CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology BLA Review	
BLA	125514
Submission Date Submission Type	February 27, 2014 Original BLA
Brand Name	KEYTRUDA™
Generic Name	Pembrolizumab
Dosage Form / Strength	50 mg/vial lyophilized powder in a single-use vial
Dosing Regimen	2 mg/kg intravenous (IV) infusion over 30 minutes every 3 weeks (Q3W)
Proposed Indication	Treatment for unresectable or metastatic melanoma in patients whose disease has progressed on or after treatment with ipilimumab and, if BRAF V600 mutation positive, received treatment with a BRAF (b) (4) inhibitor
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
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EXECUTIVE SUMMARY

Pembrolizumab was submitted as a new molecular entity (NME) BLA for treatment of unresectable or metastatic melanoma in patients whose disease progressed on or after treatment with ipilimumab and, if BRAF V600 mutation positive, received treatment with a BRAF (b) (4) inhibitor. BRAF is a human gene that makes a protein called B-Raf, and V600 is a mutation type. (b) (4)

Efficacy, safety, pharmacokinetic (PK), and immunogenicity data for this application were based on one clinical study (Study P001) that consisted of multiple cohorts, where Cohort B2 supports the marketing application. The major findings of the clinical pharmacology review are listed below.

- The apparent flat exposure-response (E-R) relationship for both efficacy and safety between the doses of 2 and 10 mg/kg of Study P001 Cohort B2 supports the use of the lower dose of 2 mg/kg every 3 weeks (Q3W) dosing regimen for the indicated patient population.
- No apparent association between systemic use of corticosteroids and objective response rate (ORR) was identified based on a retrospective analysis of data from Study P001 Cohort B2. A definitive conclusion regarding the association between systemic use of corticosteroids and ORR cannot be made due to the data limitation.
- None of the 97 evaluable patients received pembrolizumab of 2 mg/kg Q3W tested positive for treatment emergent anti-pembrolizumab antibodies in an electrochemiluminescence (ECL) based assay.
- Population PK analyses showed that age, gender, tumor type or tumor burden did not have a clinically meaningful effect on the exposure of pembrolizumab. The effect of race could not be assessed due to the limited number of non-White patients enrolled in the study.
- PK exposure was comparable among patients with normal renal/hepatic function, patients with mild and moderate renal impairment, and patients with mild hepatic impairment.

1.1 Recommendations

BLA 125514 is acceptable for approval from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language. The adequacy of the clinical pharmacology program in the overall drug development plan of pembrolizumab is summarized in the table below.

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
Proposed dosing regimen of 2 mg /kg Q3W	☒Yes ☐No Refer to **Section *2.2.4.4***	**Labeling Recommendation:** None
Dose adjustment in patients with organ impairment	☒Yes ☐No Refer to **Section *2.3.2.5* and Section *2.3.2.6***	**Labeling Recommendation:** None
(b) (4)	☐Yes ☒No Refer to **Section *2.4.2.6***	**Labeling Recommendation:** None
	☐Yes ☒No Refer to **Section *2.4.2.3***	**Labeling Recommendation:** None

1.2 Post Marketing Commitments or Requirements

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Pembrolizumab is a humanized IgG4 monoclonal anti-PD-1 antibody. Its molecular weight is 149 kDa.

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

Clinical Dose Selection*:* Two types of pharmacokinetics and pharmacodynamics (PK/PD) evaluations provided the foundation for the selection of the lowest dose studied in the clinical program. The first was a clinical biomarker (IL-2 release) based PK/PD approach and the second was a translational PK/PD projection of clinical response based on preclinical activity of an anti-PD-1 antibody. While these two approaches utilized different techniques, data, and assumptions, they converged on 1 to 2 mg/kg Q3W as the lowest doses with a high likelihood of providing substantial clinical benefit and supported the use of 2 mg/kg Q3W in the program.

Pharmacokinetics*:* Based on a population PK analysis with data from 476 patients who received 1-10 mg/kg of pembrolizumab every two weeks (Q2W) or Q3W, the population PK mean (95% CI) estimates are:

- Time to reach steady state concentrations of pembrolizumab was 129 (118, 142) days.
- Half-life was 25.8 (23.6, 28.3) days.
- Volume of distribution at steady-state was 7.66 (7.09, 8.13) L.

Population Pharmacokinetic Analysis*:* Population PK analyses (n=476) showed that age gender, tumor type or tumor burden did not have a clinically meaningful effect on the exposure of pembrolizumab. The effect of race could not be assessed due to the limited data available in non-White patients enrolled in the study. Patients with varying degrees of renal impairment and patients with mild hepatic impairment had similar exposure as patients with normal hepatic and renal function. Body weight-based dosing is acceptable based on the exposure variation.

Exposure/Dose-Response Relationship for Efficacy*:* There is a flat E-R relationship between ORR and pembrolizumab exposure in Study P001 Cohort B2 where patients were administered a pembrolizumab dose of 2 mg/kg Q3W or 10 mg/kg Q3W. In addition, time to ORR, duration of response (DoR), and adverse event rates were similar between the two doses.

Immunogenicity*:* In the 153 patients treated with the dosage regimen of 2 mg/kg Q3W, 97 of them had a concentration of pembrolizumab in the last post-dose sample below the drug tolerance level of the anti-product antibody (APA) assay. None of these 97 patients tested positive for treatment emergent anti-pembrolizumab antibodies in an ECL based assay.

Signatures:

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2. QUESTION-BASED REVIEW

2.1 General Attributes

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

Pembrolizumab is a humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4) kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The molecular weight of pembrolizumab is approximately 149 kDa (kilo-Dalton).

Pembrolizumab drug product is supplied as a sterile, lyophilized powder of 50 mg/vial in single-use vials. Water for Injection USP (United States Pharmacopeia) is used to reconstitute it into 25 mg/mL solution prior to intravenous (IV) infusion.

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

By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity. In mouse tumor xenografts, inhibition of PD-1 decreased tumor growth and prolonged survival.

The proposed indication is unresectable or metastatic melanoma in patients whose disease has progressed on or after treatment with ipilimumab and, if BRAF V600 mutation positive, received treatment with a BRAF (b) (4) inhibitor.

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

The proposed dosing regimen of pembrolizumab is 2 mg/kg administered intravenously over a 30-minute period every 3 weeks (Q3W).

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?

The current BLA is supported by one clinical trial, an ongoing, multi-center, open-label study [Protocol 001 (P001)]. Study P001 consists of a dose escalation cohort (Part A) and several dose expansion cohorts (Part B, C, D and F). The design of each cohort is briefly described in **Table 1**. Part B2 supports the marketing application of pembrolizumab for the proposed indication of unresectable or metastatic melanoma in patients whose disease has progressed on or after treatment with ipilimumab (IPI) and, if BRAF V600 mutation positive, received treatment with a BRAF (b) (4) inhibitor. The efficacy data in Parts B1 and D support the efficacy evaluations in Part B2. The overall response rates (ORR, primary endpoint) for Parts B1, B2 and D are listed in **Table 2** at dose levels of 2 mg/kg and 10 mg/kg, Q3W.

Table 1: Summary of Study P001

Part	Description	Dose	Number of Patients
A	Dose escalation in solid tumors	1, 3 and 10 mg/kg, Q2W	10
A1	Dose confirmation in solid tumors	10 mg/kg, Q2W	7
A2	Intra-patient dose titration in solid tumors	0.005 to 10 mg/kg	13
B1	Efficacy and safety in sequential IPI-naïve and IPI-treated melanoma	2 mg/kg Q3W 10 mg/kg Q2W or Q3W	135
B2	Efficacy and safety in randomized (1:1) IP1-refractory melanoma	2 mg/kg Q3W 10 mg/kg Q3W	173
B3	Efficacy and safety in randomized IPI-naïve and IPI-treated and IPI-refractory melanoma	10 mg/kg Q2W or Q3W	248
C	Efficacy and safety in non-small cell lung cancer (NSCLC)	10 mg/kg Q3W	38
D	Efficacy and safety in randomized (1:1) IPI-naïve melanoma	2 mg/kg Q3W 10 mg/kg Q3W	103
F	Efficacy and safety in randomized PD-L1 positive NSCLC	10 mg/kg Q2W or Q3W	243

Table 2: Overall Response Rate (95% CI) in All Patients as Treated in Parts B1, B2 and D

	2 mg/kg Q3W	10 mg/kg Q3W
Part B1	41% (21%, 64%)	29% (17%, 42%)
Part B2	24% (15%, 34%)	24% (15%, 34%)
Part D	33% (21%, 48%)	37% (24%, 51%)
Pooled Cohorts (B1+B2+D)	29% (22%, 37%)	29% (22%, 36%)

The present clinical pharmacology program included PK data from 476 patients enrolled in Part A, B1, B2, C and D. Part A had intensive PK sampling and Parts B1, B2, C and D had sparse sampling. The PK profile of pembrolizumab was described using population PK analysis based on data collected from Part A, B1, B2, C and D. Data for E-R analyses for clinical activity (n=365) and E-R analyses for adverse events (AEs) (n=409) were collected from Parts B1, B2 and D.

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? What is the clinical outcome in terms of efficacy and safety?

The primary efficacy endpoint for the Study P001 Cohort Part B2 is overall response rate (ORR) based on RECIST 1.1 by integrated radiology and oncology analysis (IRO) [independent central review of imaging studies + limited objective clinical data by an independent oncologist].

In Study P001 Cohort Part B2, 173 ipilimumab (IPI)-refractory melanoma patients were randomized to receive either pembrolizumab 2 mg/kg IV Q3W (n=89) or 10 mg/kg IV Q3W (n=84). Based on IRO assessment, the overall response rate (ORR), duration of response (DoR) and adverse event (AE) rates were similar between the two doses. The ORR was 23.6% for the 2 mg/kg dose and 23.8% for the 10 mg/kg dose. Time to response (mean ± SD) was 15±7 weeks for the 2 mg/kg dose and 12±2 weeks for the 10 mg/kg dose. The DoR was from >6 to >37 weeks for the 2 mg/kg dose and from >8 to >37 for the 10 mg/kg dose, with median duration not reached for either arm (**Table 3**).

Table 3: Summary of Response Rate, Time to Response and Response Duration IRO Assessment per RECIST 1.1 in Patients with Confirmed Response-- Part B2 Patients (APaT Population) of P001V01

	pembrolizumab 2 mg/kg Q3W (N=89)	pembrolizumab 10 mg/kg Q3W (N=84)
Number of Patients with Response (Rate%)†	21 (23.6%)	20 (23.8%)
Time to Response† (weeks)		
Mean (SD)	15 (7)	12 (2)
Median (Range)	12 (11-36)	12 (7-17)
Response Duration‡ (weeks)		
Median (Range)§	Not reached (6+-37+)	Not reached (8+-37+)
Number of Non-progressing Patients (%)	19 (90)	18 (90)

† Analysis on time to response and response duration are based on patients with a best overall response as confirmed complete response or partial response only.

‡ From product-limit (Kaplan-Meier) method for censored data.

§ "+" indicates non-PD at the last assessment (censored). Database Cutoff Date: 18OCT2013

Source: sponsor's clinical overview report Table 2.5:4 in Page 37.

Both doses of pembrolizumab were well tolerated. The overall pattern of adverse events observed in melanoma patients, fit a profile expected for an immune checkpoint inhibitor. Immune-related adverse events were typically grade 1-2 in severity, and were generally reversible with treatment discontinuation and use of corticosteroids.

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?

Pembrolizumab serum concentrations in the patient samples were measured using a validated electrochemiluminescence (ECL) based immunoassay. Refer to Section **2.6** for a description of the bioanalytical methodology.

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, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

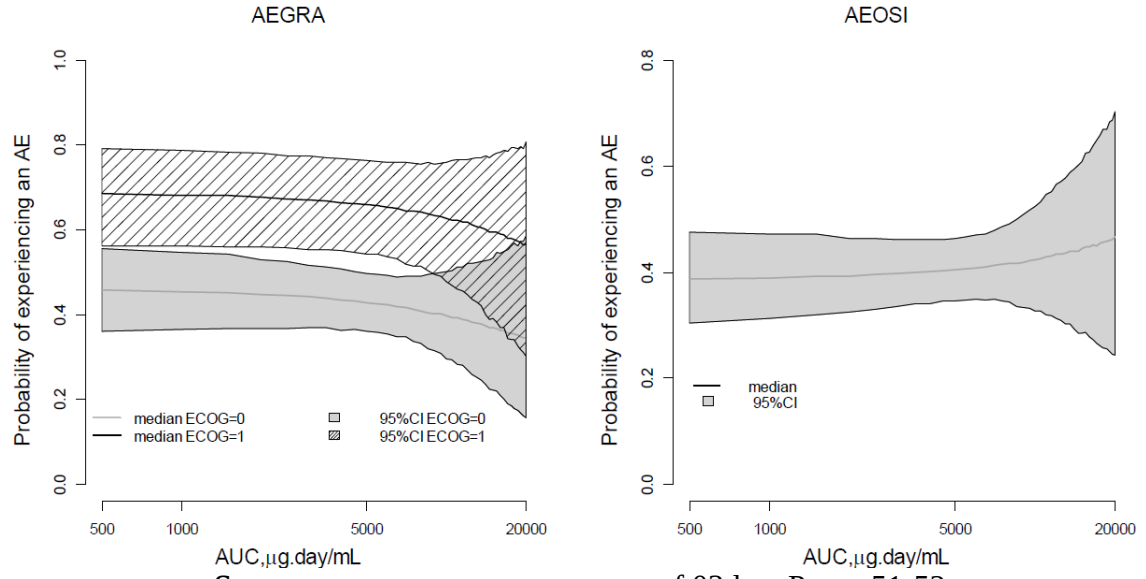
The exposure-response relationship for ORR is flat across the AUC range observed with doses of 2 mg/kg and10 mg/kg (see **3.1 Pharmacometrics Review**).

Time to response (mean ± SD) was 15±7 weeks for 2 mg/kg arm and 12±2 weeks for 10 mg/kg arm. Response duration was from >6 to >37 weeks for 2 mg/kg and from >8 to >37 for 10 mg/kg, with median duration not reached for either arm. The number of non-progressing patients was 19 (90%) for 2 mg/kg arm and 18 (90%) for 10 mg/arm. See Section ***2.2.2*** for more information.

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.

The exposure-response relationship for safety in terms of both AEGRA (adverse events of grade 3-5 or serious AE) and AEOSI (adverse events of special interest) of pembrolizumab is flat across the AUC range observed with doses ranging from 1-10 mg/kg (**Figure 1**).

Figure 1: Simulated Probability of Experiencing an AE in Function of Exposure with the Associated 95% CIs



Source: exposure-response report of 03tlcn, Pages 51-52

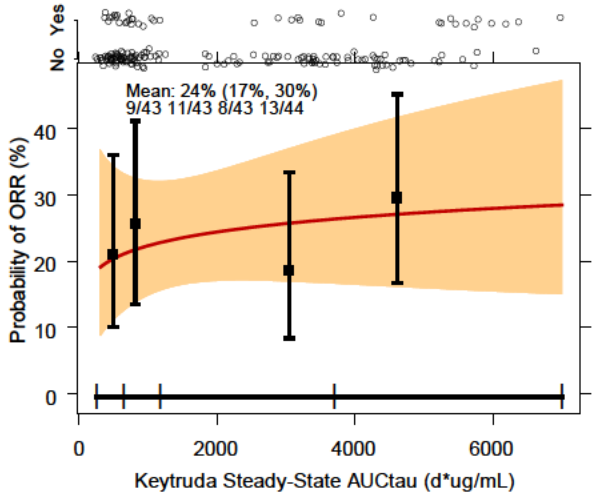
2.2.4.3 Does this drug prolong the QT/QTc interval?

This study was comprised of five-parts: Part A (including A1 and A2), Part B (including B1 and B2), Part C, Part D (melanoma) and Part F (including F1 and F2). The applicant submitted ECG data for Parts A, B1, B2, C and D of PN001. No large change (i.e., > 20 ms) in the QTc interval was detected when pembrolizumab was administered up to 10 mg/kg Q3W. The applicant did not submit positive control (moxifloxacin) arm.

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 clinical dose of 2 mg/kg IV Q3W was selected based on comparable ORR results and safety profile between 2 and 10 mg/kg for Part B2 of Study P001. In the randomized setting, the efficacy of pembrolizumab given Q3W is comparable between 2 mg/kg and 10 mg/kg doses, indicating no improvement in efficacy with a 5-fold higher dose of pembrolizumab beyond the 2 mg/kg dose. Similarly, the safety and AE profile of pembrolizumab also appear similar between the 2 mg/kg Q3W and 10 mg/kg Q3W doses. Please refer to the clinical safety review. Finally, PK analysis indicates a flat exposure-response relationship for ORR beyond the 2 mg/kg dose (**Figure 2**). Taken together, the 2 mg/kg dose has demonstrated efficacy and safety when pembrolizumab is administered on a Q3W schedule. Of note, a maximum tolerated dose (MTD) was not reached in the dose finding cohort conducted in the clinical program to date.

Figure 2: Relationship between Pembrolizumab AUC and Overall Response Rate

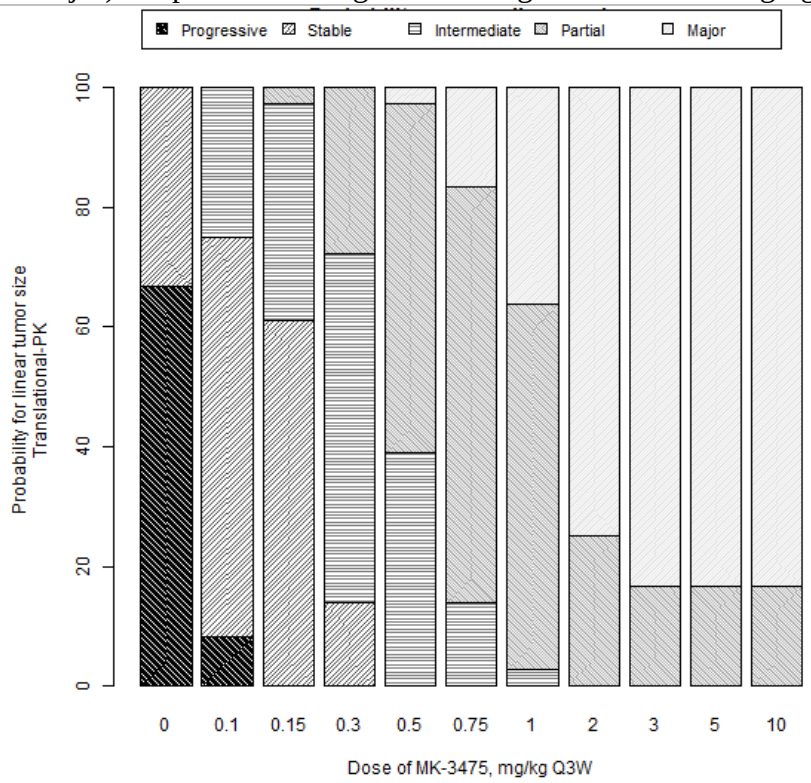


Source: Pharmacometrics Review by the FDA reviewers

The dose of 2 mg/kg was also supported by translational PK/PD analysis based on experimental data from mouse (**Figure 3**) and biomarker IL-2 results of the ex vivo study as described in **Section 2.3.3.7**.

There appeared no unresolved dosing or administration issues for the indicated population.

Figure 3: Estimated Pembrolizumab Dose-Response for Probability of Anti-Tumor Activity Using Translational PK/PD Indicates Near-Maximal (> 90% Probability of Partial and Major) Responses Starting at Dose Regimens of 1 or 2 mg/kg Q3W



Source: Summary of Clinical Pharmacology Studies, Figure 2.7.2:2, Page 18

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

The PK profile of pembrolizumab has been characterized by population PK analysis based on the data from Part A, B (except B3), C and D of Study P001. The volume of distribution of pembrolizumab at steady state is 7.7 L with a variability of 14%. The systemic clearance (CL) is 0.22 L/day with a variability of 28%. The terminal half-live is estimated to be 26 days and steady-state is achieved by 18 weeks of repeated dosing. The accumulation ratio of Q3W dosing regimen is estimated to be approximately 2.1-fold. In the clinically relevant dose range of 2 to 10 mg/kg, the exposure increases in a dose-proportional manner which is supported by the population PK analysis.

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

Non-compartmental analysis in Part A and A1

The single dose PK of pembrolizumab was evaluated up to 28 days in Part A and A1 in Study P001. The mean PK parameters are summarized in **Table 4** for doses of 1, 3 and 10 mg/kg administered Q2W. The concentration-time profiles of doses of 1, 3 and 10 mg/kg show an increase in exposure with dose (**Figure 4**). Steady state was estimated to be reached within 16 weeks of treatment for the repeating doses of 3 and 10 mg/kg Q2W.

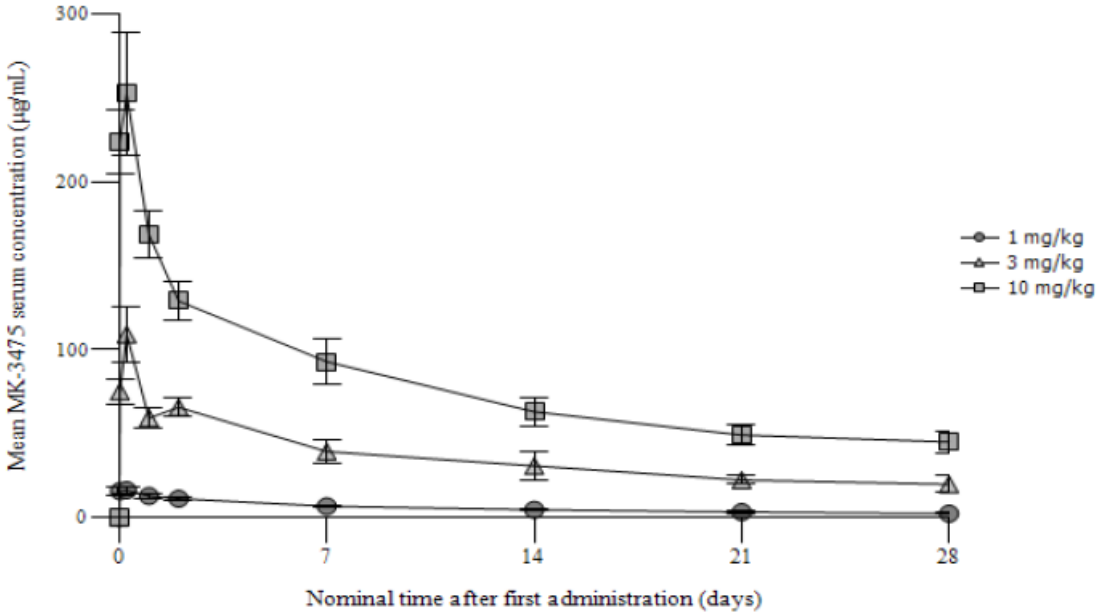
Table 4: Summary of Pembrolizumab PK Parameters after Single Dose IV Administration

Treatment	N	Cmax (µg/mL)	tmax[a] (day)	AUC0-28 (µg.day/mL)	t½[b] (day)
1.0 mg/kg	4	16.4 (22)	0.05 (0.02-0.17)	158 (20)[c]	14.1 (51)[c]
3.0 mg/kg	3	107 (26)	0.17 (0.17-0.17)	955 (23)	21.6 (10)
10 mg/kg	10[e]	256 (37)	0.17 (0.03-0.99)	2150 (31)[d]	17.7 (56)[d,f]

Geometric mean (%CV) PK parameter values for MK-3475 following IV administration of 1, 3 or 10 mg/kg to patients with solid tumors in Cycle 1 of Part A and A1 (Protocol 001).
CV = coefficient of variation; Cmax = maximum observed serum concentration; tmax = time of maximum observed serum concentration; AUC0-28 = area under the concentration-time curve from day 0 up to day 28; t½ = elimination half-life
a: Tmax: Median (range);
b: PK sampling up to 28 days following first IV administration;
c: N=3 Excluded one patient due to discontinuation (AN000002);
d: N=9 Excluded one patient due to discontinuation (AN000018);
e: 3 patients in part A and 7 patients in part A1;
f: patients (N=2) with a t½ > Tlast are included in mean value

Source: Table 11-63 on Page 206 of Clinical Study Report P001

Figure 4: Arithmetic Mean Concentration-Time Profiles of Pembrolizumab after Single Dose IV Administration of 1, 3 or 10 mg/kg

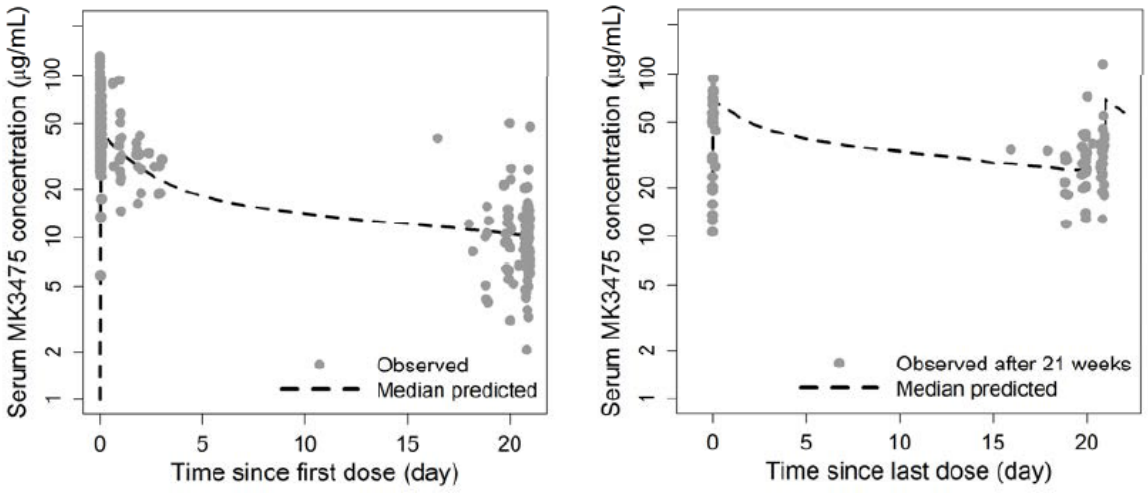


Source: Figure 11-50 on Page 208 of Clinical Study Report P001

Population PK Analysis in Parts A, B1, B2, C and D of Study P001

The concentration time profiles of pembrolizumab following single dose and at steady state of 2 mg/kg Q3W were simulated based on the population PK model and shown in **Figure 5** along with the observed PK data up to 21 days in Parts B1, B2 and D. **Table 5** lists the derived exposure parameters at steady-state for the two dosing regimens in melanoma by population PK model-based simulation.

Figure 5: Concentration –Time Profile of Pembrolizumab after a Single Dose (left panel) and at Steady-State (right panel) at a Dose of 2 mg/kg Q3W



Solid markers represent observed MK-3475 serum concentrations. Dashed line represents median predicted concentration time profile, based on population PK model.

Source: Figure 2.7.2:10 on Page 39 of Summary of Clinical Pharmacology

Table 5: Summary of Median Exposure Parameters (90% prediction interval) for Pembrolizumab at the Doses Evaluated in Melanoma

	2 mg/kg Q3W	10 mg/kg Q3W
C_{max} (µg/mL)	65.7 (50.1, 88.4)	327 (245, 454)
C_{trough} (µg/mL)	23.3 (13.3, 39.6)	117 (64.3, 206)
$AUC_{ss,6\text{-}week}$ (µg·day/mL)	1408 (931, 2225)	7079 (4405, 11372)

C_{max}: maximum concentration at end of infusion
C_{trough}: concentration at the end of the dosing interval
$AUC_{ss,\ 6\text{-}week}$: area under the concentration time curve over 6 weeks (i.e. 2 dose intervals for Q3W regimen)

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. Pembrolizumab has not been administered to healthy volunteers.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable. Pembrolizumab is administered via IV infusion.

2.2.5.4 What are the characteristics of drug distribution?

The volume of distribution at steady-state is 7.7 L based on the population PK model.

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

Mass balance studies are not generally performed for biological products such as pembrolizumab, 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?

Pembrolizumab is expected to be catabolized into amino acids by general protein degradation process. Metabolism studies are generally not performed for biologic products such as pembrolizumab, because these products are proteins which are degraded into amino acids that are then recycled into other proteins.

2.2.5.7 What are the characteristics of drug excretion and elimination?

The clearance of pembrolizumab is 0.22 L/day and is independent of dose based on the population PK analysis.

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

Pembrolizumab exhibited linear PK in a dose range of 2 to 10 mg/kg. The trough concentrations (C_{min}) of 10 mg/kg at steady-state increased approximately 5-fold comparing with those of 2 mg/kg (**Table 6**).

Table 6: Geometric Mean [% coefficient of variation (CV%)] Serum Trough Concentration for Pembrolizumab Following Multiple Doses of 2 or 10 mg/kg, Q3W

Treatment	Cycle	N of patients	Trough Concentration (µg/mL)
Part B			
2 mg/kg Q3W	5	63	19.7 (57)
10 mg/kg Q3W	5	77	110 (75)
Part D			
2 mg/kg Q3W	6	33	23.6 (42)
10 mg/kg Q3W	6	33	132 (46)

2.2.5.9 How do the PK parameters change with time following chronic dosing?

The PK parameters (i.e., clearance and volume of distribution) do not change following the administration of multiple doses of 1 to 10 mg/kg Q3W or Q2W, which is supported by the population PK analysis. The accumulation ratio is approximately 2.1 folds from the first dose to steady-state when pembrolizumab is administered Q3W.

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?

In the final population PK model, body weight, albumin and gender were covariate for CL; body weight and gender were covariates for distribution of central compartment (Vc). For the final model, the unexplained inter-individual variability (CV%) in CL was 28.1% (CV%=14.5%) and V_c or distribution volume of peripheral compartment (V_p) was 13.5% (CV=32.4%).

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?

Albumin, IgG and gender were identified as statistically significant covariates on pembrolizumab CL, while gender also was associated with a reduction in Vc and Vp. The impact of these covariate relationships on the AUC was limited and not clinically relevant, as alterations of 20% or less are predicted. Body weight-based dosing is acceptable based on exposure variation.

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

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

2.3.2.1 Elderly Patients

Age was not identified as a significant covariate influencing pembrolizumab PK based on a population PK analysis ,which included patients range of 18-94 years of age (n=476), mean of 59.7 years of age, and median of 61.5 years of age.

2.3.2.2 Gender

The population PK dataset included 284 men (59.7%) and 192 women (40.3%). Although gender was identified as a statistically significant covariate on CL and Vc, gender has no clinically meaningful influence on the distribution or clearance of pembrolizumab.

2.3.2.3 Body weight

Based on population PK analyses, pembrolizumab AUC at steady state for body weight normalized dosing, fixed dose, and body surface area normalized dosing were simulated for comparison. Among the three paradigms, body surface area normalized dosing manages the variation the best, body-weight normalized dosing the second best and the fixed dosing the worst. Although body-weight based dosing did not minimize exposure variability control as well as body-surface area normalized dosing, body weight normalized dosing is generally acceptable considering the flat exposure-response relationship in terms of efficacy and safety for pembrolizumab (refer to **Figure 2** and **Figure 1**).

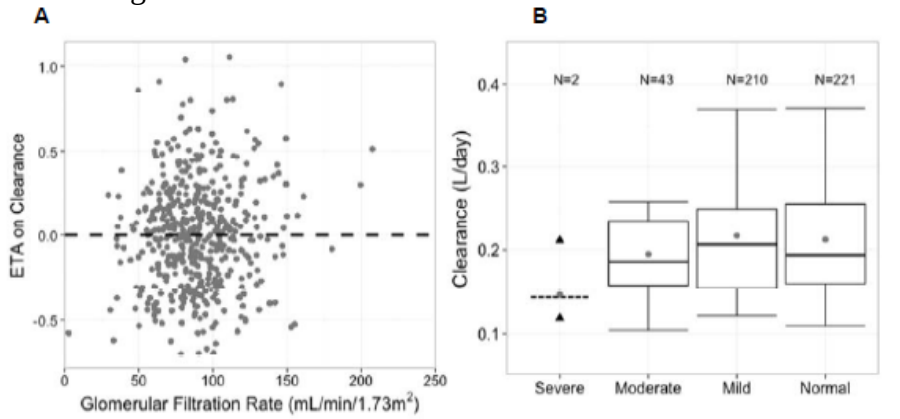
2.3.2.4 Race

The effect of race on the pembrolizumab exposure could not be assessed due to the limited data available in non-White patients.

2.3.2.5 Renal Impairment

No dedicated clinical studies were conducted to evaluate the effect of renal impairment on the PK of pembrolizumab. Based on a population PK analysis which included patients with mild (eGFR 50-80 mL/min/m^2, n=210), moderate (eGFR 30-49 mL/min/m^2, n=43), and severe (eGFR <30 mL/min/m^2, n=2) renal impairment, the effect of CL_{cr} on pembrolizumab was minor on mildly and moderately impaired patients, and not expected to be clinically meaningful (**Figure 6**). Data is not sufficient for drawing a conclusion on severely impaired patients. The eGFR values were calculated by MDRD.

Figure 6: Effect of Renal Function on Pembrolizumab Clearance



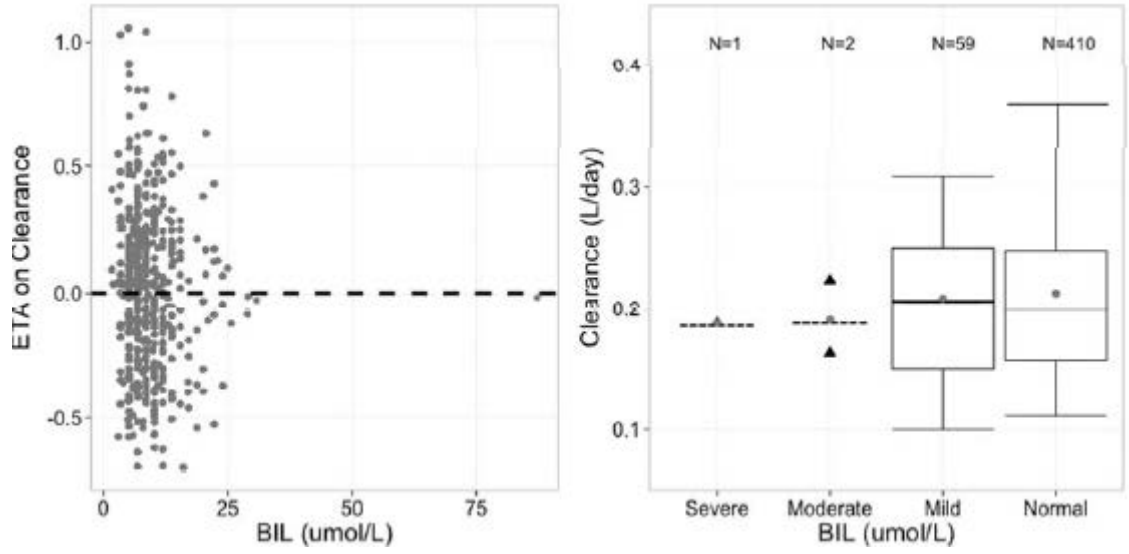
(A) Individual ETA of clearance estimates versus glomerular filtration rate (eGFR), calculated using MDRD equation. X-axis is truncated at at value of 250 mL/min/1.73m^2, 2 high eGFR values are not shown. Values above 150 mL/min/1.73m^2 are not considered biologically plausible. The lowest eGFR value is suspect of a unit entry error; correction would result in a value of 43.6 mL/min/1.73m^2. (B) Distribution of individual posthoc clearance estimates for different degrees of renal function. Out of the two severely impaired patients, one has an eGFR values just below the cut-off by NCI but still within protocol inclusion criteria for serum creatinine, while the other would qualify as moderately impaired after correction of the suspected unit entry error. Line: median; center dot: mean; box: 25th and 75th percentile, whiskers: 5th and 95th percentile.

Source: Population PK Report 03tlc8, Page 45

2.3.2.6 Hepatic Impairment

No dedicated clinical studies were conducted to evaluate the effect of hepatic impairment on the PK of pembrolizumab. Based on a population PK analysis which included patients with mild hepatic impairment (total bilirubin (TB) ≤ ULN and AST > ULN or TB > 1.0 to 1.5 x ULN and any AST or AST >ULN as defined using the National Cancer Institute criteria of hepatic dysfunction, n=59) and moderate hepatic impairment (TB >1.5 to 3 x ULN and any AST, n=2) and severe hepatic impairment (TB >3 x ULN and any AST, n=1), there was no effect of total bilirubin on the clearance of pembrolizumab (**Figure 7**). Model-derived CL values in patients with mild and moderate hepatic impairment were similar to those in patients with normal hepatic function (**Figure 7**).

Figure 7: Effect of Bilirubin on Pembrolizumab Clearance



Source: Population PK Report 03tlc8, Page 47

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

Pembrolizumab is categorized as Pregnancy Category D. Data in mice indicate that PD-1 is involved in maintaining tolerance to the fetal allograft; PD-1 ligands are expressed in the placenta and maternal lymph nodes where they mediate deletion of T cell clones that react to fetal antigens. Data in knockout mice suggest increased embryofetal loss of allogeneic fetal implants. On the basis of the known risk of fetal death for pembrolizumab, in combination with the uncharacterized teratogenic risk, a category D is recommended. There are no adequate and well-controlled studies with pembrolizumab in pregnant women. Pembrolizumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether pembrolizumab is excreted in human milk. Nonclinical PMR/PMC to explore potential toxicities related to immune recall reactions (vaccines) and chronic infection are currently being considered.

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?

A bridging ECL assay was developed for the detection of anti-product antibody (APA) in human serum using a typical 3-tiered assay approach. In the 153 patients treated with dose of 2 mg/kg Q3W, 97 of these patients had a concentration of pembrolizumab in the last post-dose sample below the drug tolerance level (25 µg/mL) of the APA assay. None of these 97 patients tested positive for treatment emergent anti-pembrolizumab antibodies in an ECL based assay. One patient had a positive pre-treatment sample for anti-pembrolizumab antibodies, but the post-dose samples were negative for APA.

Overall, 129 of 449 patients, who were treated with doses of 1 to 10 mg/kg Q2W or 2 mg/kg Q3W or 10 mg/kg, Q2W or Q3W, had a concentration of pembrolizumab in the last post-dose sample below the drug tolerance level. One patient administered a dose of 10 mg/kg Q3W had a post-dose sample tested positive for treatment emergent anti-pembrolizumab antibodies as shown in **Table 7**.

Table 7: Summary of Immunogenicity Results in Study P001

Part	dose (mg/kg)	Number of patients[a] (% of total number of patients)		Immunogenicity status			
		Total	With last sample below drug tolerance level[b]	Negative	Inconclu-sive	Treatment emergent positive	Non-treatment emergent positive
A	1	3	3 (100%)	3 (100%)	0	0	0
	3	3	0	0	3 (100%)	0	0
	10	8	1 (13%)	1 (13%)	7 (88%)	0	0
A2	Cohort 1 0.005-0.3-2.0	4	1 (25%)	1 (25%)	3 (75%)[e]	0	0
	Cohort 2 0.02-0.3-2.0	3	2 (67%)	2 (67%)	1 (33%)[f]	0	0
	Cohort 3 0.06-1.0-10	5	1 (20%)	1 (20%)	4 (80%)[e]	0	0
B	2	108	72 (67%)	72 (67%)	35 (32%)[f]	0	1 (0.9%)[c]
	10 (Q2W + Q3W)	187	20 (11%)	20 (11%)	166 (89%)[g]	1 (0.5%)[d]	0
C	10	33	3 (9%)	3 (9%)	30 (91%)	0	0
D	2	47	25 (53%)	25 (53%)	22 (47%)[f]	0	0
	10	48	1 (2%)	1 (2%)	47 (98%)	0	0
Overall		**449**	**129 (29%)**	**129 (29%)**	**318 (71%)**	**1 (0.2%)**	**1 (0.2%)**
For reference: CSR P001V01		CSR P001V01: 449	CSR P001V01: 123 (27%)	CSR P001V01: 123 (27%)	CSR P001V01: 324 (72%)	CSR P001V01: 1 (0.2%)	CSR P001V01: 1 (0.2%)

a: Included are patients with at least one ADA sample after treatment with MK-3475.
b: Drug tolerance level of the ADA assay is 25 µg/mL.
For ADA samples with missing PK results, the PK concentration is considered as above drug tolerance level.
c: AN 0263 has a confirmed positive pre-treatment sample.
d: AN 0383 has one confirmed positive post-treatment sample (Cycle 5).
e: Three patients have a last ADA sample with missing PK result.
f: One patient has a last ADA sample with missing PK result.
g: Seven patients have a last ADA sample with missing PK result.

Source: Table 3 on Page 11 of Update of Immunogenicity

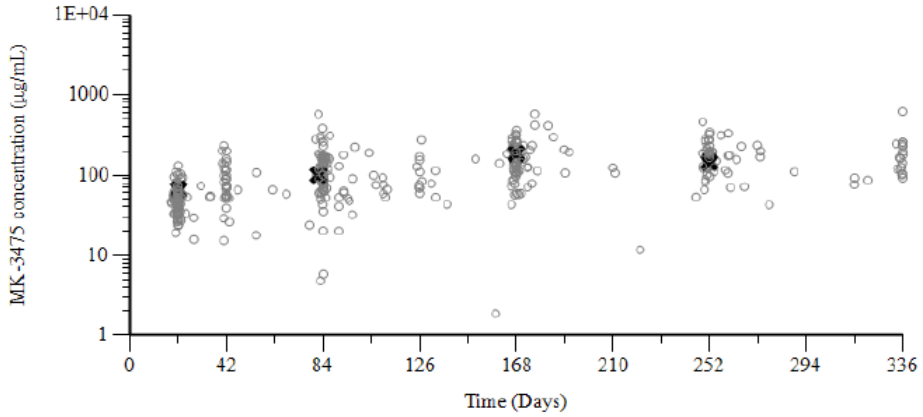
APA samples within 24 hours before infusion of pembrolizumab were collected according to the following schedule, which appears to be adequate.

Phase	Time
Baseline	Part A, B, C, D and F
Early treatment phase	Part A: every other cycle
	Part B Q2W: cycles 1, 3, 7 and 13
	Part B Q3W and Part C Q3W: cycles 1, 2, 5, 9 and 13
	Part D Q3W and Part F Q3W/Q2W: cycles 1, 3, 6, 8 and 12
Later treatment phase	Part B-F: every 12 weeks up to 12 months, every 6 months afterwards
Follow up visit	Part B-F: 30 days from last dose, then at 3 and 6 months

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

Pembrolizumab concentrations for the patient whose sample tested positive for treatment emergent APA were in the range of concentrations for other patients treated with the same dose of 10 mg/kg Q3W (**Figure 8**).

Figure 8: Pembrolizumab Concentrations for Patient Whose Sample Tested Positive for ADA as Compared to Other Patients Treated with 10 mg/kg Q3W (N=138)



Footnote: Individual MK-3475 concentrations for AN 0383 (black symbol **x**) and other patients (grey symbol o). Figure includes only trough samples. Exposure to MK-3475 was not compromised for AN0383 (treatment emergent positive).

Source: Figure 1 on Page 12 of Update of Immunogenicity

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

For the patient whose sample collected on Day 83 tested positive for treatment-emergent APA, anti-pembrolizumab antibodies were found to have neutralizing capacity in the neutralizing antibodies (NAb) assay and were confirmed to be IgG.

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

The assessment cannot be done as only one patient's sample tested positive for treatment-emergent APA and NAb.

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

2.4 Extrinsic Factors

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

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

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

No, given pembrolizumab is a therapeutic monoclonal antibody. It is expected to be catabolized into amino acids by general protein degradation process. As pembrolizumab is not considered a cytokine modulator, it is unlikely to have an effect on drug metabolizing enzymes or transporters 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 in Section 2.4.2.1.

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

No. See response in Section 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 in Section 2.4.2.1.

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

No, as pembrolizumab is expected to be degraded into amino acids and recycle into other proteins syntheses pathway.

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. Pembrolizumab is proposed as monotherapy in the current submission.

Corticosteroids was used to treat the immune-related AEs during the pembrolizumab treatment, but was avoided before the start of treatment. Systemic corticosteroids have the potential to impact the immunomodulatory effect of pembrolizumab given its mechanism of action. Systemic corticosteroids did not show a clinically important effect on pembrolizumab exposures in a population PK analysis. The effect of systemic corticosteroids on ORR is inconclusive due to the data limitation.

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 drug products were used in clinical trials as listed in **Table 8** and were shown to be analytically comparable among each other. Please refer to the CMC review. (b) (4) are the to-be-marketed products. At the time of this BLA submission, 391 patients were treated with (b) (4) and 20 patients have been treated with (b) (4) in study P001 and all 20 patients are in Part B2.

Table 8: Summary of Three Supply Chains for Pembrolizumab

	(b) (4)		(b) (4)
Drug Substance (production scale)			FMC (b) (4)
Drug Product			Brinny 50 mg lyophilized vial
Formulation	Identical final formulation: 25 mg/mL MK-3475 in (b) (4) histidine buffer pH 5.5 containing (b) (4) sucrose and (b) (4) polysorbate 80 ((b) (4) reconstituted in water for IV administration)		
Usage in Clinical Studies	P001, P002*	P001, P002*, P006*, other#	P006*, other#
Planned Commercial Usage	N/A	Initial Product Launch	Initial Product Launch

* Clinical studies in melanoma not directly associated with this application

Clinical studies in indications other than melanoma and not directly associated with this application.

Brinny = Schering-Plough, Innishannon, Ireland; FMC = Frederick Manufacturing Center, MedImmune Inc, Frederick, MD, USA; IV = intravenous; N/A = not applicable; (b) (4) (b) (4)

P001 = Protocol 001: Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma

P002 = Protocol 002: Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma

P006 = Protocol 003: A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma

Source: Table 2.7.1:1 on Page 11 of Summary of Biopharmaceutic Studies/Associated Analytical Methods

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 test to assess the comparability of [redacted] and [redacted] included release tests, extended characterization tests, forced degradation test and stability test from an analytical perspective. [redacted] was compared to [redacted] at the drug product level and the results showed that [redacted] was compared to [redacted] at both the drug substance and drug product level and the results showed that [redacted] and [redacted] FMC drug substance. Please refer to the CMC review. The applicant did not perform any PK comparability test in human among three drug materials.

2.6 Analytical Section

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

Pembrolizumab serum concentrations were measured using a validated ECL method on the Meso Scale Discovery (MSD) assay platform. Recombinant human (rH) PD-1Fc [redacted] is the capture reagent and mouse anti-Human IgG4 monoclonal antibody [redacted] is the detection reagent.

The initial ECL method was developed and validated by Merck Research laboratories [redacted] method). This original method was not used to quantify pembrolizumab concentrations in the clinical studies, but served as the foundation for later method transfer validation. A second generation assay (Method 4020) was used to support quantification of pembrolizumab concentrations collected from Study P001. The difference between the original and second generation ECL assay was the change from [redacted] The method description in the following questions describes Method 4020.

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

[redacted]

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?

A weighed 5-parameter logistic model algorithm was used to fit a standard curve that ranges in serum concentration from 4.89 to1,250 ng/mL. The calibration curve generated from nine pembrolizumab standards: 0.489, 0.977, 1.953, 3.906, 7.813, 15.625, 31.25, 62.5 and 125

ng/mL., which are equivalent to the serum concentrations of 4.89, 9.77, 19.53, 39.06, 78.13, 156.25, 312.5, 625, and 1250 ng/mL before dilution.

The concentration range of the standard curves described above is adequate for the purposes of determining serum concentrations of pembrolizumab collected in Study P001 as shown in **Table 6** and **Table 9**.

Table 9: Geometric Mean (CV%) Serum Post-dose Concentration for Pembrolizumab Following Multiple Doses of 2 or 10 mg/kg Q3W

Treatment	Cycle	Number of patients	Post-dose Concentration (µg/mL)
Part B			
2 mg/kg, Q3W	3	16	52.2 (37)
10 mg/kg, Q3W	3	27	288 (61)
Part D			
2 mg/kg, Q3W	6	28	64.8 (22)
10 mg/kg, Q3W	6	31	373 (29)

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

The LLOQ is 10 ng/mL and the ULOQ is 800 ng/mL.

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

Accuracy and Precision

A summary of the accuracy and precision at the LLOQ and the ULOQ from six run days is shown in **Table 10**, which is consistent with the recommendations described in the draft FDA Guidance for Industry entitled, “Bioanalytical Method Validation”.

Table 10: Summary of Accuracy and Precision at LLOQ and ULOQ

	LLOQ	ULOQ
Nominal Concentration	1 ng/mL in 10% matrix (equivalent to 10 ng/mL before dilution)	80 ng/mL in 10% matrix (equivalent to 800 ng/mL before dilution)
Mean Concentration Found	1.102 ng/mL	79.103 ng/mL
Inter-run SD	0.06	7.09
Inter-run %CV	5.7	9.0
Inter-run % RE	10.2	-1.1
Note: SD=standard deviation=$\sqrt{\sum}$(yi-ymean)2/(N-1) %CV=coefficient of variation=(SD/mean)*100 %RE=relative error=[(Measured value-Nominal value)/Nominal value]*100		

Selectivity from Matrix Effect

Healthy subjects (n=10) and patients with cancer (n=5), hepatitis B (n=10), or human immunodeficiency virus (n=10) were fortified with 30 [low quality control (LQC)] or 400 [high quality control (HQC)] ng/mL pembrolizumab prior to the dilution. Acceptable accuracy of +/- 30% and of +/- 20% were used for LQC and HQC, respectively. A summary of selectivity at LQC and HQC is shown in **Table 11**.

The applicant used the ECL method to differentiate pembrolizumab in the presence of serum from healthy subjects and serum from patients with different diseases at levels of LQC and HQC, but not at LLOQ level according to the guidance of bioanalytical method. Such change should have little effect on the PK analysis given the range of trough concentrations of pembrolizumab in **Table 6**.

Table 11: Summary of Selectivity from Four Matrix at LQC and HQC

Matrix	LQC	HQC
Normal serum	100% (10/10)	90% (9/10)
Cancer patients	80% (4/5)	80% (4/5)
HBV	80% (8/10)	80% (8/10)
HIV	90% (9/10)	100% (10/10)

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)?

A summary of the sample stability for pembrolizumab is shown in **Table 12**. The long-term stability tests support the shelf life of (b) (4) months at the storage condition of (b) (4) claimed by the applicant.

Table 12: Summary of Sample Stability in Human Serum for Pembrolizumab

Stability Conditions	Description
Room temperature stability	Stable up to 24 hours at ambient temperature
Freeze-thaw stability	Stable up to four freeze-thaw cycles
Long-term frozen stability in a -20^{o}C freezer	Stable up to 11 months
Long-term frozen stability in a -70^{o}C freezer	Stable up to 14 months
Calibration standard stability at 1250 ng/mL	Stable up to 13.5 months

2.6.4.5 What is the QC sample plan?

Five QC levels were used for validation as shown in **Table 13**.

Table 13: Five Levels of Quality Control Samples

QC level	Concentration (ng/mL)	Equivalent to
LLOQ	10	1 ng/mL in 10% matrix
LQC	30	3 ng/mL in 10% matrix
MQC	100	10 ng/mL in 10% matrix
HQC	400	40 ng/mL in 10% matrix
ULOQ	800	80 ng/mL in 10% matrix

A summary of the accuracy and precision of QC samples from six run days is shown in **Table 14**.

Table 14: Summary of Accuracy and Precision for QC Samples

	LLOQ	LQC	MQC	HQC	ULOQ
Nominal Concentration	1 ng/mL in 10% matrix	3 ng/mL in 10% matrix	10 ng/mL in 10% matrix	40 ng/mL in 10% matrix	80 ng/mL in 10% matrix
Mean Concentration Found (ng/mL)	1.102	3.097	10.419	41.038	79.103
Inter-run SD	0.06	0.26	0.81	3.05	7.09
Inter-run %CV	5.7	8.3	7.8	7.4	9.0
Inter-run % RE	10.2	3.2	4.2	2.6	-1.1

3. APPENDICES

3.1 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Summary of Findings

Relationship is flat between steady-state AUCτ and objective response rate (ORR) in patients of Part B2 who are on 2 mg/kg or 10 mg/kg pembrolizumab (N=173). This flat relationship supports proposed 2 mg/kg pembrolizumab Q3W as the clinical dose for the proposed indication. The influence of systemic corticosteroid co-administration with pembrolizumab on ORR is currently inconclusive based on data of Part B2.

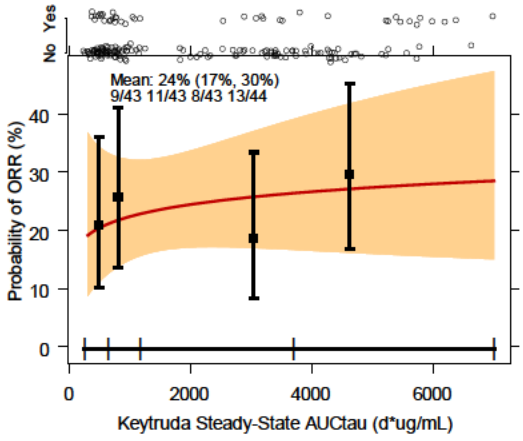
Key Review Questions

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

1. **Does the exposure-efficacy relationship support 2 mg/kg pembrolizumab Q3W as the clinical dose for the proposed indication?**

Yes. As shown in **Figure 9**, there is a flat relationship between steady-state AUCτ and overall response rate (ORR) for patients in study Part B2 who were on 2 mg/kg or 10 mg/kg pembrolizumab (N=173). This is consistent with observed dose-response relationship for efficacy (see the table in **Figure 9**). This flat relationship supports the proposed 2 mg/kg as opposed to 10 mg/kg pembrolizumab Q3W regimen for the proposed indication.

Figure 9: Relationship between Steady-State AUCτ and Overall Response Rate (ORR) of Part B2 Patients



Number of Patients Achieved Overall Response		
	2 mg/kg	10 mg/kg
Yes	21	20
No	68	64
Total	89	84

Source: FDA Reviewer's analysis based on dataset p001pkeffae.xpt from the sponsor

2. What is the influence of systemic corticosteroid co-administration with pembrolizumab on the primary efficacy endpoint?

As shown in **Table 15**, there is no apparent association between the users and non-users of corticosteroids on ORR based on the Cohort B2 data. However, the impact of systemic corticosteroid use on ORR remains inconclusive due to the limited clinical information such as number of days of use before the event.

Table 15:. Similar ORR for Systemic Corticosteroid Users and Non-users (Cohort B2)	
Patient Group	ORR ($N_{Responder}/N_{Total}$)
2mg/kg keytruda + systemic corticosteroid	26% (5/19)
2mg/kg keytruda only	23% (16/70)
10 mg/kg keytruda + systemic corticosteroid	15% (2/13)
10 mg/kg keytruda only	25% (18/71)
Keytruda + systemic corticosteroid (pooled)	22% (7/32)
Keytruda only (pooled)	24% (34/141)
Source: FDA Reviewer's analysis based on dataset p001pkeffae.xpt from the sponsor	

Recommendations

- This application is acceptable from pharmacometrics perspective. See Clinical Pharmacology QBR for final recommendations.

Pertinent regulatory background

A Biologics License Application (BLA 125514) was submitted for pembrolizumab on February 27, 2014. Pembrolizumab, a humanized monoclonal anti-PD-1 antibody, is proposed for the treatment of unresectable or metastatic melanoma in patients who progressed on or after treatment with ipilimumab and, if BRAF V600 mutation positive, received treatment with a BRAF (b) (4) inhibitor. Pembrolizumab is seeking accelerated approval based on tumor response rate and durability of response. The proposed dose is 2 mg/kg infusion over 0.5 hour every three weeks.

Results of Sponsor's Analysis

Population Pharmacokinetic Analysis

Parameters estimates of the final covariate model are presented in **Table 16**. Confidence intervals of these parameter estimates were obtained from bootstrap simulation.

Table 16: Parameter Estimate of the Final Covariate Model

Parameters	Estimates	% RSE[c]	Shrinkage[d]
CL (L/day)	0.218	2.64	
Vc (L)	3.68	1.91	
Q (L/day)	0.897	13.2	
Vp (L)	3.91	5.91	
d_α for CL and Q[a]	0.589	14.8	
d_α for Vc and Vp[b]	0.474	13.4	
Albumin on CL	-1.06	10.9	
IgG on CL	0.373	12.7	
Gender on CL	-0.133	28.3	
Gender on Vc	-0.142	20.8	
Random Effect	**Estimates (%CV)**	**%RSE**	**%Shrinkage[d]**
[e]IIV on CL and Q	0.076 (28.1%)[f]	14.4	14.9
IIV on Vc and Vp	0.018 (13.4%)	33.1	29.7
IIV on Residual	0.181 (44.5%)	16.6	8.32
Residual Error	**Estimates**	**% RSE**	
	30.1%	3.25	4.73

[c]RSE: Relative standard error;

[e]IIV: inter-individual variability

[a]$CL=0.218\ (WGT/median(WGT))^{0.589} \times (ALB/median(ALB))^{(-1.06)} \times (IgG/median(IgG))^{0.373} \times [(1-0.133)\ \text{if female}]$

[b]$Vc=3.68(WGT/median(WGT))^{0.474} \times [(1-0.142)\ \text{if female}]$

[d]α= power value for weight-based scaling

Percentage of coefficient of variation (%CV)

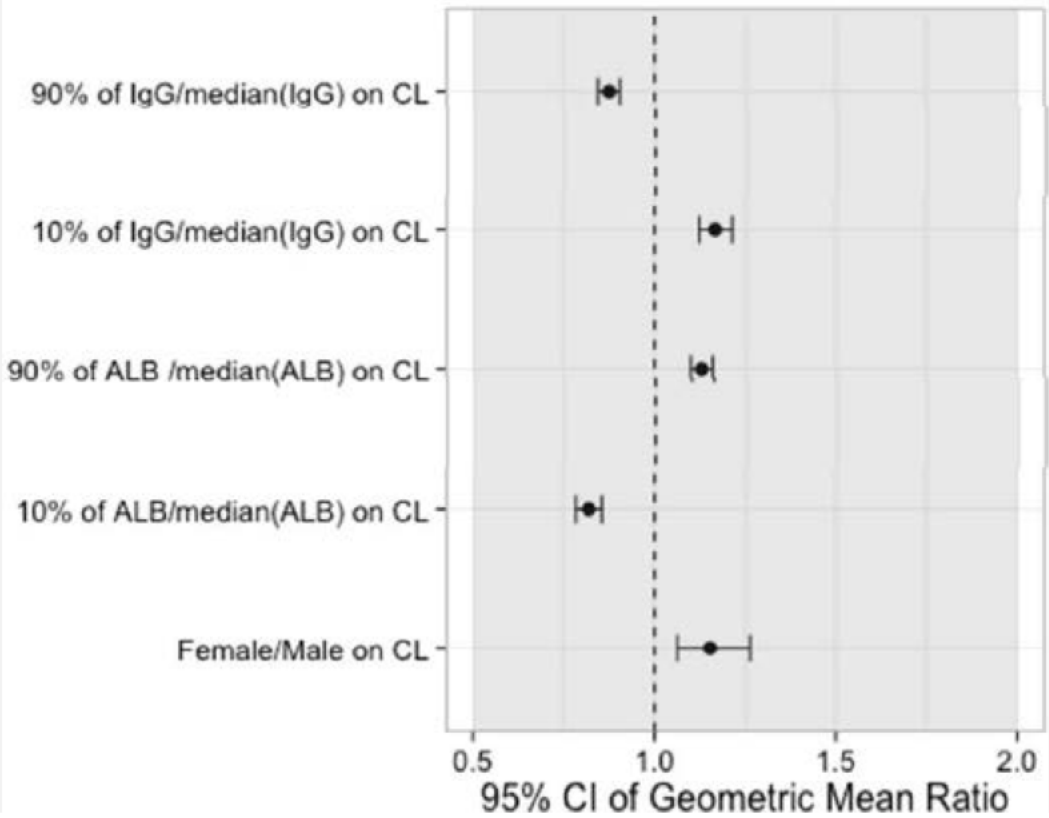
Source: Population PK Report 03tlc8, Page 57

Reviewer's Comments: The pembrolizumab's population PK model reasonably described the data and is generally acceptable. None of the covariates tested appeared to have a clinically meaningful effect on pembrolizumab clearance. Individual estimates of exposure can be used for exposure-response analyses given a shrinkage on clearance of 14.9%.

-Major Covariate Effect

Covariates investigated for the development of the final model included body weight, age, gender, creatinine clearance, ALP, AST, ALT, albumin and bilirubin, anti-drug antibody (ADA), race, tumor burden (SLD), geographic location, cancer type, coadministered drugs, baseline ECOG Performance and baseline IgG level. In the final model, gender, IgG, and albumin were selected as covariate on CL, and gender was also selected as covariate for central volume. Simulation based on the final model showed none of the selected covariates changed CL by more than 30% (**Figure 10**).

Figure 10: GMR Distribution for the Covariates Obtained from the Final Model



Source: Population PK Report 03tlc8, Page 63

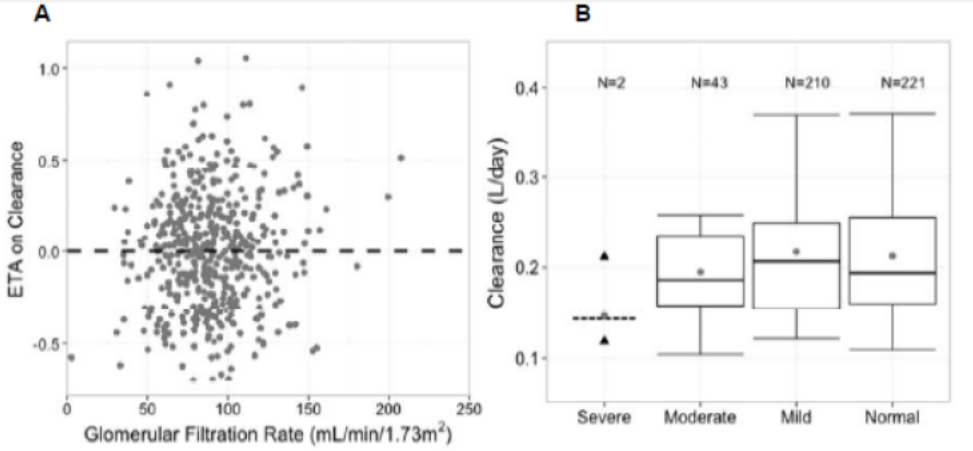
--Renal Function

The effect of eGFR on clearance is shown in **Figure 11**. There appears to be no obvious trend between clearance and eGFR, either as a continuous covariate or as a categorical covariate broken out by impairment severity classification. So no dose adjustment is needed for patients with mild or moderate renal impairment. Data for patients with severe renal impairment is limited. Note that renal function was classified as normal when eGFR $\geq$ 90 mL/min/1.73m^2 (N=221), mild impairment for eGFR starting from 60 to 90 mL/min/1.73m^2 (N=210), moderate impairment for eGFR starting from 30 to 60 mL/min/1.73m2 (N=43), and severe impairment when eGFR is less than 30 mL/min/1.73m^2 (N=2).

--Hepatic Function

Figure 12 and **Figure 13** do not show any trend between clearance and Aspartate Aminotransferase (AST) or Bilirubin. Hence there appears to be no effect of AST or Bilirubin on clearance. So no dose adjustment is needed for patients with mild hepatic impairment. Data for patients with moderate and severe hepatic impairment is limited.

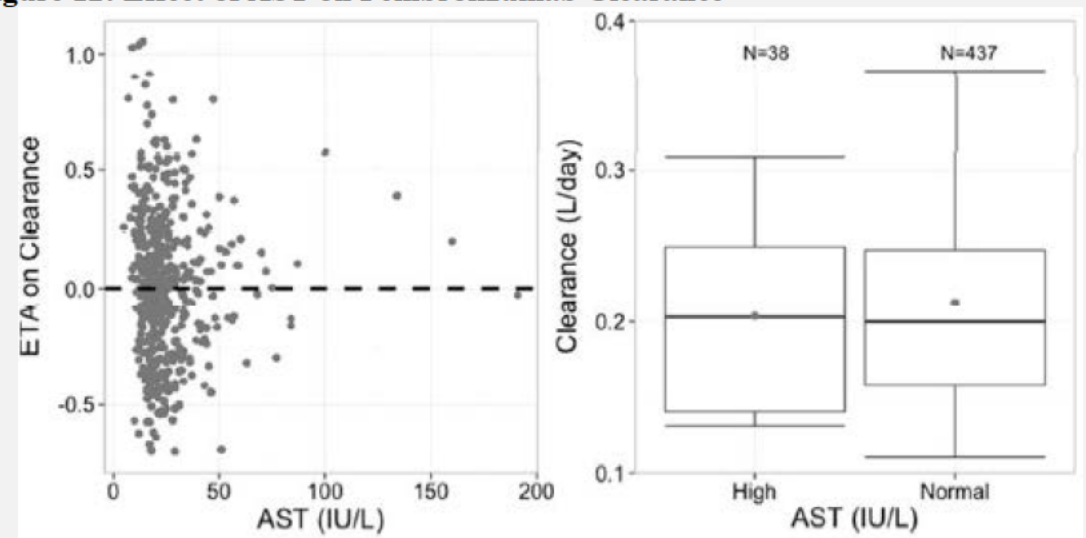
Figure 11: Effect of Renal Function on Pembrolizumab Clearance



(A) Individual ETA of clearance estimates versus glomerular filtration rate (eGFR), calculated using MDRD equation. X-axis is truncated at at value of 250 mL/min/1.73m^2, 2 high eGFR values are not shown. Values above 150 mL/min/1.73m^2 are not considered biologically plausible. The lowest eGFR value is suspect of a unit entry error; correction would result in a value of 43.6 mL/min/1.73m^2. (B) Distribution of individual posthoc clearance estimates for different degrees of renal function. Out of the two severely impaired patients, one has an eGFR values just below the cut-off by NCI but still within protocol inclusion criteria for serum creatinine, while the other would qualify as moderately impaired after correction of the suspected unit entry error. Line: median; center dot: mean; box: 25th and 75th percentile, whiskers: 5th and 95th percentile.

Source: Population PK Report 03tlc8, Page 45

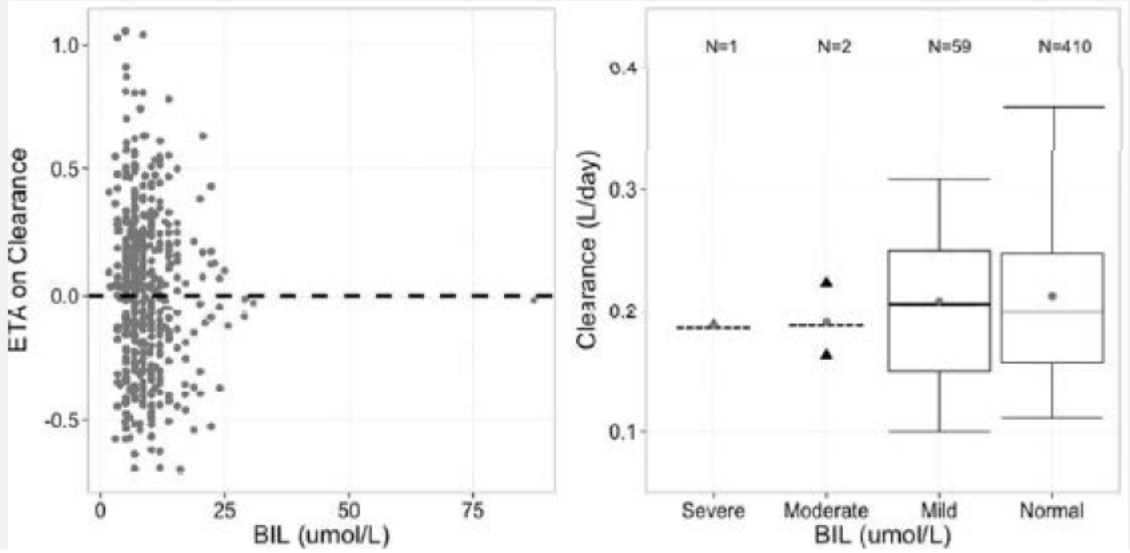
Figure 12: Effect of AST on Pembrolizumab Clearance



* AST level >43 IU/L was considered high

Source: Population PK Report 03tlc8, Page 47

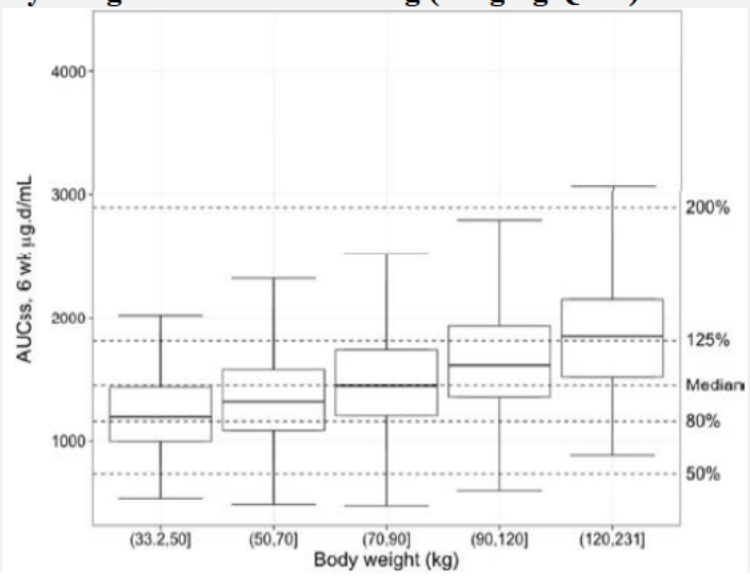
Figure 13: Effect of Bilirubin on Pembrolizumab Clearance



Source: Population PK Report 03tlc8, Page 47

--Effect of Body Weight

Figure 14: Simulated Pembrolizumab Exposure versus Categories of Body Weight in Setting of Body Weight Normalized Dosing (2 mg/kg Q3W)



Source: Population PK Report 03tlc8, Page 68

Reviewer's comments: Body weight normalized dosing is reasonable as the exposure variability across different weight group is not likely to lead to clinically significant efficacy response based on the flat ER relationship for ORR.

Reviewer's Analysis

--Objectives

- To conduct an exposure-efficacy analysis in terms of ORR for Part B2 of Study P001.
- To evaluate the influence of systemic corticosteroid use on ORR based on data for Part B2 of Study P001.

--Methods: Logistic regression and descriptive statistics.

--Data Sets: Data sets used are summarized in **Table 17.**

Table 17: Analysis Data Sets

Name	**Link:** \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pembrolizumab BLA 125514 HLI JYU
p001pkeffae	\Sponsor_Data_Reports\Data
p001cster.xpt	\Sponsor_Data_Reports\Data

--Software: S-Plus® (TIBCO Spotfire S+ Version 8.1) was used for data organization, graphics, logistic regression and related statistical analyses.

--Results: The results are presented in Section **Key Review Questions**.

Listing of Analyses Codes and Output Files

File Name	**Description**	**Location in \\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pembrolizumab_BLA 125514 HLI JYU**
ORR.ssc	S+ code for Exposure-ORR	\ER Analyses
OS.ssc	S+ code for Exposure-OS	\ER_Analyses
Table orr.ssc	S+ code for corticosteroid effect on ORR	\ER_Analyses
Table os.ssc	S+ code for corticosteroid effect on OS	\ER_Analyses
ORR.sgr	S+ plot for Exposure-ORR	\ER Analyses
OS.sgr	S+ plot for Exposure-OS	\ER_Analyses

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

/s/

HONGSHAN LI
08/01/2014

JINGYU YU
08/01/2014

RUNYAN JIN
08/01/2014

STACY S SHORD
08/01/2014

HONG ZHAO
08/01/2014
I concur.

LIANG ZHAO
08/01/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR BLA 125514

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125514/0	**Brand Name**	Keytruda
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Pembrolizumab
Medical Division	DOP2	**Drug Class**	IgG4 mAb
OCP Reviewers	Runyan Jin, Ph.D. (CP) Hongshan Li, Ph.D. (PM) Jingyu, Yu, Ph.D. (PM)	**Indication(s)**	Unresectable or advanced melanoma in patients who have been previously treated with Ipilimumab
OCP Acting Team Leaders	Lillian Hua Zhang, Ph.D. (CP) Liang Zhao, Ph.D. (PM)	**Dosage Form**	50 mg lyophilized powder in a single-use vial
Date of Submission	Rolling submission: Nonclinical: 11/22/2013 Quality: 12/20/2013 & 1/30/2014 Clinical: 2/17/2014 & 2/27/14	**Dosing Regimen**	2 mg/kg, Q3W
Estimated Due Date of OCP Review	8/1/14	**Route of Administration**	IV
Medical Division (CDTL) Due Date	9/30/14	**Sponsor**	Merck Sharp and Dohme Corp.
PDUFA Due Date	10/28/14	**Priority Classification**	Priority

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**8**		
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**		Study PN001
multiple dose:	**x**	**1**		Study PN001
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

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In-vitro:				
Subpopulation studies -				
ethnicity:				Pop PK report 03TLC8
gender:				Pop PK report 03TLC8
pediatrics:				
geriatrics:				
renal impairment:				Pop PK report 03TLC8
hepatic impairment:				Pop PK report 03TLC8
PD -				
QT assessment	**x**	**1**		PK-QT report 03TLCF
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**1**		Report 03TLC9
Preclinical study in mice:	**x**	**1**		Report 03V4KH
Population Analyses -				
Data rich:				
Data sparse:	**x**	**3**		• Pop PK report 03TLC8 • Exposure-AE report 03TLCN • Exposure-tumor size report 03TLCV
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Immunogenicity assessment	**x**	**1**		Study PN001
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Pediatric waiver granted
Literature References				
Total Number of Studies		**17**		

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	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	IV administration
4	Did the sponsor submit data to allow the evaluation of the	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR BLA 125514

	validity of the analytical assay?				
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			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			Please see the comment #B below
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
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	Orphan drug
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Waiver granted
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
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	

Reviewer's Comments

A. QT-IRT consult was requested on March 25, 2014.

B. Clinical pharmacology/Pharmacometric information requests (IRs) and the Applicant's responses

- The following IR was sent to the Applicant on March 25, 2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR BLA 125514

Based on the following xpt files submitted for Section 5.3.5.3 "Reports of Analyses of Data from More Than One Study", your output files cannot be reproduced by your NONMEM or R programs included in the submission:

1. "NonMDataAnalP001poppk.xpt" and "NonMDataAnalP001poppkFinal.xpt" associated with Report "03tlc8 (M&S analysis report of Population PK of MK-3475)".

2. "p001pkqtc009d.xpt" associated with Report "03tlcf (PK/QTc Report MK-3475)".

3. "p001pkaes05.xpt", "p001pkaeosi05.xpt", and "p001pkaegra05.xpt" associated with Report "03tlcn (M&S report MK-3475 – PK-AE)".

4. "p001pkest.xpt" and "p001pkiddiam08.xpt" associated with Report "03tlcv (M&S analysis report MK-3475)".

5. "MousePK_M32_M46.xpt" and "MousePKPD_3832.xpt" associated with Report "03v4kh (M&S analysis report MK-3475 – Translational PKPD)".

Please resubmit runnable XPT datasets that match the associated NONMEM control streams or the R script by Friday, March 28th.
The two datasets associated with Report 03tlc9 (M&S report MK-3475 – Pop PK and PK/PD) did reproduce your output files.

Applicant's Response on March 27, 2014

Merck is resubmitting the corrected datasets and supportive documents for the requested study reports in Module 5.3.5.3. Merck is providing the datasets in SAS XPT format, as requested. Merck is also providing the datasets in CSV format, which the agency stated was acceptable to submit during the follow-up correspondences.

- Subsequently, another IR shown as following was sent to the applicant on April 15, 2014 as it was still difficult reproducing some of the analysis results based on the resubmitted datasets and control streams dated March 27, 2014. In addition, four revised PK-PD datasets and a new dataset for further exposure-response analysis was requested by the clinical pharmacology reviewer and the pharmacometric reviewer, respectively. At the applicant's request, three output files after running the datasets with difficulty were sent to the applicant by email on April 17, 2014 for reference. Updated NONMEM control streams for the models associated with three output files and four requested revised PK-PD datasets were re-submitted on April 22, 2014 and the applicant's responses were also shown below.

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AGENCY COMMENT:

1. Translational PKPD: Resubmit the original dataset "MousePKPD_3832.csv" associated with report "03v4kh.pdf". Dataset "MousePKPD_3832.csv" as referred to in the output file "pkpd-run6-lst-out.txt" is still missing and the two resubmitted datasets "p001pkpdmouse383201.csv" and "p001tvmouse383201.csv" cannot be used to reproduce the result.

2. Exposure-Response (Safety) Analysis: Resubmit the original datasets and programs associated with output files "run3007.ctl.lst" and "run3011.ctl.lst" in the analysis report "03tlcn.pdf". The output files cannot be reproduced by FDA.

COMPANY RESPONSE:

Following receipt of the output file information on April 17, 2014, Merck has come to better understand the underlying issues in reproducing the original results. Merck believes the issue is not related to the data set but most likely due to differences in the software and hardware settings used by the two respective organizations.

Specifically, the settings used at Merck are the following: Platform Xeon E5540 @ 2.53GHz on linux Redhat 5.3 – 64 bits / compiler ifort (IFORT) 12.0.0 20101116 with settings o=' -Gs -nologo -nbs -w -Ob1gyti -prec-div -4Yportlib -traceback -vec-report0 ' opstat=' -static '.

It would be very helpful if the Agency reviewers could provide a summary of the settings used at the FDA, as this information may enable Merck to run the models under those settings to help address the current issues.

Additionally, we are providing in Module 5.3.5.3, updated codes for the models associated with pkpd-run6-lst-out.txt (Translational PK-PD model - 03v4kh) as well as "run3007.ctl.lst" and "run3011.ctl.lst" (PK-AE - 03tlcn). In these updates we have made slight adjustments (e.g., different initial estimates, decrease TOL, skip initial FO step) to increase the likelihood that these models will run across both systems.

AGENCY COMMENT:

3. Exposure-Response (Efficacy) Analysis: Submit a new dataset for Part B2 of Study P001. Include the following variables:
   AN (NONMEM ID), USUBJID (unique subject identifiers), TREATMENT, DOSE, AUC_Tau_ss, Cmax_ss, Cmin_ss, ORR (yes or no), PFS_Week24 (yes or no), OS_Month6 (yes or no), Corticosteroid Use (yes or no), along with all the AE variables as listed in Table 2.7.4: 21 of "Summary of Clinical Safety.pdf", Page 62-66) such as Anemia (yes or no), Leukocytosis (yes or no), Atrial Fibrillation (yes or no), etc.

COMPANY RESPONSE:

Merck is completing the creation of the requested dataset. Please confirm that the following definition of "Corticosteroid Use" is in line with the Agency's expectations. We propose to include the following two variables:

- Any systemic corticosteroid use (Y/N)
- Cumulative duration of use (days)

Merck would like to note that a response was submitted on April 3, 2014 to the Clinical Information Request received on March 26, 2014 in regards to the initiation of corticosteroid use due to an adverse event.

AGENCY COMMENT:

4. Resubmit the 4 PKPD datasets (p001pkdm012c.xpt, p001pkada009c.xpt, p001pkparametersparta.xpt and p001pkparametersparta2.xpt) including (1) USUBJID as used in the clinical datasets in Study P001 and (2) another variable differentiating the sub-cohort IDs (ie, A, A1, A2, B1 and B2) as the sub-cohort IDs are missing in the current variable PART.

COMPANY RESPONSE:

New PKPD datasets (including define documentation) including (1) USUBJID as used in the clinical datasets in Study P001 and (2) another variable differentiating the sub-cohort IDs (ie, A, A1, A2, B1 and B2) as the sub-cohort IDs in the current variable PART are provided [Ref. 5.3.5.2: define.pdf].

- A teleconference was held between FDA and the Applicant on April 23, 2014 to clarify any remaining underlying issues with the datasets. The discussions that occurred at the meeting are captured in the meeting minutes. Following are the brief points:
  1. FDA acknowledged that the re-submitted datasets dated March 27, 2014 and the re-submitted codes dated April 22, 2014 can reproduce all population PK analysis results and exposure-response analysis results except for pkpd-run6-lst-out.txt; and the four PKPD datasets resubmitted on April 22, 2014 with two new variables appear adequate.
  2. The FDA reviewer was still working on the model reproduction for translational PK-PD analysis results (pkpd-run6-lst-out.txt) based on mouse data and additional IR might be needed if it is deemed necessary.
  3. The applicant agreed to provide the information of corticosteroid use as (1) any systemic corticosteroid use (Y/N) and (2) systemic or topical use as FDA requested. FDA agreed the limited data of duration of use (50% not available) would still be informative and asked the applicant to document the missing data handling approach.

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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.

Runyan Jin (CP) /Hongshan Li (PM)	4/28/2014
Reviewing Clinical Pharmacologists	Date
Lillian Zhang (CP) /Liang Zhao (PM)	4/28/2014
Acting Team Leader/Team Leader	Date

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

/s/

RUNYAN JIN
04/28/2014

HONGSHAN LI
04/28/2014

LIANG ZHAO
04/28/2014

LILLIAN H ZHANG
04/28/2014