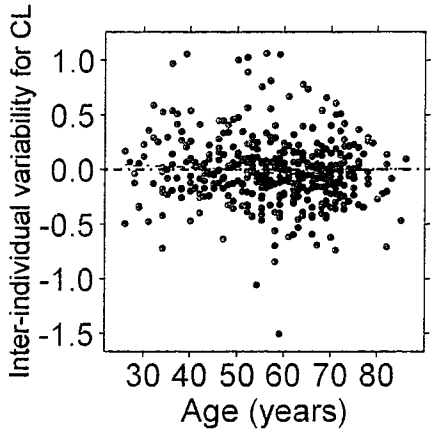

Figure 9: Inter-individual variability on clearance vs. age

There is a trend for increase in clearance with increasing body weight (Figure 10). Although, weight is included as a covariate in the sponsor's final model, it is not likely to be significant because a small reduction in the inter-individual variability on clearance was observed due to weight (for details see reviewer's comments in section 2.1.2). Similar exposures (AUC) are achieved across patients of varying body weights upon administration of a weight-based dosing regimen (Figure 11).

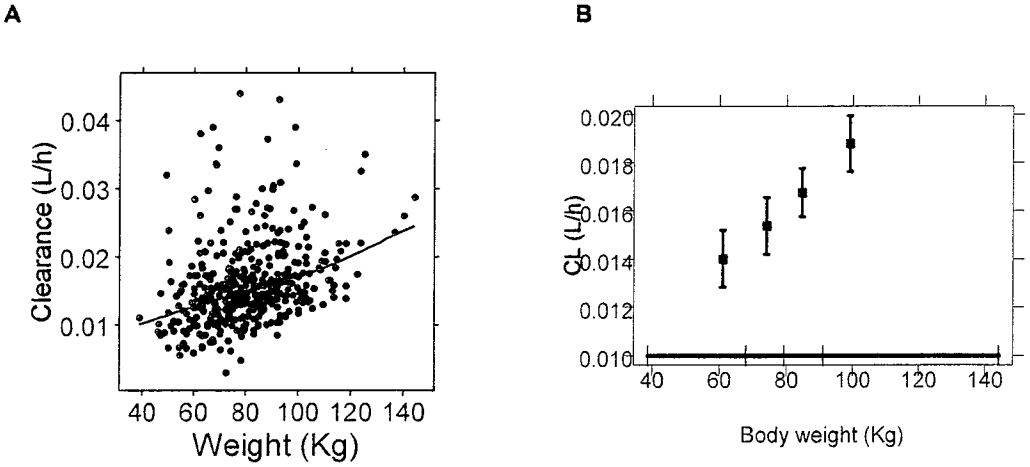

Figure 10: A) Scatter plot and B) Quantile plot of Clearance vs. Weight

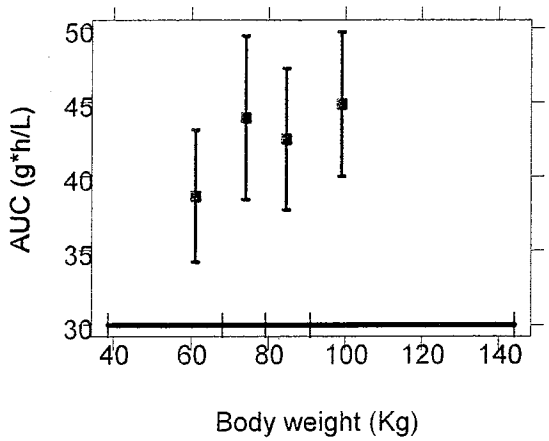

Figure 11: Quantile plot of AUC vs. Weight

Gender/ECOG status: Gender and ECOG status do not significantly affect the pharmacokinetics of ipilimumab. Boxplot of the inter-individual variability on clearance show that there is no systematic trend between males and females as evidenced by a median of zero (Figure 12). Similarly, no systematic trend is observed based on the ECOG status of patients (Figure 12).

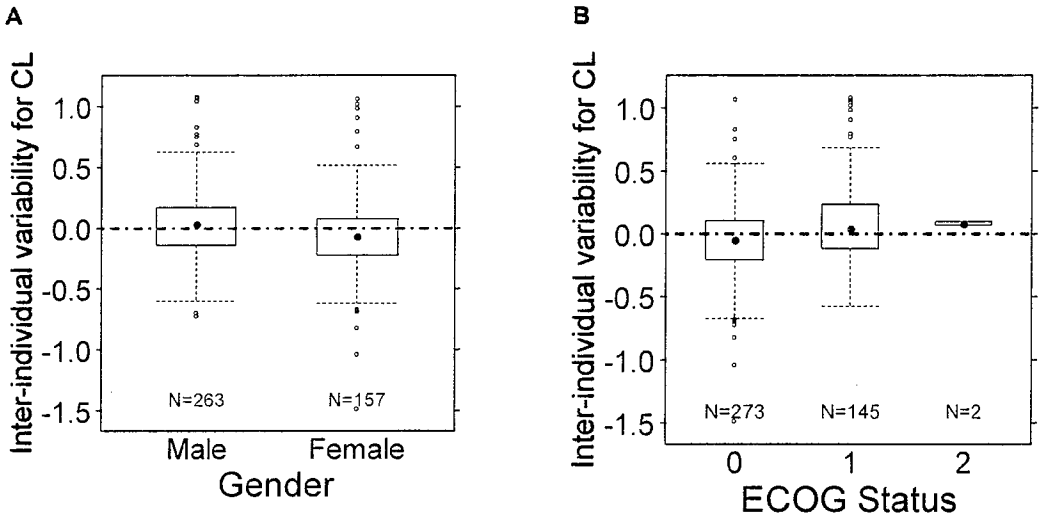

Figure 12: Inter-individual variability on clearance vs. A) Gender and B) ECOG status.

Immunogenicity/ HLA status: There is no effect on ipilimumab PK immunogenicity status and HLA status (Figure 13).

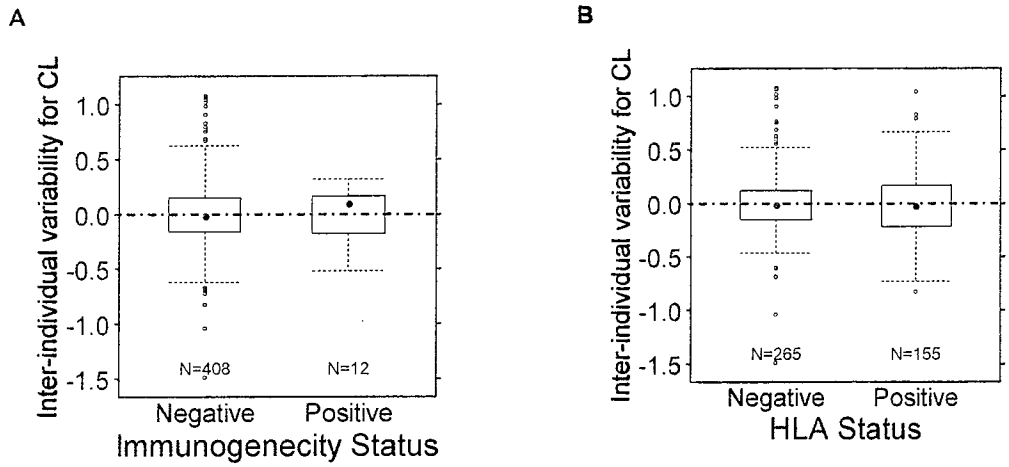

Figure 13: Inter-individual variability on clearance vs. A) Immunogenecity status and B) HLA status.

Baseline lactate dehydrogenase: There is a trend for increase in clearance with increasing baseline levels of lactate dehydrogenase (Figure 14). Although, LDH is included as a covariate in the sponsor's final model, it is not likely to be significant because a small reduction in the inter-individual variability on clearance was observed due to LDH (for details see reviewer's comments in section 2.1.2). Corresponding to an increase in clearance, a decrease in AUC is observed with increasing baseline LDH (Figure 15). The AUC is 1.4 fold higher in the lowest quartile compared to the highest quartile. As AUC is less than 2 fold different in the highest quartile compared to the lowest quartile and because the unexplained inter-individual variability on clearance is high (34.4 %), no dose adjustment based on LDH is needed.

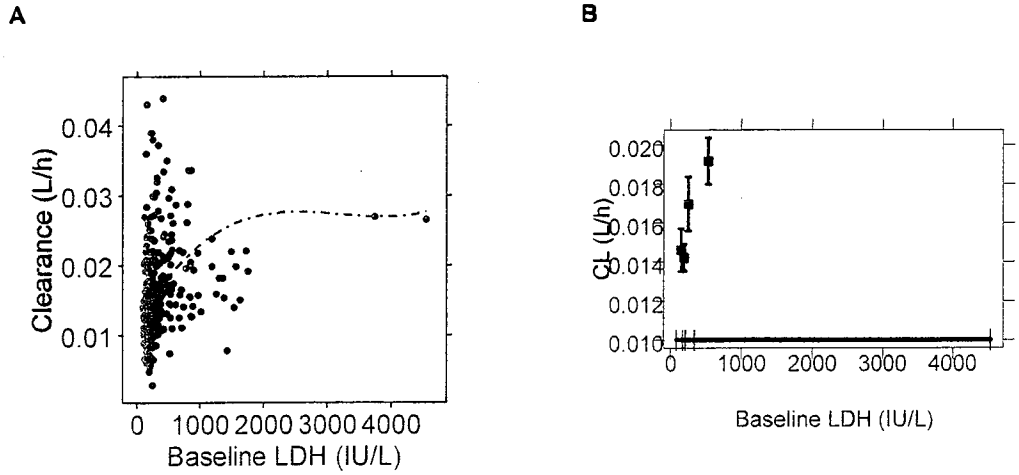

Figure 14: A) Scatter plot and B) Quantile plot of Clearance vs. Baseline lactate dehryrogenase (LDH)

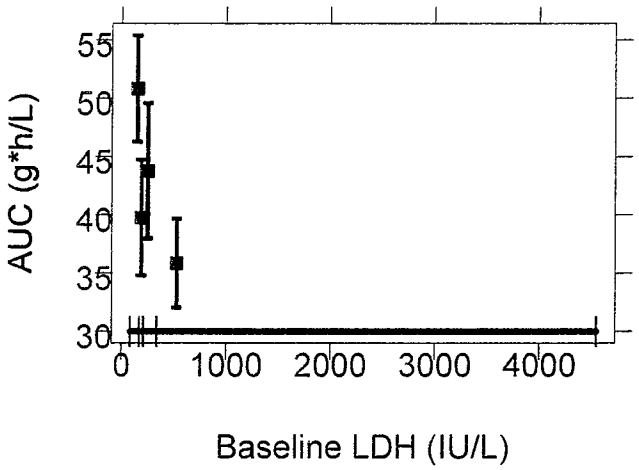

Figure 15: Quantile plot of AUC vs. Baseline lactate dehryrogenase (LDH)

Concomitant use of budesonide/ Prior anti-cancer therapy: There is no effect on ipilimumab PK due to concomitant use of budesonide and prior anti-cancer therapy (Figure 16).

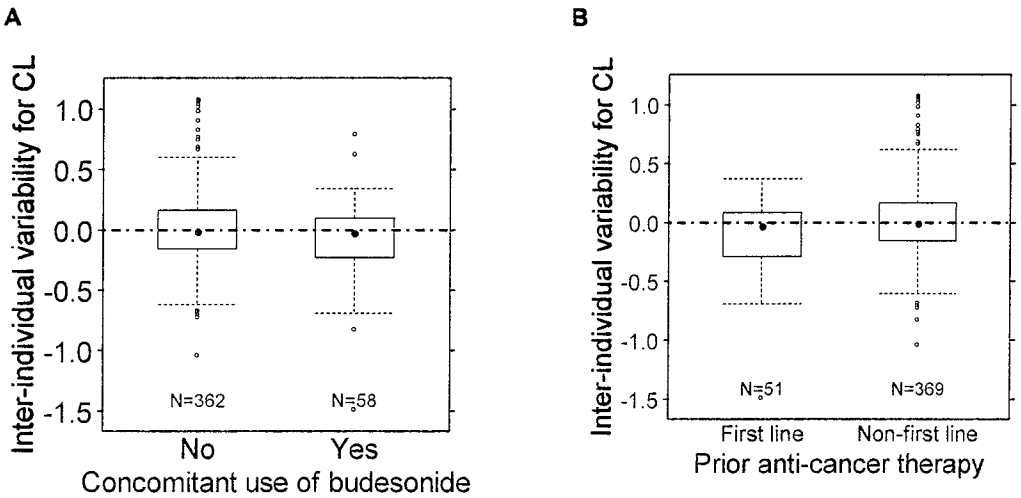

Figure 16: Inter-individual variability on clearance vs. A) Concomitant use of budesonide and B) Prior anti-cancer therapy.

Renal Function: Figure 17 shows that the inter-individual variability in clearance cannot be explained by renal function. There is no trend between inter-individual variability on clearance and glomerular filtration rate (GFR) for patients with mild and moderate renal impairment. There were only 4 patients with severe renal impairment. Median clearance in various renal function groups were similar (Table 14). Similar results were obtained using creatinine clearance as a measure of renal function (Figure 18).

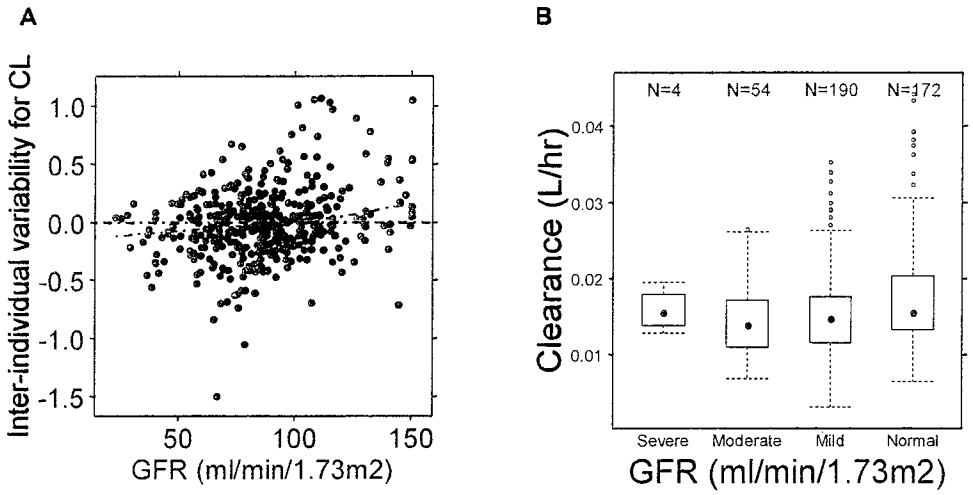

Figure 17: A) Inter-individual variability on clearance and B) Clearance vs. Glomerular filtration rate (GFR). Renal function was classified as normal (≥ 90), mild impairment (60 to <90), moderate impairment (30 to <60), and severe impairment (< 30). The dashed line

Table 14: Clearance by renal function status

Renal function group based on GFR	Median Clearance (L/hr) – stratified by GFR	Median Clearance (L/hr) – stratified by CRCL
Normal	0.0157	0.0157
Mild	0.0148	0.0147
Moderate	0.0140	0.0132
Severe	0.0157	0.0149

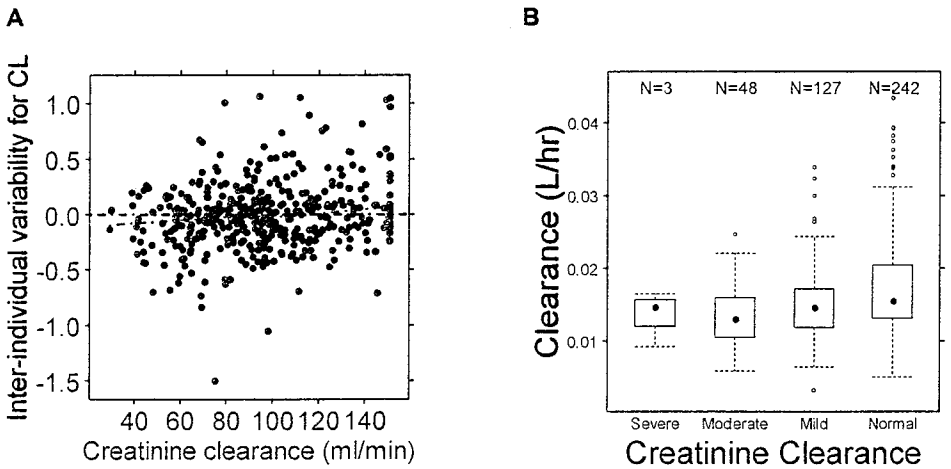

Figure 18: A) Inter-individual variability on clearance and B) Clearance vs. Creatinine Clearance. Renal function was classified as normal (≥ 90), mild impairment (60 to <90), moderate impairment (30 to <60), and severe impairment (< 30)

Hepatic Function: There is a trend for increase in inter-individual variability for clearance with baseline levels of alkaline phosphatase (ALP) as shown in Figure 19. This is likely not to be significant because categorical analysis showed that patients with high baseline ALP (> 115 IU/L) had 1.14-fold higher clearance than patients with normal levels of ALP (≤ 115 IU/L). There was no clear trend for inter-individual variability for clearance and baseline aspartate aminotransferase (AST), total bilirubin and alanine aminotransferase (ALT) as shown in Figure 20 and Figure 21. A slight increase in clearance (1.17-fold) was observed for patients with low levels albumin compared to normal patients. There is limited information from 31 patients in the low albumin group because only 1 patient has albumin level less than 2.5 g/dL. The median albumin level in the low group was 3.4 g/dL which is close to normal.

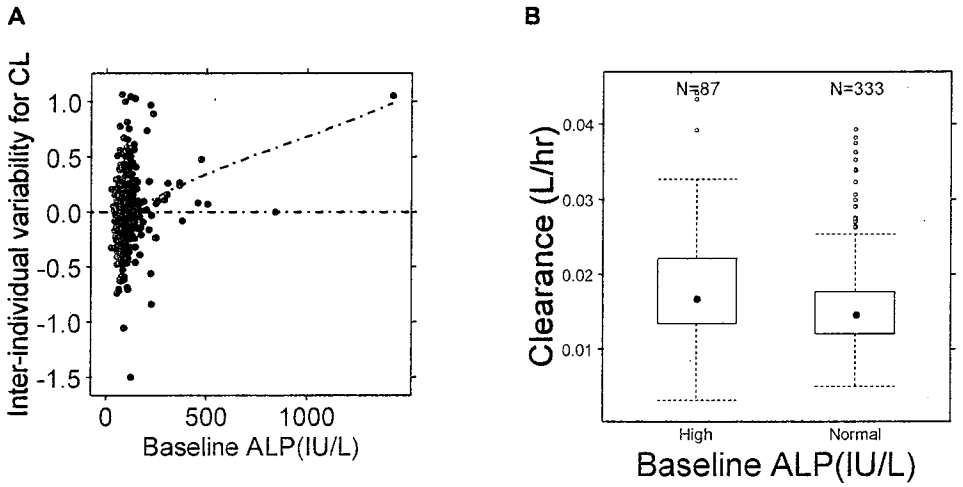

Figure 19: A) Inter-individual variability on clearance and B) Clearance vs. baseline alkaline phosphatase (ALP). ALP level ≤ 115 IU/L was considered normal. Median values of clearance in the high and normal groups are 0.0169 and .0148 L/h. Median values of ALP in the high and normal groups are 142 and 79 IU/L.

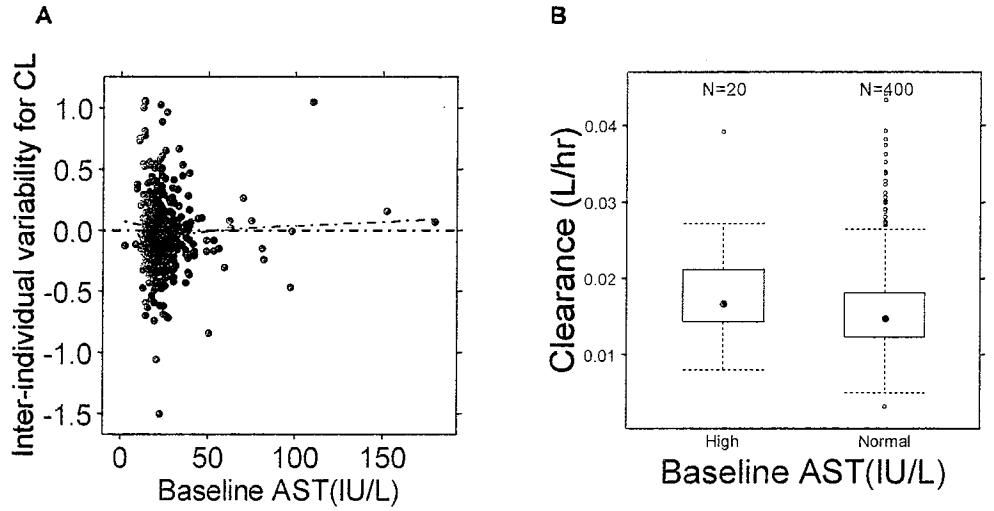

Figure 20: A) Inter-individual variability on clearance and B) Clearance vs. baseline aspartate aminotransferase (AST). AST level ≤ 43 IU/L was considered normal. Median values of clearance in the high and normal groups are 0.0168 and .0150 L/h. Median values of albumin in the high and normal groups are 62.5 and 20 IU/L.

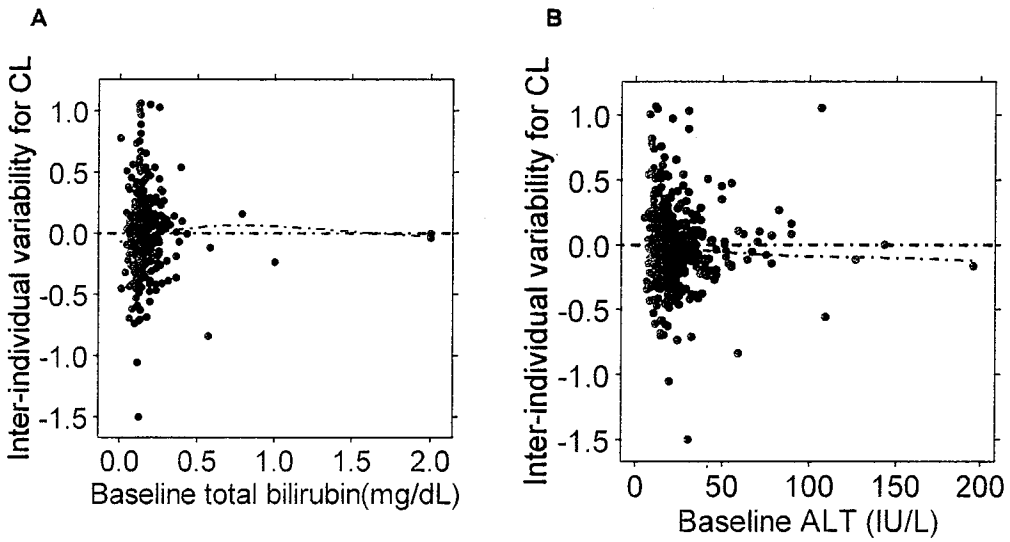

Figure 21: Inter-individual variability on clearance vs. A) baseline total bilirubin and B) baseline alkaline transaminoferase (ALT)

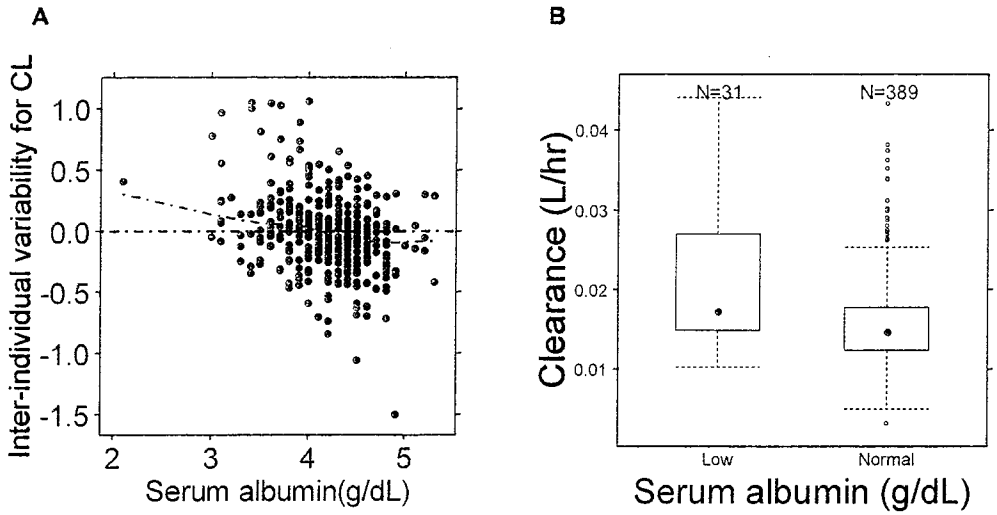

Figure 22: A) Inter-individual variability on clearance and B) Clearance vs. serum albumin. Albumin level > 3.5 g/dL was considered normal. Median values of clearance in the low and normal groups are 0.0175 and .0149 L/h. Median values of albumin in the low and normal groups are 3.4 and 4.3 g/dL.

3.3.2 Exposure-Response Analysis for Efficacy

Exposure-response for data pooled from phase 2 studies: Exposure-efficacy analysis was conducted using data from 498 patients from studies CA184-004, -007, -008 and -022 because pharmacokinetic data was not collected in the phase 3 trial (MDX010-20). The studies utilized doses of 0.3, 3 and 10 mg/kg with sparse pharmacokinetic data (Table 9). A time-to-event analysis for overall survival was performed with patients stratified into four groups according to their Cmin (0.61 - 19.4, 19.5 - 43.7, 44 – 65.3, >65.3 - 155.3 μg/ml) and the results are shown in Figure 1. A clear separation between the survival curves of patients in different Cmin-quartile groups is observed, thus indicating exposure–response relationship. An increase in survival is observed with increasing exposures. A stepwise Cox proportional hazard model also identified Cmin as a significant predictor of overall survival. Baseline level of lactate dehydrogenase (LDH) and ECOG status (0 vs. 1) were also identified as risk factors for overall survival. The parameters from the Cox model are shown in Table 1. This analysis excluded two patients who had an ECOG status of 2. The model predicted that for 10 μg/ml increase in exposure, the hazard would decrease by 10%. The p-value was less than 0.0001 and the confidence interval of the hazard ratio excluded 1 (see section 1.1.1 for details).

Exposure-response analysis was also performed using observed trough concentrations from 356 patients instead of model predicted C_{min}. A clear separation between the survival curves of patients in the lower C_{min}-quartile groups (0.51-15.2, 15.3-36.7) versus higher groups (37.1-59.3, 59.4-319) is observed, thus indicating exposure–response relationship (Figure 23). A stepwise Cox proportional hazard model also identified C_{min} as a significant predictor of overall survival (Table 15). The model predicted that for 10 μg/ml increase in exposure, the hazard would decrease by 8 %.

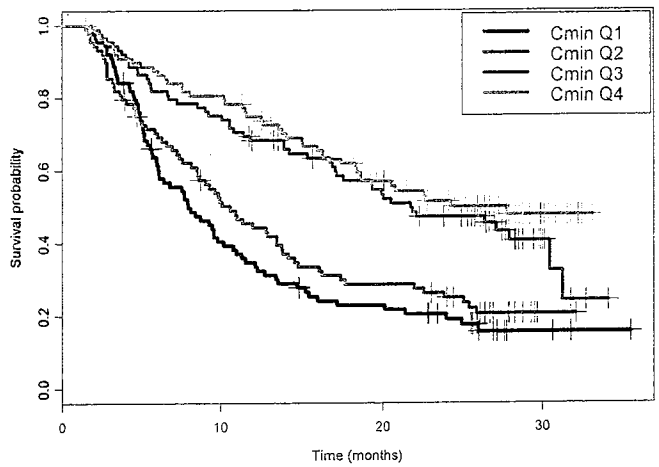

Figure 23: The exposure-response relationship for Ipilimumab in Phase 2 studies. Overall survival by observed steady state trough concentrations (C_{min}) of ipilimumab. Data were pooled from studies CA184-004, -007,-008 and -022.

Table 15: Cox model parameter estimates (observed C_{min} used for analysis)

Predictor	Slope estimate	Std. error on estimate	P-value	Hazard ratio (HR)	95% HR confidence limits
C_{min} per 10 μg/ml	-0.0821	0.021	<.0001	0.921	0.884 – 0.96
LDH per 100 IU/L	0.22	0.027	<.0001	1.25	1.18 – 1.31
ECOG (0 vs. 1)	-0.574	0.139	<.0001	0.563	0.428 – 0.74

A sub-group analysis was also performed by excluding study CA184-007 and patients who were administered 0.3 mg/kg of ipilimumab. Study 007 was removed because at the studied dose of 10 mg/kg of ipilimumab, the median survival was 19.3 months which was higher than the median survival observed for ipilimumab in other phase 2 studies. Thus, any potential bias due to study 007 was removed. The 0.3 mg/kg dose group was removed because we wanted to confirm that the exposure-response relationship is not biased by the low dose group with very low exposures. There were 339 patients in the analysis dataset. Separation between the survival curves of patients in low and high C_{min}-quartile groups is observed (Figure 24). Stepwise Cox proportional hazard model also identified C_{min} as a significant predictor of overall survival (Table 16). The model predicted that for 10 μg/ml increase in exposure, the hazard would decrease by 10 %.

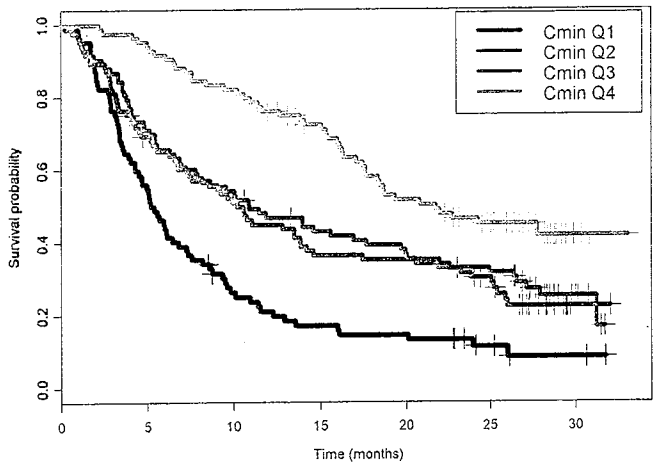

Figure 24: The exposure-response relationship for Ipilimumab in Phase 2 studies. Overall survival by steady state trough concentrations (C_{min}) of ipilimumab. Data were pooled from studies CA184-004, -008 and -022. Only the 3 and 10 mg/kg dose groups were included in the analysis.

Table 16: Cox model parameter estimates for subgroup analysis (excluding 0.3 mg/kg dose group and study CA184-007)

Predictor	Slope estimate	Std. error on estimate	P-value	Hazard ratio (HR)	95% HR confidence limits
C_{min} per 10 μg/ml	-0.101	0.0253	<.0001	0.904	0.86 – 0.949
LDH per 100 IU/L	0.166	0.023	<.0001	1.18	1.13 – 1.24
ECOG (0 vs. 1)	-0.493	0.137	.0003	0.611	0.467 – 0.799

Exposure-response from study CA184-022: A subgroup analysis was conducted using data from 160 patients from study CA184-022 alone because this phase 2 study included all three dose levels of 0.3, 3 and 10 mg/kg. Kaplan-Meier curves for overall survival of patients stratified into four groups according to their C_{min} (0.61 – 2.61, 2.7 – 17.4, 17.5 – 39, >39 - 127 μg/ml) are shown in Figure 25. Separation between the survival curves of patients in the lower and highest C_{min}-quartile groups is observed. Stepwise Cox proportional hazard model also identified Cmin as a significant predictor of overall survival. Baseline level of lactate dehydrogenase (LDH) and ECOG status (0 vs. 1) were also identified as risk factors for overall survival. The parameters from the Cox model are shown in Table 17. This analysis excluded one patient who had an ECOG status of 2. The model predicted that for 10 μg/ml increase in exposure, the hazard would decrease by 8.6%. The p-value was less than 0.05 and the confidence interval of the hazard ratio excluded 1.

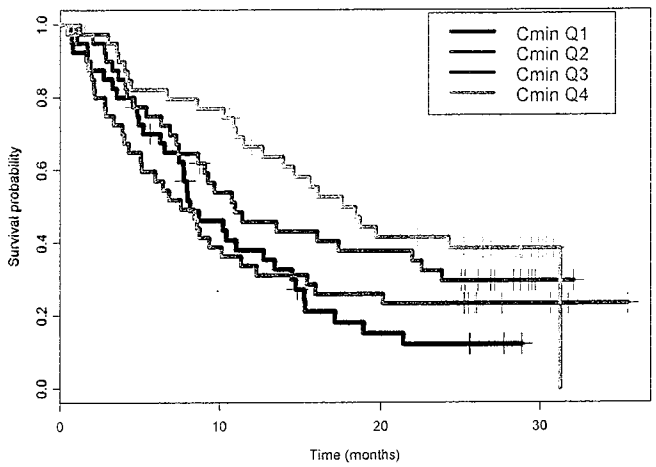

Figure 25: The exposure-response relationship for Ipilimumab in study CA184-022. Overall survival by steady state trough concentrations (C_{min}) of ipilimumab.

Table 17: Cox model parameter estimates for study CA184-022

Predictor	Slope estimate	Std. error on estimate	P-value	Hazard ratio (HR)	95% HR confidence limits
C_{min} per 10 μg/ml	-0.0896	0.0361	0.013	0.914	0.852 – 0.981
LDH per 100 IU/L	0.129	0.0268	<.0001	1.14	1.08 – 1.2
ECOG (0 vs. 1)	-0.496	0.201	0.0136	0.609	0.41 – 0.903

Cox proportional hazard model by dose group shows that slope of the exposure-response relationship is steeper for the lower doses compared to the higher dose (Table 18). For 1 μg/ml increase in exposure at the 0.3 mg/kg dose, the hazard would decrease by 63%. For 10 μg/ml increase in exposure at the 3 mg/kg dose, the hazard would decrease by 43%. The exposure-response relationship was not statistically significant at the highest dose of 10 mg/kg in this study. However, pooled data from all studies shows a statistically significant exposure-response relationship in the 10 mg/kg dose but with a shallow slope of -0.151 (data not shown). This suggests that the exposure-response relationship is non-linear and there is likely to be a saturation phase where increasing exposures might not significantly increase survival. At the proposed dose of 3 mg/kg, the exposure-response relationship is significant which suggests that increasing exposures for these patients would result in increased survival.

Table 18: Cox model parameter estimates for study CA184-022 by dose

Predictor	Slope estimate	Std. error on estimate	P-value	Hazard ratio (HR)	95% HR confidence limits
Dose = 0.3 mg/kg					
C_{min} per 1 μg/ml	-1.01	0.266	0.0002	0.366	0.217 – 0.616
LDH per 100 IU/L	0.054	0.0331	0.102	1.06	0.989 – 1.13
ECOG (0 vs. 1)	-0.988	0.394	0.0122	0.372	0.172 – 0.806
Dose = 3 mg/kg					
C_{min} per 10 μg/ml	-0.553	0.224	0.0135	0.575	0.371 – 0.892
LDH per 100 IU/L	0.169	0.0816	0.0385	1.18	1.01 – 1.39
ECOG (0 vs. 1)	0.102	0.407	0.803	1.11	0.499 – 2.46
Dose = 10 mg/kg					
C_{min} per 10 μg/ml	-0.112	0.0787	0.154	0.894	0.766 – 1.04
LDH per 100 IU/L	0.248	0.101	0.0146	1.28	1.05 – 1.56
ECOG (0 vs. 1)	-0.164	0.374	0.662	0.849	0.408 – 1.77

The results obtained from various sub-group analyses and the analysis utilizing observed C_{min} as a stratification factor are consistent with the overall results utilizing all the data and predicted C_{min} as the stratification factor. This suggests that the exposure-response relationship is robust. Thus, an exposure-response relationship was identified for overall survival in phase 2 studies that provides supportive evidence for the effectiveness of the drug.

APPENDIX A: SPONSOR'S POPULATION PK ANALYSIS

Table 19: Sponsor's Final PK Model parameters for Ipilimumab

Parameter [Units]	Estimate[a]	95% Confidence Interval[b]
Structural Model Parameters		
CL_{REF} [L/h]	0.0149	0.0144 - 0.0155
VC_{REF} [L]	4.16	4.08 - 4.27
Q_{REF} [L/h]	0.0434	0.0381 - 0.0515
VP_{REF} [L]	3.20	2.96 - 3.46
CL_{BW}[c] *(REF=80 [kg])*	0.660	0.434 - 0.811
VC_{BW} *(REF=80 [kg])*	0.710	0.619 - 0.805
CL_{LDH}[c] *(REF=206 [IU/L])*	1.07	0.732 - 1.44
Inter-Individual Variability Model Parameters		
ω^2_{CL}	0.118 (0.344)	0.0964 - 0.155
ω^2_{VC}	0.0251 (0.158)	0.0177 - 0.0355
$\omega_{CL}:\omega_{VC}$	0.0246 (0.452)	0.00918 - 0.0341
Residual Error Model Parameters		
Proportional error [-]	0.154	0.136 - 0.165
Additive error [µg/mL]	0.209	0.00500 - 0.476

[a] Estimate values in parentheses are *standard deviation* for estimated variances and *correlation* for estimated covariances

[b] Confidence Interval values are taken from bootstrap calculations (449 successful out of a total of 500)

[c] BW: baseline body weight in kg; LDH: lactate dehydrogenase in IU/L

Source: Appendix 5.1.1.3C

(Source: Sponsor's Table 5.1.13 in the Population PK Report)

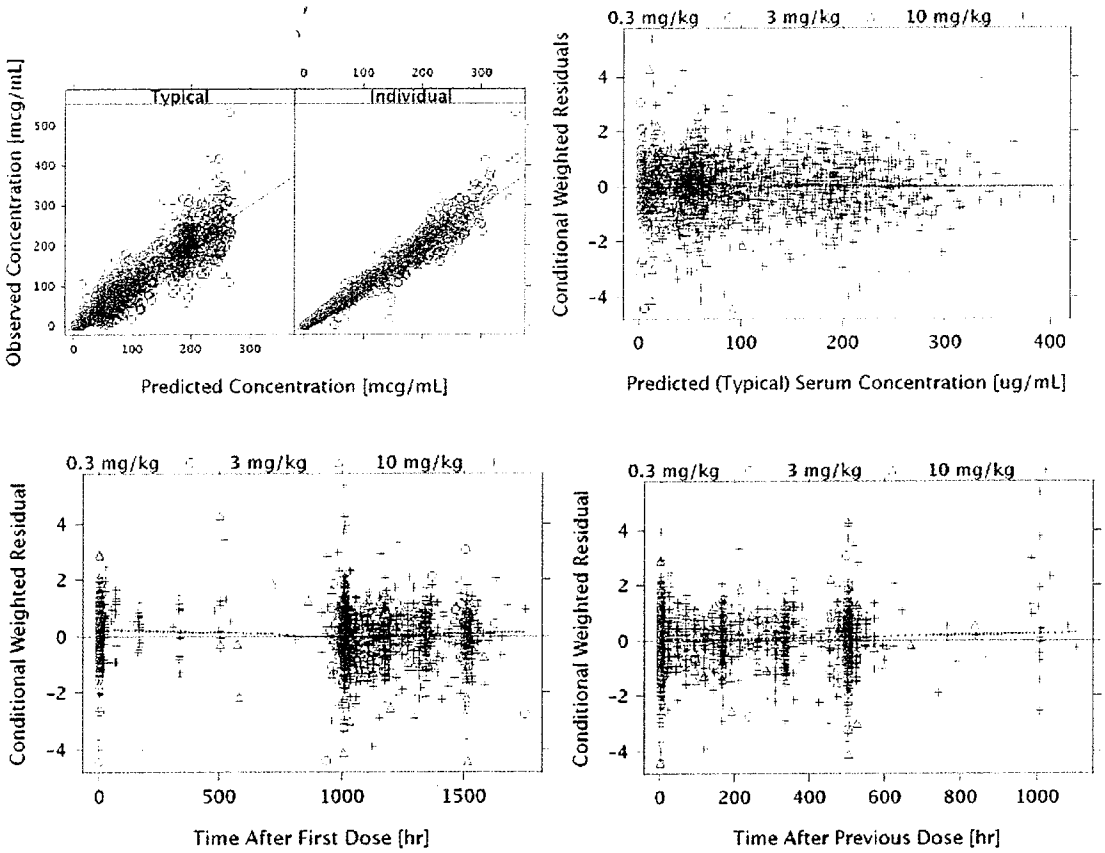

Figure 26: Basic goodness of fit plots for the Sponsor's final model.
(Source: Sponsor's Figures 5.1.1.3 A-D in the Population PK Report)

APPENDIX B: DESCRIPTION OF PHASE 3 AND PHASE 2 STUDIES

MDX010-20: This is a phase 3 randomized double-blind multicenter study comparing the overall survival in ipilimumab monotherapy, ipilimumab in combination with a melanoma peptide vaccine (gp100) and gp100 monotherapy in HLA-A*0201-positive patients with previously treated unresectable stage III or stage IV melanoma. The ipilimumab dose in the study was 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of four doses during the induction phase. The results from the study are shown in Table 20.

Table 20: Overall Survival in MDX010-20 (phase 3 study)

	Primary Comparison	**Ipilimumab + gp100**	**gp100**
Overall Survival	N	403	136
p-value = 0.0004	Number of deaths	306	119
	Number censored	97	17
	Hazard ratio (95% CI)	0.68 (0.55, 0.85)	
	Median OS, months (95% CI)	9.95 (8.48, 11.50)	6.44 (5.49, 8.71)
	Secondary Comparisons	**Ipilimumab**	**gp100**
Overall Survival	N	137	136
p-value = 0.0026	Number of deaths	100	119
	Number censored	37	17
	Hazard ratio (95% CI)	0.66 (0.51, 0.87)	
	Median OS, months (95% CI)	10.12 (8.02, 13.80)	6.44 (5.49, 8.71)
		Ipilimumab + gp100	**Ipilimumab**
Overall Survival	N	403	137
p-value = 0.7575	Number of deaths	306	100
	Number censored	97	37
	Hazard ratio (95% CI)	1.04 (0.83, 1.30)	
	Median OS, months (95% CI)	9.95 (8.48, 11.50)	10.12 (8.02, 13.80)

Source: MDX010-20 CSR[39]

CI = confidence interval; OS = overall survival

(Source: Sponsor's Table 4.4.1A in the Clinical Overview Report)

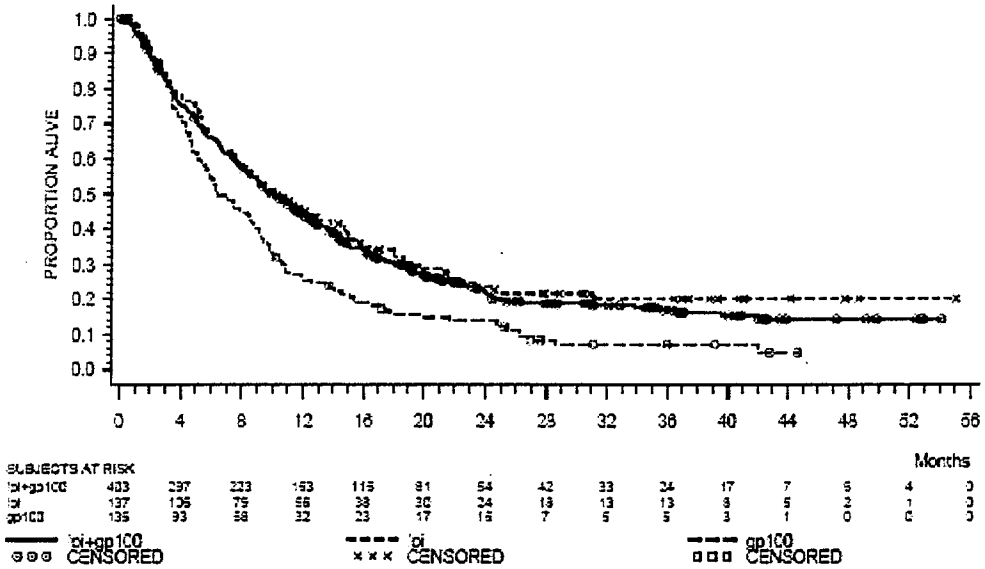

Figure 27: Kaplan-Meier plot of overall survival in phase 3 study, MDX-.010-20. Source: Sponsor's Figure 4.4.1 in Clinical Overview Report.

CA184-004: A brief description of the study is provided in Table 9. . The results for overall survival from the study are shown in Table 21.

Table 21: Overall Survival in CA184-004 (phase 2 study)

	3 mg/kg Ipilimumab N = 40	10 mg/kg Ipilimumab N = 42
Survival Rate at 1 Year (%)	52.00	45.24
95% CI (a)	(36.59, 67.32)	(30.95, 59.52)
Survival Rate at 18 Months (%)	33.80	35.19
95% CI (a)	(19.78, 49.08)	(21.16, 49.89)
Overall Survival (Months)		
Median	12.81	11.20
95% CI (b)	(9.49, 17.64)	(6.08, 16.92)

(Source: Sponsor's Table 7.2.2.2A in the Clinical Study Report for CA184004)

CA184-007: A brief description of the study is provided in Table 9. The results for overall survival from the study are shown in Table 22.

Table 22: Overall Survival in CA184-007 (phase 2 study)

	10 mg/kg Ipilimumab + Budesonide N = 58	10 mg/kg Ipilimumab + Placebo N = 57
Survival Rate at 1 Year (%)	55.37	62.41
95% CI (a)	(42.71, 68.79)	(49.37, 75.07)
Survival Rate at 18 Months (%)	47.93	50.87
95% CI (a)	(34.71, 61.19)	(37.51, 64.09)
Survival Rate at 2 Years (%)	40.57	41.78
95% CI (a)	(27.12, 54.37)	(28.30, 55.46)
Overall Survival (Months)		
Median	17.68	19.29
95% CI (b)	(6.30, ---)	(11.99, ---)

(Source: Sponsor's Table 7.2.2.2 in the Clinical Study Report for CA184007)

CA184-008: A brief description of the study is provided in Table 9. The results for overall survival from the study are shown in Table 23.

Table 23: Overall Survival in CA184-008 (phase 2 study)

	10 mg/kg Ipilimumab N = 155
Survival Rate at 1 Year (%)	47.22
95% CI (a)	(39.52, 55.11)
Survival Rate at 18 Months (%)	39.33
95% CI (a)	(31.73, 47.24)
Survival Rate at 2 Years (%)	32.83
95% CI (a)	(25.37, 40.49)
Overall Survival (Months)	
Median	10.22
95% CI (b)	(7.59, 16.30)

(Source: Sponsor's Table 7.2.2.2 in the Clinical Study Report for CA184008)

CA184-022: A brief description of the study is provided in Table 9. The results for overall survival from the study are shown in Table 24 and Figure 28.

Table 24: Overall Survival in CA184-022 (phase 2 study)

	0.3 mg/kg ipilimumab N = 73	3 mg/kg ipilimumab N = 72	10 mg/kg ipilimumab N = 72
Survival Rate at 1 Year (%)	39.58	39.32	48.64
95% CI (a)	(28.20, 51.19)	(27.97, 50.37)	(36.84, 60.36)
Survival Rate at 18 Months (%)	23.04	30.24	34.52
95% CI (a)	(13.39, 33.61)	(19.76, 41.43)	(23.35, 46.16)
Survival Rate at 2 Years (%)	18.43	24.20	29.81
95% CI (a)	(9.62, 28.22)	(14.42, 34.75)	(19.13, 41.14)
Overall Survival (Months)			
Median	8.57	8.74	11.43
95% CI (b)	(7.69, 12.71)	(6.87, 12.12)	(6.90, 16.10)

(Source: Sponsor's Table 7.2.3.2 in the Clinical Study Report for CA184022)

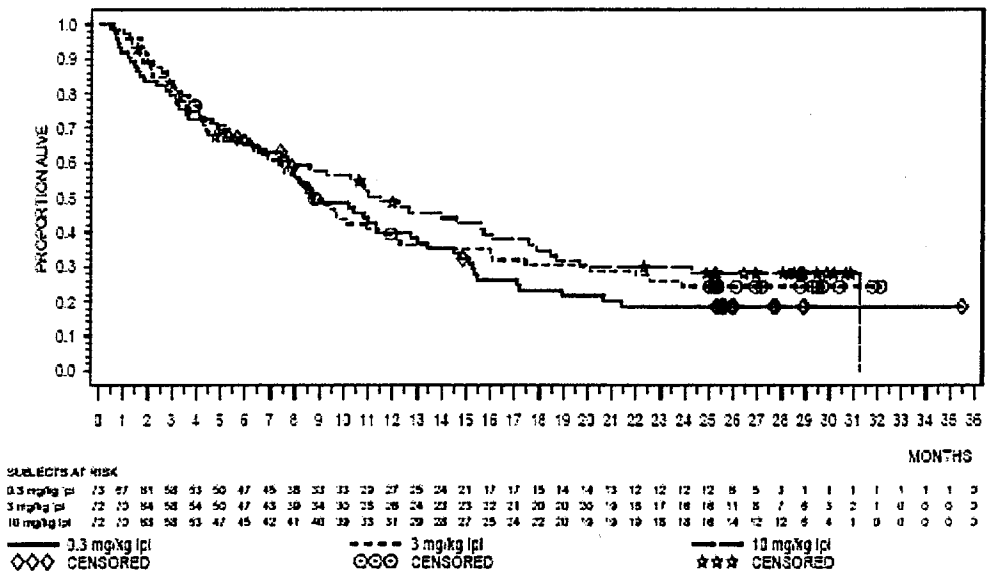

Figure 28: Kaplan-Meier plot of overall survival in study CA184-022. Source: Sponsor's Figure 7.2.3.2A in the Clinical Study Report.

CA184-024: This is an ongoing randomized double blind placebo controlled phase 3 trial in patients with chemotherapy-naïve, unresectable or metastatic melanoma to compare the overall survival of 10 mg/kg dose of ipilimumab in combination with dacarbazine compared to placebo plus dacarbazine.

Appendix 4.3

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

BLA	125377
Brand Name	YERVOY
Generic Name	Ipilimumab
Sponsor	Bristol-Myers Squibb Company
Indication	Advanced melanoma
Dosage Form	Intravenous (IV) infusion
Drug Class	Monoclonal antibody
Therapeutic Dosing Regimen	3 mg/kg administered intravenously (IV) over 90 minutes every 3 weeks for a total of 4 doses.
Duration of Therapeutic Use	(b) (4)
Maximum Tolerated Dose	Not determined
Submission Number and Date	STN 0; August, 3, 2010
Review Division	DDOP/DBOP/HFD150

Summary

Overall Summary of Findings

No large QT prolongation effects of ipilimumab (3 mg/kg and 10 mg/kg) were detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the change from baseline in QTcF was 11.4 and 9.6 ms for 3- and 10-mg/kg doses, respectively. Since this was not a thorough QT study, placebo and positive control (moxifloxacin) were not evaluated as part of this study.

In this randomized, double blind, multicenter, biomarker study, 82 patients received ipilimumab 3 and 10 mg/kg. Overall summary of findings is presented in **Table 1**.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Ipilimumab (3 mg/kg and 10 mg/kg) for Day 1 and Day 64 (FDA Analysis)

Treatment	Day	Time (hour)	ΔQTcF (ms)	90% CI (ms)
Ipilimumab 3 mg/kg	1	2.5	0.4	(-3.4, 4.2)
Ipilimumab 3 mg/kg	64	2.5	3.9	(-3.6, 11.4)
Ipilimumab 10 mg/kg	1	1.5	3.8	(0.3, 7.3)
Ipilimumab 10 mg/kg	64	1.5	4.8	(0.0, 9.6)

The doses of ipilimumab evaluated in the study are acceptable. The C_{max} after 10-mg/kg dose is approximately 3.3 fold that of the therapeutic dose (3 mg/kg). There are no known intrinsic or extrinsic factors that might affect pharmacokinetics of ipilimumab. Thus, the

highest dose studied (10 mg/kg) should cover the exposures possible after therapeutic dose of 3 mg/kg. Also, the reviewer's independent exposure-response analysis did not show any concentration dependent prolongation in QT.

QT Interdisciplinary Review team's Comments

- In general a QT assessment is not recommended for monoclonal antibodies since we expect hERG liability to be low. We recommend ECG monitoring in clinical studies (baseline and periodic on therapy ECGs) to capture large ECG effects that may be due to off-target cardiotoxicity. In this case, the sponsor has conducted two ECG sub-studies since routine ECG monitoring was not incorporated in the development program.
- The sponsor should be advised to incorporate safety ECGs post-treatment in on-going and future trials for other indications, and submit an integrated cardiac safety report with categorical ECG analysis and related AE data. This would be especially useful in trials where comparator arms are available.
- Study CA184004 seems adequate to exclude large effects on the ECG intervals to support approval for the advanced melanoma indication. Although ΔQTcF exceeded the regulatory threshold on Day 64 with the 3-mg/kg dose, it seems to be related to increased variability in QTc in the patient population compared to healthy volunteers and does not seem to be suggestive of a positive signal for QT prolongation. In addition the exposure-response relationship was flat.

Proposed Label

The sponsor has not proposed any labeling related to ECG effects in the PI and we concur.

BACKGROUND

Product Information

Ipilimumab (MDX-010, BMS-734016), a fully human anti-human CTLA-4 (CD152) monoclonal antibody of the IgG1-κ isotype, with a predicted molecular weight of 147,991 Daltons. It is an immunomodulatory agent that is being developed for use in the treatment of cancer. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4, expressed on a subset of activated T cells, with B7 (CD80/CD86) molecules on professional antigen-presenting cells. This results in T-cell potentiation due to blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4/B7 interaction.

Market approval status

Ipilimumab is not approved for marketing in any country.

Preclinical Information

"In accordance with ICH S7, evaluations of the potential effects of intravenous administration of ipilimumab on the cardiovascular, central/peripheral nervous and respiratory systems were included as part of the pivotal GLP repeat-dose toxicity studies

in monkeys. These studies assessed dosing-interval normalized dose/exposure multiples approximately 3- to 10-fold greater than those in humans given 3 mg/kg every 3 weeks. No drug-related findings were observed in standard clinical evaluations of cardiovascular, respiratory and neurologic function (including behavior, posture, coordination, neurologic exams that included peripheral and cranial nerve evaluations, peripheral reflexes, proprioception, and eye movements, and in the 1-month study, electrocardiograms) conducted in monkeys as part of the pivotal repeat-dose toxicity studies for up to 6 months duration with ipilimumab."
(*Source: Non-clinical Overview eCTD 2.4*)

Previous Clinical Experience

The clinical safety summary describes the safety data from 1107 subjects (975 of whom received ipilimumab, 622 at 3 mg/kg and 353 at 10 mg/kg) treated in Phase 2 and 3 studies to support an indication for ipilimumab 3 mg/kg as monotherapy in patients with advanced pretreated melanoma. ECGs have been collected for this patient population only in CA184004.

Adverse events regardless of relationship to study drug that could potentially be clinical manifestations of torsade de pointes/QT prolongation (e.g., syncope, loss of consciousness, ventricular arrhythmia, cardiac arrest, ventricular tachycardia, sudden death) or dizziness/seizures (e.g., convulsion, epilepsy, partial seizures) were summarized across all completed studies in melanoma, including those not included in this application (N = 1498 subjects across all doses and for the entire on-study period in CA184004, CA184007, CA184008, CA184022, CA184042, MDXCTLA-02, MDXCTLA-04, MDX010-03, MDX010-05, MDX010-08, MDX010-13, MDX010-15, MDX010-19 and MDX010-20).

Adverse events that could potentially be clinical manifestations of torsade de pointes/QT prolongation were reported in 15 (1.0%) subjects, most commonly syncope (8 subjects, 0.5%) (Table 4.2). All but 1 of the events was considered unrelated to study drug (Grade 3 syncope in Subject CA184004-7-4002 was considered related to study drug). An additional event (Grade 3 syncope in Subject M13-001-5024) was reported as related to IL-2 and unrelated to ipilimumab in the combination study MDX010-13. Two (0.1%) subjects experienced Grade 5 events, both were considered unrelated to study drug (sudden death in Subject CA184004-15-4082 and cardiac arrest in Subject CA184007-21-7051).

Adverse events of dizziness were reported in 5.8% of subjects and were predominately Grade 1-2 in severity. The majority of these events were considered unrelated to study drug.

Table 4.2: On-Study Adverse Events that Could Potentially be Clinical Manifestations of Torsade De Pointes/QT Prolongation in Completed Studies in Melanoma - Ipilimumab Treated Subjects

SYSTEM ORGAN CLASS / PREFERRED TERM	NUMBER OF SUBJECTS (%) WORST CTC GRADE — POOLED (N = 1493) GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5	UNKNOWN	ANY GRADE
ANY ADVERSE EVENT	2 (0.1)	2 (0.1)	7 (0.5)	2 (0.1)	2 (0.1)	0	15 (1.0)
NERVOUS SYSTEM DISORDERS	1 (<0.1)	2 (0.1)	6 (0.4)	0	0	0	9 (0.6)
SYNCOPE	1 (<0.1)	1 (<0.1)	6 (0.4)	0	0	0	8 (0.5)
LOSS OF CONSCIOUSNESS	0	1 (<0.1)	0	0	0	0	1 (<0.1)
CARDIAC DISORDERS	1 (<0.1)	0	1 (<0.1)	2 (0.1)	1 (<0.1)	0	5 (0.3)
VENTRICULAR ARRHYTHMIA	1 (<0.1)	0	1 (<0.1)	1 (<0.1)	0	0	3 (0.2)
CARDIAC ARREST	0	0	0	1 (<0.1)	1 (<0.1)	0	2 (0.1)
VENTRICULAR TACHYCARDIA	0	0	0	1 (<0.1)	0	0	1 (<0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	0	0	1 (<0.1)	0	1 (<0.1)
SUDDEN DEATH	0	0	0	0	1 (<0.1)	0	1 (<0.1)

MedDRA Version 12.1

Subjects may have more than one event.
On-study events are events reported between first dose and 70 days after last dose of study therapy.
Unknown intensities are included in "Any Grade" column. MDX010-08,13,15 do not report grade 5 intensities.
CTC Version 2.0: MDX010-02,04,MDX010-03,15,08,13.
CTC Version 3.0: MDX010-15,13,20,CA184004,007,008,022,042.

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PROGRAM SOURCE: /wbdn/clin/proj/ca/184/iss01/val/cpp/programs/sfty_aesum.sas RUN DATE: 12-MAY-2010 13:43

Source: SCS-A Appendix 4.2

The sponsor had also submitted an interim report of ECG findings from Study MDX010-21 entitled "A Phase I/II, Open-label, Dose-escalation Study of MDX-010 Administered Every 3 Weeks for 4 Doses in Patients with Metastatic Hormone-Refractory Prostate Cancer".

Twenty-eight patients (average age 62 years) had at least one ECG after screening. These ECGs were read centrally by [redacted] (b) (4). ECGs were mainly taken at screening and one at Visit 6. The number of patients with changes from screening baseline ECGs are shown below. No ECGs in the 28 patients had a QTcF measurement greater than 500 ms. After the screening ECGs, there was a trend towards higher heart rates.

Table 2 – Number of Patients with Changes from Screening ECGs by Variable.

QTcF	N	Average Max Change	Maximum Change
Increase	10	23.8	47
Decrease	17	-17.7	-57
No Change	1		
> 500 msec	0		
Heart Rate			
Increase	25	12.6	57
Decrease	2	-14.0	-15
No Change	1		
QRS Duration			
Increase	15	6.9	14
Decrease	15	-7.1	-23
No Change	1		
> 110 msec and increase > 10%	2		
PR-Interval			
Increase	7	13.0	29
Decrease	20	-18.3	-47
No Change	1		

Only three patients had an abnormal, clinically significant ECG (pts 21001, 26046, and 73016). Patient 21001 had two abnormal ECGs due to non-specific ST and T-wave

abnormalities after a normal screening ECG. Patient 26046 had atrial fibrillation at screening, with left anterior hemi-block, and non-specific T wave abnormalities at screening and at the V6 visit. Patient 73016 had atrial fibrillation at the V6 visit after Normal Sinus Rhythm was reported on the Screening ECG. A subsequent, unscheduled ECG showed an Ectopic Atrial Rhythm.
(Source: Summary of Clinical Safety and Interim ECG report for study MDX010-21)
Reviewer's Comment: The ECG changes reported above can be expected considering this older population with advanced prostate cancer. Overall, in the melanoma program, there does not appear to be a significant concern regarding AEs related to QT prolongation. Cardiac arrest narrative for Subject CA184007-21-7051 was also reviewed in the CSR for CA 184007. This subject had history of MI, CABG and CVA and had a cardiac arrest 28 days post-treatment with ipilimumab.

Clinical Pharmacology

Appendix 0 summarizes the key features of Ipilimumab's clinical pharmacology.

SPONSOR'S SUBMISSION

Overview

The QT-IRT did not review the protocol prior to conduct of this study. The sponsor submitted the study report CA184004 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

QT Study

Title

An exploratory study to determine potential predictive markers of response and/or toxicity in patients with unresectable stage III or IV malignant melanoma randomized and treated with ipilimumab (MDX-010/BMS-734016) at two dose levels.

Protocol Number

CA184004

Study Dates

Study initiation date was 16 Nov, 2005.

Objectives

The primary objective of the study to analyze pre-treatment characteristics of the patient and/or tumor with clinical tumor response in patients with unresectable Stage III and IV melanoma, in order to identify candidate markers predictive of response and/or serious toxicity to ipilimumab dosed at 3 or 10 mg/kg every 3 weeks.
One of the secondary objectives was to assess the effects of ipilimumab on electrocardiogram (ECG) parameters.

Study Description

This was a Phase 2, randomized, double-blind, multicenter study to determine predictive markers of response in subjects with advance melanoma randomized in a 1:1 ratio to 3

mg/kg or 10 mg/kg of ipilimumab, stratified by use of prior immunotherapy for malignant melanoma.

Treatment Regimen

Ipilimumab was administered at either 3-mg/kg or 10-mg/kg as a 90-minute intravenous (IV) infusion.

Infusions were given according to the following schedule:

- Induction Period: 1 infusion at Weeks 1, 4, 7, and 10 (total of 4 doses)
- Maintenance Period: 1 infusion every 12 weeks (e.g., Weeks 24, 36, 48+) until progression, study drug-related toxicity leading to discontinuation of further ipilimumab dosing, withdrawal of consent, or study closure.

Sponsor's Justification for Doses

"The doses of ipilimumab used in this study were based on the safety, PK, and efficacy of ipilimumab monotherapy in Phase 1 and 2 studies in subjects with advanced melanoma at a range of doses and schedules. In Phase 1 and 2 studies ipilimumab demonstrated durable tumor responses as monotherapy at 3 mg/kg every 3 weeks (MDXCTLA4-02 and MDX010-08) and when escalated to 9 mg/kg every 3 weeks in an intrasubject dose-escalation study (MDX010-19). Ipilimumab was tolerable in all of these studies.

Ipilimumab 10 mg/kg was tolerable in MDX010-15, which was amended to treat a cohort of 23 subjects at 10 mg/kg every 3 weeks. Based on these data, it was expected that 10 mg/kg every 3 weeks would have an acceptable safety profile and potentially a higher response rate than 3 mg/kg every 3 weeks."

(Source: Sponsor's study report, CA184004, Page 63-64)

Reviewer's Comment: The dose selection seems to be acceptable. There are no known intrinsic or extrinsic factors that might affect pharmacokinetics of ipilimumab. Thus, the highest dose studied (10 mg/kg q3wk) should cover the exposures possible after therapeutic dose of 3 mg/kg q3wk.

Instructions with Regard to Meals

There is no instruction given in the sponsor's report.

Reviewer's Comment: Effect of food on ipilimumab PK is not anticipated due to intravenous route of administration.

ECG and PK Assessments

"Serum PK samples were collected according to the following schedule: Pre-dose on Days 1 and 43; 90-min post-infusion on Days 1 and 43; between 3 to 7 days post-dose on Days 45 to 49 and between 10 to 15 days post-dose on Days 52 to 57.

Table 7.3.5.1: Sampling Schedule

Study Day	Time (Relative To Dosing) Hour	PK[a] Blood Sample	Flow Cytometry/ ELISPOT/ RT-PCR	Antibody Titers to NY-ESO-1	Antibody Titers to Tetanus/Influenza / Pneumococcal	HAHA
- Day 10	Pre-Dose				X	
Day 1	Pre-Dose	X	X	X		X
Day 1	After 90min infusion	X				
Day 22	Pre-Dose					X
Day 23-25			X	X		
Day 43	Pre-Dose	X				X
Day 43	After 90min infusion	X			X	
Day 45-49	Between Day 3-7 post dose	X				
Day 52-57	Between Day 10-15 post dose	X		X		
Day 64	Pre-dose	X				X
Day 78			X	X		
Day 162	Pre-dose					X
Day 246	Pre-dose					X

"Triplicate, serial ECGs were collected at screening, baseline (Day -1), Day 1, and Day 64 (prior to infusion and 90 minutes and 150 minutes after starting infusion) on all treated subjects and analyzed by a third party ECG core lab for interval duration measurements and waveform morphology. A limited number of subjects had ECGs collected at Week 24."

(Source: The sponsor's report CA184004, page 78, 163)

Reviewer's Comment: The sampling times seems to be reasonable as they were measured at and after t_{max} (90 min).

Baseline

The sponsor used the time-matched baselines over both pre-treatment days (Day -1) in their primary analyses.

ECG Collection

Electrocardiograms were collected digitally and transferred to an independent third-party vendor for determination of the ECG intervals and interpretation of morphology by a trained cardiologist. Further details regarding ECG interpretation (lead, method, blinding etc) are unavailable.

Sponsor's Results

Study Subjects

A total of 101 subjects with advanced melanoma were enrolled and 82 were randomized. Exclusion criteria:

Uncontrolled or significant cardiovascular disease including myocardial infarction within 12 months, uncontrolled angina within 6 months, Class III-IV New York Heart Association congestive heart failure, diagnosed or suspected congenital long QT syndrome, any history of clinically significant ventricular arrhythmias, prolonged QTc interval > 450 ms on pre-entry ECG, history of 2nd or 3rd degree heart block (could be eligible with a pacemaker).

Protocol deviation: five subjects had missing or prolonged QTc interval at screening. One of these subjects (CA184004-32-4034 in the 3-mg/kg group) reported prolonged QTc (> 450 ms); the rest had missing values.

Disease progression was the most common reason overall for treatment discontinuation, all occurring during the induction period (3 mg/kg: 55.0%, 10 mg/kg: 52.4%). The rates of treatment discontinuation due to study drug toxicity, as reported on the completion/discontinuation page of the CRF, were similar between groups (3 mg/kg: 5 [12.5%] subjects; 10 mg/kg: 7 [16.7%] subjects). The most common drug related toxicities leading to treatment discontinuation in the 3-mg/kg group were panhypopituitarism in 2 subjects and anorexia in 2 subjects (the anorexia was accompanied by severe colitis and depression in 1 subject). The most common drug-related toxicities leading to treatment discontinuation in the 10-mg/kg group were GI (diarrhea and/or colitis in 2 subjects, diarrhea accompanied by anorexia and rash in 1 subject, and left colon/proximal jejunal perforation in 1 subject). The table below summarizes reason for discontinuation of treatment.

Table 6.2: Discontinuation of Study Therapy - Treated Subjects

	NUMBER OF SUBJECTS (%)		
	3.0 MG/KG IPILIMUMAB N = 40	10 MG/KG IPILIMUMAB N = 42	TOTAL N = 82
Subjects Treated	40	42	82
STILL ON TREATMENT	0	0	0
OFF TREATMENT	40 (100.0)	42 (100.0)	82 (100.0)
Reason Off Treatment			
DISEASE PROGRESSION	22 (55.0)	22 (52.4)	44 (53.7)
OTHER	7 (17.5)	7 (16.7)	14 (17.1)
STUDY DRUG TOXICITY	5 (12.5)	7 (16.7)	12 (14.6)
DEATH	3 (7.5)	3 (7.1)	6 (7.3)
DETERIORATION W/O PROGRESSION	1 (2.5)	2 (4.8)	3 (3.7)
ADVERSE EVENT UNRELATED TO STUDY DRUG	0	1 (2.4)	1 (1.2)
PHYSICIAN DECISION	1 (2.5)	0	1 (1.2)
SUBJECT REQUEST	1 (2.5)	0	1 (1.2)

Percentages are based on the number of subjects treated.

LIBRARY: /wwbdm/data/ca/184/004/fa_all/blinded/analysis
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RUN DATE: 29-MAR-2010 16:30

(Source: Sponsor's report CA184004, page 115)

Statistical Analyses

Central Tendency Analysis

Table 2 shows the mean changes from time-matched baseline and 90% CIs for QTcF interval on Days 1 and 64. The maximum mean QTcF change from time-matched baseline at 3 mg/kg was 4 ms (upper 90% CI limit of 12.12 ms). After infusion of 10 mg/kg, the maximum mean change was 4.68 ms (upper 90% CI limit of 9.638). Although the changes seen after treatment with ipilimumab were small, precise quantification is difficult due to the lack of a placebo and positive control group.

Table 2: Summary Statistics for ΔQTcF on Days 1 and 64

Nominal Time Post-Infusion (minutes)	Treatment					
	Ipilimumab 3 mg/kg			Ipilimumab 10 mg/kg		
	n	Mean Difference (msec)	90% CI	n	Mean Difference (msec)	90% CI
Day 1						
0	34	-1.59	-4.927, 1.751	38	2.24	-2.202, 6.676
90	33	-1.91	-5.502, 1.684	36	3.69	0.126, 7.263
150	30	0.47	-3.489, 4.422	35	0.46	-4.460, 5.375
Day 64						
0	24	-2.79	-7.794, 2.210	25	1.68	-5.043, 8.403
90	19	-3.74	-13.068, 5.595	22	4.68	-0.274, 9.638
150	16	4.00	-4.121, 12.121	21	0.57	-5.127, 6.270

(Source: Sponsor's report CA184004, page 165)

Reviewer's Comments: The reviewer confirmed the sponsor's conclusion and analysis by the reviewer is also provided in section 5.2.

Assay Sensitivity

Since there was no moxifloxacin arm in the study, assay sensitivity cannot be established.

Categorical Analysis

"The majority of subjects had QTcF intervals < 450 ms for the duration of the study.
One subject in the 3-mg/kg group had a QTcF > 500 ms after treatment with ipilumimab; no subject in the 10-mg/kg group had a QTcF interval> 500 ms.
"The majority of the subjects had QTcF changes from time-matched baseline that were ≤ 30 ms. There were no QTcF changes from baseline > 60 ms in either treatment group. The frequency of subjects with QTcF changes from time-matched baseline between 31-60 ms was low and did not appreciably change after treatment with ipilimumab.
"One subject in the 3-mg/kg group had a QTcF > 500 ms. after treatment with ipilumimab; no subject in the 10-mg/kg group had a QTcF interval > 500 ms. The subject in the 3-mg/kg group (CA184004-32-4034), with an on-treatment QTcF interval > 500 ms (507 ms, Grade 3) had a baseline Grade 2 QTcF prolongation (range 470 to 475 ms) accompanied by QRS prolongation (> 150 ms), consistent with a medical history of left bundle branch block (LBBB). Other significant medical history included hypothyroidism

for which the subject was receiving levothyroxine. On Day 1, the QTcF was 467 ms pre-infusion, 475 ms at 90 minutes, and 484 ms at 150 minutes. On Day 64, the QTcF was 470 ms pre-infusion, 467 ms at 90 minutes, and 507 ms (Grade 3) at 150 minutes. The QTcF changes from time-matched baseline for this subject ranged from -3 ms to 37 ms after treatment with ipilimumab. Week 24 ECG data were not available for this subject."
(Source : Sponsor's report CA184004, page 165-166)
Reviewer's Comments: The reviewer confirmed the sponsor's conclusion and analysis by the reviewer is also provided in section 5.2.

Safety Analysis

A total of 25 (62.5%) treated subjects in the 3-mg/kg group and 28 (66.7%) treated subjects in the 10-mg/kg group died, most within 70 days of the last dose of ipilimumab. The sponsor reports progressive disease was the most common reason for death in each group. The sponsor reports no Investigator-reported AEs, discontinuations, or deaths related to ECG abnormalities

Subject CA 184004-15-4082 had the last dose of ipilimumab on Day 23 and died on Day 36; 14 days after post-2nd dose of study therapy, the subject could not breathe and became unconscious. He was taken to the emergency room, where he was pronounced dead. Cause of death was reported as possibly, cardiac infarction. No other information was available. An autopsy was not performed. ECGs were performed at screening and on Day 1 ((b) (6)). All QTc intervals for this subject were normal at screening and after treatment with ipilimumab.

CA184004-31-4038 had the last dose of ipilimumab on Day 44 and died on Day 46 due to Grade 5 dyspnea (respiratory insufficiency), 3 days after post-3rd dose of study therapy. Autopsy information is not available. QTc intervals at baseline and Day 1 are available and were reported normal.

Reviewer's Comment: These cases are confounded due to co-morbidity and lack of information limits assessment. An arrhythmic event with association to study drug cannot be completely excluded based on timing (t1/2 = 11-27 days).

CA184004-7-4002 had Grade 3 syncope on Day 103, 61 days after post- 3rd dose of study therapy. The subject did not receive treatment and the event resolved on Day 104 (01-May-2006). ECGs were performed at baseline, on Day 1 (18-Jan-2006), and on Day 64 (22-Mar-2006). All QTc intervals for this subject were normal at screening and after treatment with ipilimumab.

CA184004-22-4058 with CNS metastasis, had a convulsion on Day 98, 35 days after the last dose of study therapy. ECGs were performed at baseline, on Day 1 (02-May-2007), and on Day 64 (04-Jul-2007). All QTc intervals for this subject were normal at screening and after treatment with ipilimumab.

CA184004-32-4089 had convulsions on day 18, 18 days past 1st dose of study therapy, As a result of seizure, he was discontinued from the study therapy. He had received his last dose of study therapy on Day 1 (12-Apr-2007). Results from a CT scan and MRI of the brain showed a space occupied lesion at the left frontal lobe and a new brain metastasis (Grade 4). ECGs were performed at baseline and on Day 1 (12-Apr-2007), and all QTc intervals were normal.

Reviewer's Comment: Association to study drug is unlikely with the above cases-syncope based on timing and seizures based on underlying CNS metastasis.

QTcF prolongations > 480 ms were observed in a single subject in the 3-mg/kg group; no subject in the 10-mg/kg group had a QTcF interval > 480 ms (which is discussed in section 0).

There were no QTcF changes from baseline > 60 ms in either treatment group. The frequency of subjects with QTcF changes from time-matched baseline between 31-60 ms was low and did not appreciably change after treatment with ipilimumab

Reviewer's Comment: Table S.7.14 in the CSR was reviewed, and we agree with sponsor's statement.

Abnormal findings in ECG intervals, rhythm, and/or waveform morphology were reported for 60 treated subjects. No clinically meaningful changes from baseline were identified. In most cases, these abnormal findings were present at baseline and consistent with pre-existing medical conditions (cardiovascular disease) and concomitant medications used for their treatment. The most frequent abnormal findings were sinus bradycardia (heart rate 50 to 60 beats per minute) and non-specific ST/T wave changes.

Appendix 7.24 was reviewed, and we agree with sponsor.

Clinical Pharmacology

Pharmacokinetic Analysis

The summary statistics for PK parameters after the first and third dose at 10 mg/kg are provided in Table 3.

Table 3: Summary Statistics for PK parameters in the Study CA184008

PK Parameters (Units)	Dose 1 (N=4)		Dose 3 (N=4)	
	Mean (CV%[a])	Range	Mean (CV%)[a]	Range
Cmax (µg/mL)	200 (16%)	163 - 240	251 (24%)	189 - 338
Tmax (hr)	1.58	1.58 - 1.67	1.58	1.5 - 1.58
AUC(0-21d) (µg•hr/mL)	36110 (24%)	25640 - 44261	52713 (17%)	41276 - 62306
AUC(INF) (µg•hr/mL)	45547 (32%)	28955 - 60050	N/A[b]	N/A
Terminal T-HALF (day)	8.87 (2.14)	6.78 - 11.7	16.9 (7.11)	11 - 27
CL (mL/hr)	16.2 (3.10)	13.7 - 20.7	N/A[b]	N/A
VSS (L)	4.97 (0.46)	4.43 - 5.45	N/A[b]	N/A

a All values are expressed as arithmetic means (SD), except for AUC and Cmax, which are expressed as geometric means (CV%), Tmax is expressed in median (range).
b AUC(INF),CL and VSS for the third dose was not calculated (not available, N/A).

(Source: Sponsor's report, "Summary of clinical pharmacology studies", page 27)

The predicted mean C_{max} (%CV) after 3 mg/kg multiple dose was 76.8 µg/ml (20%).

Exposure-Response Analysis

The sponsor did not perform exposure-response analysis.

Reviewer's Comment: We performed an independent analysis using a linear mixed effect model. The analysis is presented in section 5.2

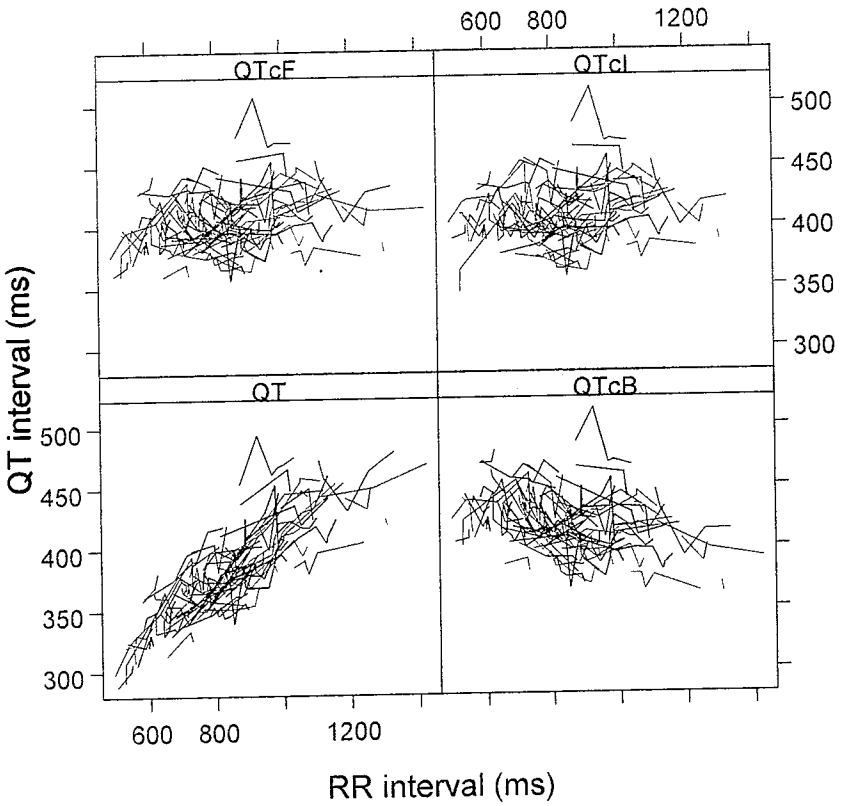
REVIEWERS' ASSESSMENT

Evaluation of the QT/RR Correction Method

The QT-RR interval relationship is presented in Figure 1 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

The sponsor used QTcF for the analysis which seems to be appropriate. To be consistent, the FDA reviewer also used QTcF for further analysis.

Figure 1: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



Statistical Assessments

QTc Analysis

The Primary Analysis for Ipilimumab

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes the time-matched baseline and gender as covariates. The analysis results are listed in the following tables.

Table 4: Analysis Results of ΔQTcF Ipilimumab on Day 1

	ΔQTcF: Ipilimumab 3 mg/kg			ΔQTcF: Ipilimumab 10 mg/kg		
Time (hour)	N	Mean	90% CI	N	Mean	90% CI
0	34	-1.7	(-4.9,1.5)	38	2.3	(-2.0,6.6)
1.5	33	-1.9	(-5.4,1.6)	36	3.8	(0.3,7.3)
2.5	30	0.4	(-3.4,4.2)	35	0.5	(-4.3,5.2)

Table 5: Analysis Results of ΔQTcF Ipilimumab on Day 64

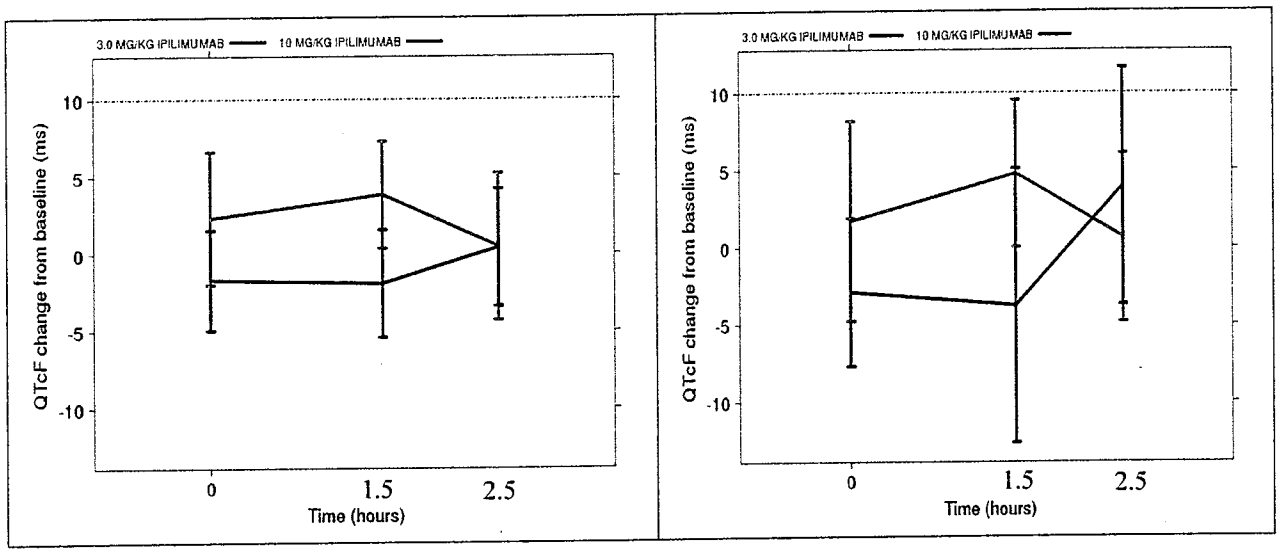
	ΔQTcF: Ipilimumab 3 mg/kg			ΔQTcF: Ipilimumab 10 mg/kg		
Time (hour)	N	Mean	90% CI	N	Mean	90% CI
0	24	-2.9	(-7.6,1.8)	25	1.7	(-4.7,8.1)
1.5	19	-3.8	(-12.6,5.1)	22	4.8	(0.0,9.6)
2.5	16	3.9	(-3.6,11.4)	21	0.6	(-4.8,6.0)

The largest upper bound of 2-sided 90% CI for mean QTcF change from time-matched baseline was 11.4 ms.

Graph of ΔQTcF Over Time

The following figure displays the time profile of ΔQTcF for different treatment groups.

Figure 2: Mean and 90% CI ΔQTcF Time course on Day 1 (left) and Day 64 (right)



Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ **450 ms,** between 450 ms and 480 ms. One subject's QTcF was above 480 ms.

Table 6: Categorical Analysis of QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms	
Treatment Group	# Subj	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
Ipilimumab 3 mg/kg	38	282	35 (92.1%)	270 (95.7%)	2 (5.3%)	10 (3.5%)
Ipilimumab 10 mg/kg	41	301	34 (82.9%)	289 (96.0%)	7 (17.1%)	12 (4.0%)

Table 7 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 7: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Ipilimumab 3 mg/kg	35	156	33 (94.3%)	154 (98.7%)	2 (5.7%)	2 (1.3%)
Ipilimumab 10 mg/kg	38	177	34 (89.5%)	171 (96.6%)	4 (10.5%)	6 (3.4%)

PR Analysis

The mean change in PR interval is shown in the table below (*done by Huifang Chen, data manager QT-IRT*).

Table 8: Mean Change in PR

Treatment	Visit	MEANCHG	STDDEV	LOWER 90% CI	UPPER 90% CI
10 mg/kg ipilimumab	induction phase – week 1	1.99	9.73	0.44	3.55
10 mg/kg ipilimumab	induction phase- week 10	-1.49	9.31	-3.37	0.40
3.0 mg/kg ipilimumab	induction phase- week 1	1.75	11.62	-0.24	3.74
3.0 mg/kg ipilimumab	induction phase – week 10	-1.73	14.14	-4.89	1.43

Outlier analysis for PR interval is included in the appendix, there were no categorical changes in PR post-treatment that were clinically relevant (> 25% change from baseline).

QRS Analysis

The same statistical analysis was performed on QRS interval. The mean change in QRS interval is shown in the table below.

Table 9: Mean Change in QRS Interval

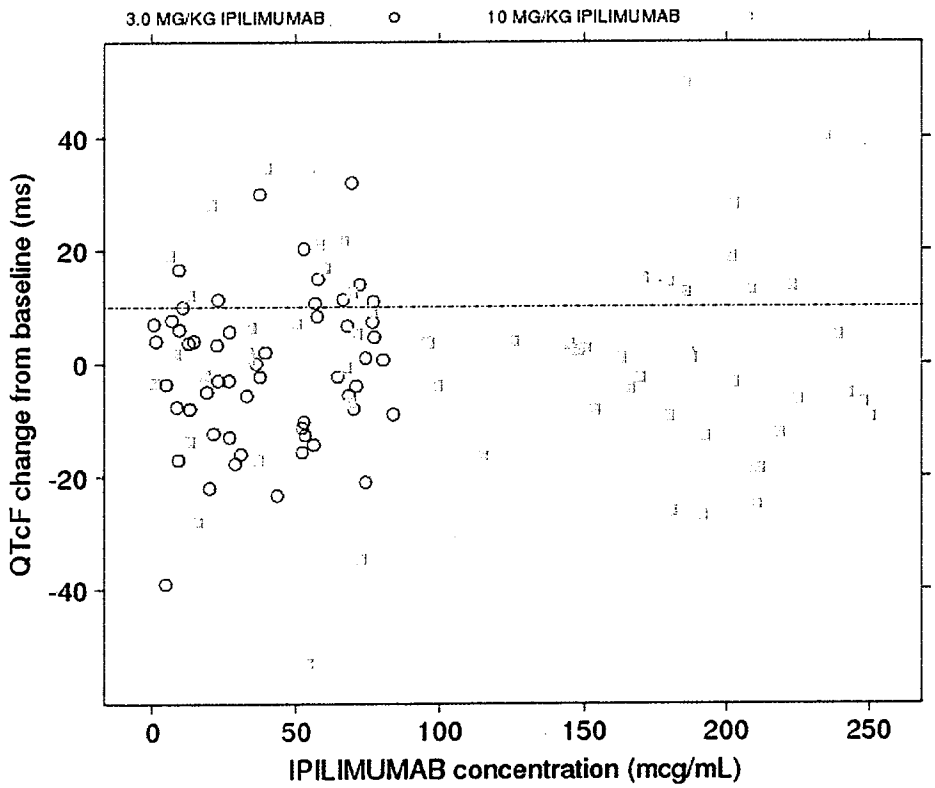
TREATMENT	VISIT	MEANCHG	STDDEV	LOWER C 90% CI	UPPER 90% CI
10 mg/kg ipilimumab	induction phase -week 1	0.76	5.29	-0.08	1.61
10 mg/kg ipilimumab	induction phase -week 10	0.06	7.18	-1.39	1.52
3.0 mg/kg ipilimumab	induction phase -week 1	-0.30	4.88	-1.12	0.53
3.0 mg/kg ipilimumab	induction phase -week 10	-1.67	7.84	-3.37	0.04

Outlier analysis for QRS interval is included in the appendix. No subject with an absolute QRS interval over 110 ms post-treatment had a change from baseline that was over 25%. Subject CA184004-32-4034 had a baseline and post-treatment QRS of over 150 ms with LBBB.

Clinical Pharmacology Assessments

The relationship between ΔQTcF and ipilmumab concentrations is visualized in Figure 3 with no evident exposure-response relationship.

Figure 3: Δ QTcF vs. Ipilimumab concentration



Clinical Assessments

Safety assessments

Events of clinical importance per the ICH-E14 guidance occurred in this study and have been reviewed in detail in section 0. Except for the sudden death and respiratory arrest where association to study drug although unlikely cannot be entirely excluded, the other events seem unrelated to study drug.

ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics, over 91% of the ECGs were annotated in the primary lead II. Less than 0.8% of ECGs were reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

PR and QRS Interval

There were no clinically relevant effects on the PR and QRS interval.

APPENDIX

Highlights of Clinical Pharmacology

Therapeutic dose	3 mg/kg administered intravenously (IV) over 90 minutes every 3 weeks for a total of 4 doses..	
Maximum tolerated dose	Not determined	
Principal adverse events	Most common adverse events: Nausea, diarrhea, vomiting, constipation, abdominal pain, fatigue pyrexia, peripheral edema, pruritus, rash, decreased appetite, headache, insomnia Dose limiting adverse events: diarrhea, colitis	
Maximum dose tested	Single Dose	20 mg/kg IV over 90 min.
	Multiple Dose	10 mg/kg administered intravenously (IV) over 90 minutes every 3 weeks for a total of 4 doses.
Exposures Achieved at Maximum Tested Dose	Single Dose	At 20 mg/kg: Mean Cmax (CV%):533 μg/mL (33%) Mean AUC(0-21d) (%CV): 64808μg.h/mL (23%)
	Multiple Dose	At 10 mg/kg: Mean $Cmax_{ss}$ (%CV): 233 μg/mL (24%) Mean $AUC(0\text{-}21d)_{ss}$(%CV): 48924 μg.h/mL (24%)
Exposures Achieved at Therapeutic Dose	Multiple dose	At 3 mg/kg (simulated from PPK) Mean $Cmax_{ss}$ (%CV): 76.77 μg/mL (20%) Mean $AUC(0\text{-}21d)_{ss}$(%CV): 16590 μg.h/mL (37%)
Range of linear PK	Linear across dose range of 0.3-10 mg/kg when administered IV over 90 min. every 3 weeks for 4 doses.	
Accumulation at steady state	Accumulation index ≤ 1.5 fold when administered IV over 90 min. every 3 weeks for 4 doses.	
Metabolites	No known active metabolites	
Absorption	Absolute/Relative Bioavailability	Not applicable (N/A) because administered IV
	Tmax	• Median (range) for parent: 1.58 h (1.45-24) • Median (range) for metabolites N/A

Distribution	Vss	Mean (%CV): 7.21 L (10.5%)
	% bound	N/A
Elimination	Route	• Primary route: no mass balance performed as ipilimumab is human monoclonal antibody (mAB). • Other routes: Monoclonal antibodies are cleared through interactions with specific receptors on the target cell surfaces, via interactions with the FcγR1 receptors, and via non specific proteolysis by proteases and peptidases in the liver and spleen. These non-specific mechanisms of clearance are the presumed primary expected routes of elimination of ipilimumab.
	Terminal t½	• Mean (%CV) for parent 14.7 h (30.1%) • Mean (%CV) for metabolites N/A
	CL	Mean (%CV) 15.3 mL/hr (38.5%)
Intrinsic Factors	Age	No impact of age on the PK of ipilimumab as determined via population PK analysis (PPK)
	Sex	No gender effect on the PK of ipilimumab as determined via PPK
	Race	Not determined as most subjects in the melanoma program were Caucasian
	Body weight	Ipilimumab CL and V increase with body weight. However, ipilimumab systemic exposure was similar across body weight after dosing ipilimumab on a mg/kg basis.
	Hepatic & Renal Impairment	No formal renal or hepatic impairment studies were performed. However, renal function (as measured by GFR), and hepatic function (as measured by baseline serum albumin and alkaline phosphatase) did not impact the PK of ipilimumab in the PPK. No impact of renal or hepatic impairment on the PK of ipilimumab as determined via PPK

Extrinsic Factors	Drug interactions	Concurrent use of budesonide, a corticosteroid, did not influence the PK of ipilimumab as determined via PPK. A separate study (CA184078) not included in this filing (because it was ongoing) evaluated the potential interaction between ipilimumab and 2 standard chemotherapy used in melanoma: dacarbazine and carboplatin/paclitaxel. Two of these chemotherapy agents are metabolized by P450 enzymes: dacarbazine (via CYP1A1, CYP1A2 and CYP2E1), and paclitaxel (via CYP2C8 and CYP3A4). Based on preliminary results, these 2 chemotherapy regimens did not have a clinical meaningful impact of systemic exposure of ipilimumab and vice versa.
	Food Effects	N/A as ipilimumab is given IV
Expected High Clinical Exposure Scenario	There are no intrinsic or extrinsic factors known to increase ipilimumab exposure in humans. The highest ipilimumab exposure in humans is expected to occur at the end of infusion. In the program the highest clinical dose given was 20 mg/kg IV as single dose, or 10 mg/kg every 3 weeks for 4 doses.	

Categorical PR and QRS analysis

Table 10: Categorical PR analysis

usubjid	treat	visit	ECG time point	day	time	PR	PR baseline
ca184004-32-4034	3.0 mg/kg ipilimumab	enrollment	end of infusion	-1	1.5	202	202
ca184004-32-4089	3.0 mg/kg ipilimumab	induction phase -week 1	pre-dose	1	0	216	186
ca184004-32-4089	3.0 mg/kg ipilimumab	induction phase -week 1	end of infusion	1	1.5	226	180
ca184004-32-4089	3.0 mg/kg ipilimumab	induction phase -week 1	1 hour post infusion	1	2.5	240	188
ca184004-35-4079	3.0 mg/kg ipilimumab	enrollment	end of infusion	-1	1.5	200.666667	200.666667
ca184004-24-4077	10 mg/kg ipilimumab	enrollment	1 hour post infusion	-1	2.5	201.333333	201.333333
ca184004-24-4077	10 mg/kg ipilimumab	induction phase -week 10	pre-dose	64	0	201.333333	192.666667
ca184004-24-4077	10 mg/kg ipilimumab	induction phase -week 10	end of infusion	64	1.5	200.666667	198
ca184004-24-4077	10 mg/kg ipilimumab	induction phase -week 10	1 hour post infusion	64	2.5	206	201.333333
ca184004-32-4056	10 mg/kg ipilimumab	induction phase -week 1	end of infusion	1	1.5	218	200
ca184004-32-4056	10 mg/kg ipilimumab	induction phase -week 1	1 hour post infusion	1	2.5	232	200
ca184004-32-4056	10 mg/kg ipilimumab	induction phase -week 10	pre-dose	64	0	210	200
ca184004-33-4094	10 mg/kg ipilimumab	enrollment	screening	.	.	201.333333	.
ca184004-33-4094	10 mg/kg ipilimumab	enrollment	pre-dose	-1	0	201.333333	201.333333
ca184004-33-4094	10 mg/kg ipilimumab	enrollment	end of infusion	-1	1.5	202	202

ca184004-33-4094	10 mg/kg ipilimumab	induction phase -week 1	pre-dose	1	0	207.333333	201.333333
ca184004-33-4094	10 mg/kg ipilimumab	induction phase -week 1	end of infusion	1	1.5	216.666667	202
ca184004-33-4094	10 mg/kg ipilimumab	induction phase -week 1	1 hour post infusion	1	2.5	207.333333	.
ca184004-33-4094	10 mg/kg ipilimumab	induction phase -week 10	1 hour post infusion	64	2.5	204	.

Table 11: Categorical QRS Analysis

usubjid	treat	visit	egtpt	day	time	QRS	QRS_baseline
ca184004-1-4044	3.0 mg/kg ipilimumab	induction phase - week 10	end of infusion	64	1.5	112	97.3333333
ca184004-1-4044	3.0 mg/kg ipilimumab	induction phase - week 10	1 hour post infusion	64	2.5	113.333333	96.6666667
ca184004-24-4028	3.0 mg/kg ipilimumab	enrollment	1 hour post infusion	-1	2.5	110.666667	110.666667
ca184004-24-4087	3.0 mg/kg ipilimumab	enrollment	end of infusion	-1	1.5	112	112
ca184004-24-4087	3.0 mg/kg ipilimumab	enrollment	1 hour post infusion	-1	2.5	112.666667	112.666667
ca184004-24-4087	3.0 mg/kg ipilimumab	induction phase - week 1	end of infusion	1	1.5	113.333333	112
ca184004-24-4087	3.0 mg/kg ipilimumab	induction phase - week 1	1 hour post infusion	1	2.5	112.666667	112.666667
ca184004-32-4034	3.0 mg/kg ipilimumab	enrollment	pre-dose	-1	0	158	158
ca184004-32-4034	3.0 mg/kg ipilimumab	enrollment	end of infusion	-1	1.5	160	160
ca184004-32-4034	3.0 mg/kg ipilimumab	enrollment	1 hour post infusion	-1	2.5	154	154
ca184004-32-4034	3.0 mg/kg ipilimumab	induction phase - week 1	pre-dose	1	0	154	158
ca184004-32-4034	3.0 mg/kg ipilimumab	induction phase - week 1	end of infusion	1	1.5	152	160
ca184004-32-4034	3.0 mg/kg ipilimumab	induction phase - week 1	1 hour post infusion	1	2.5	150	154
ca184004-32-4034	3.0 mg/kg ipilimumab	induction phase - week 10	pre-dose	64	0	160	158
ca184004-32-4034	3.0 mg/kg ipilimumab	induction phase - week 10	end of infusion	64	1.5	154	160
ca184004-32-4034	3.0 mg/kg ipilimumab	induction phase -	1 hour post	64	2.5	156	154

		week 10	infusion				
ca184004-32-4037	3.0 mg/kg ipilimumab	induction phase - week 1	pre-dose	1	0	112	106
ca184004-33-4081	3.0 mg/kg ipilimumab	induction phase - week 1	1 hour post infusion	1	2.5	113.333333	100
ca184004-33-4093	3.0 mg/kg ipilimumab	enrollment	end of infusion	-1	1.5	115.333333	115.333333
ca184004-33-4093	3.0 mg/kg ipilimumab	enrollment	1 hour post infusion	-1	2.5	114.666667	114.666667
ca184004-33-4093	3.0 mg/kg ipilimumab	induction phase - week 1	end of infusion	1	1.5	112	115.333333
ca184004-33-4093	3.0 mg/kg ipilimumab	induction phase - week 1	1 hour post infusion	1	2.5	114.666667	114.666667
ca184004-35-4075	3.0 mg/kg ipilimumab	enrollment	screening	.	.	110.666667	.
ca184004-23-4031	10 mg/kg ipilimumab	induction phase - week 1	end of infusion	1	1.5	112	108
ca184004-32-4029	10 mg/kg ipilimumab	induction phase - week 1	1 hour post infusion	1	2.5	112	106
ca184004-32-4056	10 mg/kg ipilimumab	induction phase - week 1	pre-dose	1	0	114	86
ca184004-35-4098	10 mg/kg ipilimumab	induction phase - week 10	end of infusion	64	1.5	115.333333	102
ca184004-35-4098	10 mg/kg ipilimumab	induction phase - week 10	1 hour post infusion	64	2.5	117.333333	100

Date: February 25, 2011

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

Appendix 4.4

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	BLA 125377/0	Brand Name	TBD
OCP Division (I, II, III, IV, V)	DCPV	Generic Name	Ipilimumab
Medical Division	DBOP	Drug Class	Monoclonal Antibody
OCP Reviewer	Aakanksha Khandelwal, Ph.D	Indication(s)	Pre-treated advanced melanoma
OCP Team Leader	Hong Zhao, Ph.D.	Dosage Form	50 mg/vial (5 mg/mL) or 200 mg/vial (5 mg/mL)
Pharmacometrics Reviewer	Anshu Marathe, Ph.D	Dosing Regimen	(b) (4) 3 mg/kg Q3Wx4
Date of Submission	June 25, 2010	Route of Administration	Intravenous Infusion
Estimated Due Date of OCP Review	November 12, 2010	Sponsor	Bristol Myers Squibb
Medical Division Due Date	November 26, 2010	Priority Classification	Priority
PDUFA Due Date	December 25, 2010		

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	27		8 Completed; 11 On-going; 8 External
HPK Summary	X	6		
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2		STM1693 & Human Serum ELISA
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	1		MDX010-15
multiple dose:	X	6		CA184008, CA184007, CA184022, CA184004, MDX010-15, MDX010-08
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			PopPK (budesonide)
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:	X			PopPK
pediatrics:				
geriatrics:				
renal impairment:	X			PopPK
hepatic impairment:	X			PopPK
PD -				
Phase 2:	X	4		CA184004, CA184007, CA184008, CA184022
Phase 3:	X	1		MDX010-20
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	2		CA184007, CA184008
Data sparse:	X	3		CA184007, CA184008, CA184022
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		MDX010-15 (Process A & Process B)
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				
Genotype/phenotype studies	X			PopPK
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
ECG Monitoring	X	1		CA184004
Biomarkers	X	2		CA184004, CA184007
Immunogenicity Testing	X	7		MDX010-08, MDX010-15, MDX010-20, CA184004, CA184007, CA184008, CA184022
Total Number of Studies		7		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Process B
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			

5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		X		See comment below
11	Is the appropriate pharmacokinetic information submitted?	X			
12	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			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	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			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

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

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

There is no filing issue for this submission from a clinical pharmacology perspective. Listed below are requests to be included in the 74-day letter.

Comment from Dr. Christian Grimstein, the GG reviewer:

Please submit individual genotype data for subjects who provided a DNA sample in CA184004, CA184007, CA184008, and CA184022. SAS data sets would be fine, a formal report is not needed.

Comment from Dr. Anshu Marathe, the pharmacometrics reviewer:

1. Please submit the dataset (analysis and external validation dataset), NONMEM control streams (base, covariate and final models) and the output listing for the population PK analysis (Module 5.3.3.5) by August 6th 2010.
2. Please submit the dataset, associated program codes and the output files for the exposure-response analysis for efficacy and safety (Module 5.3.3.5) by August 6th 2010.

We encourage the Applicant to refer to the following pharmacometric data and models submission guidelines.
(http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm):

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

5. REFERENCES

1. Egen JG, Kuhns MS, Allison JP. CTLA-4: New insights into its biological function and use in tumor immunotherapy. Nat Immunol. 2002; 3: 611-618