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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 3, 2014
From	Marc Theoret, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 125514
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	February 27, 2014
PDUFA Goal Date	October 28, 2014
Proprietary Name / Established (USAN) names	Keytruda / Pembrolizumab
Dosage forms / Strength	50 mg/vial lyophilized powder in a single-dose vial
Proposed Indication(s)	Treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab.
Recommended:	Approval (21 CFR part 601, subpart E)

Material Reviewed / Consultants	Primary/ Secondary Reviewer
Clinical Review	Meredith Chuk, M.D. and Jennie Chang, Pharm.D./ Marc Theoret, M.D.
Statistical Review	Emmanuel Sampene, Ph.D./ Kun He, Ph.D.
Regulatory Project Manager	Sharon Sickafuse / Monica Hughes
Pharmacology Toxicology Review	Shawna Weiss, Ph.D./ Whitney Helms, Ph.D.
Product Reviews	Product: Mark Paciga, Ph.D. & Deborah Schmiel, Ph.D. / Rashmi Rawat, Ph.D Quality Micro: (DS) Maria Candauchacon, Ph.D., (DP) Kalavati Suvama, Ph.D. / Patricia Hughes, Ph.D.
Clinical Pharmacology Review	Clin Pharm: Runyan Jin, Ph.D. / Stacy Shord, Pharm.D. and Hong Zhao, Ph.D. Pharmacometrics: Hongshan Li, Ph.D and Jingyu Yu, Ph.D. / Liang Zhao, Ph.D.
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1. Introduction

On February 27, 2014, Merck Sharp & Dohme Corp. completed the rolling submission of Biologics License Application (BLA) 125514 upon submission of the final components to Modules 1, 2, and 5. The Applicant proposed the following indication: treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab.

FDA granted MK-3475 (pembrolizumab) as Breakthrough Therapy Designation on January 17, 2013, for the treatment unresectable or metastatic melanoma that is refractory to ipilimumab treatment and for the treatment of unresectable or metastatic melanoma in patients who have not received prior ipilimumab therapy. The request for breakthrough designation, as amended, consisted of preliminary clinical evidence of the anti-tumor activity of pembrolizumab 10 mg/kg administered once every 2 (n=57) or 3 (n=28) weeks in patients with unresectable or metastatic melanoma; the confirmed overall response rates (ORR) by RECIST 1.1 as assessed by blinded independent central review (BICR) was 34/85 [40%; 95% confidence interval (CI): 29%, 51%] in patients with unresectable or metastatic melanoma.

The Applicant relies on the results from Trial P001, an international, multicenter, multiple cohort, pharmacology and activity-estimating trial, to serve as the primary evidence in support of the safety and efficacy of MK-3475. Part B2 of Trial P001, a multicenter, open-label, randomized (1:1), dose-comparative, activity-estimating cohort evaluated two doses of pembrolizumab (2 mg/kg or 10 mg/kg) administered once every 3 weeks (Q3W) in 173 patients with unresectable or metastatic melanoma who were refractory to ipilimumab and, if BRAF V600 mutation positive, to a BRAF or MEK inhibitor (refer to Section 5.3 of the FDA Clinical BLA Review for Applicant defined criteria of ipilimumab refractory). The BICR-assessed, confirmed overall response rate (ORR) per RECIST version 1.1 in the pembrolizumab 2 mg/kg arm (n=89) was 24% (95% CI: 15, 34), consisting of 20 partial responses and 1 complete response. Objective responses were ongoing in 18 (86%) of the 21 responders with durations of response (DOR) ranging from 1.4+ to 8.5+ months, including 8 patients with ongoing responses for greater than 6 months as of the data cutoff date. These results are similar in patients with and without BRAF V600 mutations and in the pembrolizumab 10 mg/kg arm (n=84) of Part B2.

A major consideration for this BLA is the durability of the objective responses, given the modest ORR observed in the indicated population at the recommended dose of 2 mg/kg once every three weeks (i.e., 2 mg/kg arm of Part B2). Results of ORR and DOR analyses from Part B1 of Trial P001, which had the longest duration of follow-up (minimum of 1 year in all patients), supported the magnitude of the point estimate of ORR observed in Part B2 and the durability of responses with median durations of response that were not reached in any of the three arms of Part B1 and response durations ranging from 9+ to 60+ weeks, 11+ to 72+ weeks, and 8+ to 76+ weeks in the pembrolizumab 2 mg/kg Q3W arm [ORR 41% (9/22)], 10 mg/kg Q3W arm [ORR 29% (16/56)], and 10 mg/kg once every 2 weeks (Q2W) arm [ORR 49% (28/57)], respectively. This is discussed in further detail in Section 7 of this review.

2. Background

- Indicated Population

Melanoma is the fifth most common cancer in men and seventh most common cancer in women in the United States. In 2014, it is estimated that there will be 76,100 new melanoma cases and 9,710 deaths from melanoma in the U.S.¹ Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases.² Melanoma, once metastatic, carries a grim prognosis—the five year survival rate is historically less than 10%—and develops at a relatively early age which results in a substantial number of years of life lost per person.³

In general, FDA-approved treatment options in use for treatment of metastatic melanoma include immunotherapy (interleukin-2, ipilimumab), chemotherapy (DTIC), and, if BRAF V600 mutation positive, BRAF inhibitors (vemurafenib, dabrafenib) and/or a MEK inhibitor (trametinib). Only ipilimumab and vemurafenib have been demonstrated in clinical trials to prolong overall survival compared with conventional therapy (Refer to Table Appendix A, reproduced from the FDA Clinical Review of BLA 125514, for description of treatment effects of FDA approved therapies for metastatic melanoma). There are no drugs approved specifically for treatment of patients refractory to ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor. DTIC and interleukin-2 are FDA-approved products that could be considered available therapy for treatment of the indicated population; however, dacarbazine and interleukin-2 have not been formally studied in this treatment refractory setting. Nevertheless, objective response rates with either product are low (< 20%) and neither has demonstrated an improvement in overall survival. Furthermore, treatment with interleukin-2 is associated with substantial on-treatment toxicity and is an appropriate therapeutic option only in a selected subgroup of patients.

- Mechanism of Action/Pharmacology

Pembrolizumab is a monoclonal antibody that blocks PD-1. PD-1 is a member of the CD28 family of coreceptors and is expressed in an inducible manner, found mainly on T cells (CD4+

¹ Siegel, R, J Ma, Z Zou, and A Jemal, 2014, Cancer Statistics, 2014, CA Cancer J Clin, 64:9-29.

² Howlader, N, AM Noone, M Krapcho, N Neyman, R Aminou, et al., 2012, SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site, 2012.

³ Ekwueme, DU, GP Guy, C Li, SH Rim, P Parelkar et al., 2011, The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity-United States, 2000 to 2006, J Am Acad Dermatol, 65 (5 Suppl 1):S133-43.

and CD8+), NK cells, B cells, and activated monocytes.⁴ Two ligands have been identified for PD-1, PD-L1 and PD-L2; expression of PD-L1 is present on hematopoietic cells, including T cells, B cells, dendritic cells, macrophages, as well as nonhematopoietic cells while the expression of PD-L2 appears to be relatively limited to antigen presenting cells. As a negative regulator of T-cell responses, PD-1 is upregulated on T cells following antigen-specific stimulation and, upon subsequent binding to PD-1 ligands, recruits SH2-domain containing tyrosine phosphatase (SHP2) thereby inhibiting T-cell receptor signaling and attenuating downstream T-cell proliferation and cytokine production.⁵ In addition, other mechanisms for dampening the immune response have been described for the PD-1 pathway.⁶ Blocking the interaction of PD-1 with its ligands, PD-L1 and PD-L2, can release the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

- Regulatory History

I reviewed the presubmission regulatory history for this BLA and agree with the summary as provided in the FDA Clinical Review with the following addition. On July 18, 2013, FDA held an informal teleconference with the Applicant to determine its plan for submission of an expanded access program and to update FDA on its plan for a BLA submission. The Applicant stated that it was in the process of evaluating an expanded access program to provide access to ipilimumab treated melanoma patients. The Applicant noted that their clinical program was actively recruiting patients with ipilimumab-refractory melanoma and in a wide geographic distribution. The Applicant also noted that it had not received a large number of single patient requests. A BLA submission was planned for late December 2013.

3. CMC/Device

The primary reviewers of the product quality sections of the BLA were Mark Paciga, Ph.D., and Deborah Schmiel, Ph.D., from the Division of Monoclonal Antibodies (DMA). The product quality reviewers recommended approval of Keytruda (pembrolizumab) for human use under conditions specified in the package insert. This recommendation was based on the conclusion that the data submitted in the BLA supports that

the manufacture of Keytruda (pembrolizumab; MK-3475) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs at both manufacturing sites presented.

⁴ Reviewed in Kamphorst, AO, and R Ahmed, 2013, Manipulating the PD-1 pathway to improve immunity, *Curr Opin Immunol*, 25:381-388.

⁵ Reviewed in Okazaki, T, S Chikuma, Y Iwai, S Fagarasan, and T Honjo, 2013, A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application, *Nat Immunol*, 14:1212-1218.

⁶ Reviewed in Sharpe, AH, EJ Wherry, R Ahmed, and GJ Freeman, 2007, The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection.

The primary product quality review recommended an expiry period of (b)(4) months for pembrolizumab drug substances (DS) manufactured in the (b)(4) facility and in the Frederic Manufacturing Center facility (FMC) when stored at (b)(4) and (b)(4) respectively. DMA recommended an expiry period of 18 months for pembrolizumab (b)(4) and (b)(4) drug product (DP) when stored at $5 \pm 3^{\circ}\text{C}$.

As summarized in the FDA Product Quality Addendum dated August 29, 2014, the Applicant withdrew the (b)(4) DS and DP from BLA 125514 on August 28, 2014, based on the timing of a pre-approval inspection scheduled for one of the facilities (b)(4) facility) where in-process testing for pembrolizumab DS is performed. Prior to the Applicant's withdrawal of the (b)(4) DS and consequently, DP made from (b)(4) DS and other facilities associated with the testing of the (b)(4) DS and DP from the BLA, inspection of the (b)(4) facility, planned in late (b)(4) was required prior to a regulatory action on the application. FDA held a teleconference with the Applicant on August 27, 2014, to clarify the requirement of the pre-approval inspection of (b)(4) prior to a regulatory action on the BLA. Based on the high unmet medical need of the indicated population, a regulatory action for the BLA is planned ahead of the PDUFA goal date.

The Applicant plans to (b)(4) Information on (b)(4) DS and DP remains in the remainder of this Section of the review based on the timing of its withdrawal from this BLA.

- General product quality considerations

Dr. Candau-Chacon and Dr. Hughes recommended approval of pembrolizumab DS from a quality microbiology perspective. Dr. Suvarna and Dr. Hughes recommend approval from a product quality microbiology perspective (drug product).

Pembrolizumab is an IgG4 κ humanized monoclonal antibody that binds to programmed death 1 (PD-1) receptor and blocks the interaction with its ligands, PD-L1 and PD-L2. (b)(4)

(b)(4) The molecular weight of (b)(4) pembrolizumab is approximately 149 kilodaltons (kDa).

The formulation and storage conditions of pembrolizumab DS are based on the manufacturing location:

(b)(4)

- FMC DS is formulated as (b) (4)

(b) (4) DP and (b) (4) DP are both manufactured at the Brinny fill/finish facility from (b) (4) DS and FMC DS, respectively. The composition of pembrolizumab (b) (4) DP and (b) (4) DP is (b) (4) a sterile, preservative-free, white to off-white lyophilized powder packaged in (b) (4) Type I glass 15 mL vials stoppered with (b) (4) 20 mm (b) (4) stoppers sealed with (b) (4) 20 mm (b) (4) seals. The vial contains an excess fill to ensure the recovery of the label claim of 50 mg pembrolizumab DP when reconstituted with 2.3 mL of water for injection. Each 2 ml of reconstituted solution of pembrolizumab consists of 50 mg of pembrolizumab, 3.1 mg of L-histidine, 0.4 mg of polysorbate 80, 140 mg of sucrose, and sodium hydroxide and/or hydrochloric acid to adjust pH to 5.5, if needed.

- Facilities review/inspection

FDA conducted pre-license inspections of pembrolizumab DS at MedImmune, LLC; Frederick Manufacturing Center (FMC) from April 21 to April 25, 2014, by the Biotechnology Manufacturing Assessment Branch (BMAB; Patricia Hughes and Reyes Candau-Chacon) and Division of Monoclonal Antibodies (DMA; Subramanian Muthukkumar and Mark Paciga) and at (b) (4) from (b) (4) by BMAB (Reyes Candau-Chacon) and DMA (Subramanian Muthukkumar). FDA identified three 483 observations at the (b) (4) facility consisting of quality systems deviations resulting in bioburden events, inadequate conduct of root-cause investigations, and inadequate maximum hold times during (b) (4). FDA identified two 483 observations at the FMC facility consisting of (1) insufficient procedures to ensure correct labeling of DS and (2) inability to follow written procedures.

FDA performed a surveillance inspection of the drug product manufacturing site, Schering Plough Brinny Co., located at Ballinacurra Road, Innishannon, Cork, Ireland, from January 27 to February 4, 2014, which was classified as NAI. Thus, FDA waived the pre-license inspection of this site.

4. Nonclinical Pharmacology/Toxicology

Shawna Weis, Ph.D., the primary nonclinical reviewer, and Whitney Helms, Ph.D., the secondary reviewer, concluded that the pharmacology and toxicology data in the BLA support the approval of pembrolizumab for the treatment of patients with unresectable or metastatic melanoma whose disease has progressed on or after treatment with ipilimumab.

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

Pembrolizumab binds human PD-1 with high affinity (29 pM) and interferes with PD-1 binding to its ligands, PD-L1 and PD-L2, with IC₅₀s of between 500 pM and 1 nM.

The Applicant selected cynomolgus monkey as the relevant toxicological species based on amino acid sequence homology, binding affinity, and pharmacodynamic target inhibition studies in monkeys and humans. Compared with the amino acid sequence of PD-1 in humans, sequence homology was 96% in monkeys (rhesus and cynomolgus), 72% in dogs, 66% in rats, and 62% in mice according to the Applicant. Flow cytometry studies demonstrated little or no binding of pembrolizumab to dog or rat peripheral blood lymphocytes (PBL) or to mouse PD-1 on CHO cells stably transfected with this isoform; however, binding studies based on flow cytometry and cell-based ELISA methods demonstrated binding of pembrolizumab to human and cynomolgus monkey PD-1 with similar affinity. In target inhibition assays performed with CHO cells stably transfected with either human PD-1 or cynomolgus monkey PD-1, pembrolizumab demonstrated similar IC₅₀s in each species for inhibition of PD-1 binding to PD-L1 and PD-L2.

In pharmacodynamic studies, the Applicant performed *in vitro* studies with pembrolizumab with whole blood from humans and monkeys and performed *in vivo* studies with a murine surrogate molecule (anti-mouse-PD-1 monoclonal antibody) in mice and rats. Pembrolizumab enhanced cytokine production in human whole blood *in vitro*. Incubation of whole blood from healthy donors and from patients with advanced melanoma and prostate cancer with pembrolizumab followed by exposure to staphylococcus enterotoxin B (SEB) resulted in relative increases in IL-2, TNF, IL-6, and IL-17 from both populations while levels of IL-5 decreased in this assay. The applicant used a murine surrogate molecule (anti-mouse-PD-1 monoclonal antibody) for *in vivo* tumor studies. In one study, administration of a hamster anti-mouse PD-1 monoclonal antibody compared with a control antibody in C57BL/6 mice implanted with syngeneic MC38 colon adenocarcinoma cells decreased the growth of tumors and prolonged survival at the highest dose of the antibody tested.

The non-clinical reviewer described the findings from two repeat-dose toxicology studies, a 1-month and a 6-month study, conducted in cynomolgus monkeys. As stated in the review, neither study demonstrated severe toxicities and patterns of histopathological change that were suggestive of specific target organ toxicity. Both studies demonstrated no pre-term deaths, clinical signs, body weight, food consumption, cardiovascular measurements, or clinical pathology endpoints; however, there was a tendency toward increased monocytic and/or lymphocytic infiltration of tissues, generally of a low magnitude in severity, which did not exhibit a tendency toward increasing severity with increasing duration of exposure. Of note, pharmacodynamic saturation, which was assessed by the inability of exogenous pembrolizumab to increase SEB-induced IL-2 production in cells from treated animals, was demonstrated in both repeat-dose toxicology studies through the end of dosing interval at the lowest dose of pembrolizumab administered.

- Carcinogenicity

The Applicant did not conduct carcinogenicity studies with pembrolizumab based on its intended use in patients with advanced cancer, which is in accordance with the International Conference on Harmonization Guideline S9 (Nonclinical Evaluation of Anticancer Pharmaceuticals).

- Reproductive toxicology

The Applicant did not evaluate pembrolizumab in a dedicated embryofetal toxicity study but provided a reproductive toxicology study assessment. PD-1 deficient mice and mice treated with PD-L1 neutralizing antibodies experience adverse pregnancy outcomes of allogeneic pregnancy in a manner consistent with immunological rejection, suggesting that PD-1 pathway inhibition is abortifacient. In addition, IgG4 mAb are capable of crossing the placental barrier but the effect of PD-1 inhibition during organogenesis and risk of malformations is not well described in the literature. However, as pointed out by the FDA nonclinical review staff, blocking PD-1 signaling during development may result in alterations of the developing immune system. The FDA non-clinical review staff recommended that pembrolizumab not be used during pregnancy unless the benefits to the mother outweigh the risks to a fetus.

- Other notable issues (resolved or outstanding)

The FDA nonclinical reviewers described two other notable potential issues: (1) detrimental alterations in the immune response to pathogens and (2) increased antigen responsiveness to vaccination.

The FDA Nonclinical reviewers noted that aberrations in PD-1 signaling may result in immune responses to pathogens that detrimental to the host. Published reports of PD-1 deficient mice infected with *M. tuberculosis* described decreased survival compared to wild-type mice; similar decreases in survival were reported in murine models of lymphocytic choriomeningitis virus infection. The Applicant provided data in monkeys with naturally occurring, chronic hepatitis B infection following administration of pembrolizumab, a study which was not requested by FDA, that demonstrated increases in liver enzymes without clear effects on viral load.

The FDA Nonclinical reviewers also noted the potential for pembrolizumab to exacerbate the response to recall antigen stimulation. The Applicant data demonstrated IFN- γ production that was increased from two to five times in cultures of peripheral blood cells from healthy volunteers that had been recently vaccinated with tetanus toxoid when cultures were re-stimulated with tetanus toxoid in the presence of anti-PD-1 blocking antibodies. The FDA Nonclinical Reviewers recommend as a postmarketing commitment an animal study to evaluate the effect of PD-1 inhibition on the magnitude of the primary and recall antibody responses to antigen challenge.

5. Clinical Pharmacology/Biopharmaceutics

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The FDA Clinical Pharmacology Review Team recommended approval of the BLA from the clinical pharmacology perspective. The Office of Clinical Pharmacology did not recommend post-marketing requirements or commitments.

The Applicant provided a population pharmacokinetic analysis (PK) with data from 476 patients who received pembrolizumab 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. The data provided by the Applicant as described in the FDA Clinical Pharmacology review supports a volume of distribution of pembrolizumab at steady state of 7.7 L with a variability of 14%. The mean clearance is 0.22 L/day with a % coefficient of variation of 28% and the mean terminal half-life is 26 days with a coefficient of variation of 24%. Steady state was achieved by 18 weeks of repeat pembrolizumab with an accumulation ratio of approximately 2.1 fold when dosed on an every 3-week schedule. The median exposure parameters (90% prediction interval) for pembrolizumab increased in a dose proportional manner with a C_{max} (ug/mL), C_{trough} (ug/mL) and $AUC_{ss,6-week}$ (ug-day/mL) of 65.7 (50.2, 88.4), 23.3 (13.3, 39.6), and 1408 (931, 2225), respectively, with pembrolizumab at a dosage of 2 mg/kg Q3W and a C_{max} (ug/mL), C_{trough} (ug/mL) and $AUC_{ss,6-week}$ (ug-day/mL) of 327 (245, 454), 117 (64.3, 206), and 7079 (4405, 11372), respectively, with pembrolizumab at a dosage of 10 mg/kg Q3W.

- Drug-drug interactions

The FDA Clinical Pharmacology reviewer described the possibility of drug-drug interactions as unlikely, either as a direct mechanism considering the elimination pathway of a therapeutic protein or as an indirect mechanism as pembrolizumab is not considered a modulator of cytokines which may affect drug metabolizing enzymes or transporters.

- Pathway of elimination

As summarized by the FDA Clinical Pharmacology reviewer, metabolism studies are generally not performed for biologic products such as pembrolizumab, because it is expected to be catabolized into amino acids by general protein degradation process.

- Demographic interactions/special populations

The Applicant investigated the effect of age, gender, hepatic insufficiency, and renal impairment in population pK analyses of 476 patients with advanced solid tumors. In summary, the FDA Clinical Pharmacology review did not identify any clinically significant impact on the clearance of pembrolizumab in analyses of the following intrinsic factors (description of analysis populations):

- Age (range 18 to 94 years, n=476)
- Gender (men, n=284; women, n=192)
- Renal impairment (eGFR 50-80 mL/min/m² [mild], n=210; eGFR 30-49 mL/min/m² [moderate], n=43; eGFR < 30 L/min/m² [severe], n=2)
- Mild hepatic impairment (total bilirubin [TB] ≤ upper limit of normal [ULN] and AST > ULN or TB between 1.0 to 1.5 times ULN and any AST or AST > ULN, n=59)
- Tumor burden

Of note, analyses of intrinsic factors identified albumin, IgG, and gender as statistically significant covariates on pembrolizumab clearance, but the impact on the relationship of these

covariates with AUC was limited and described as not clinically relevant. Simulations of dosing based on body weight normalized dosing, fixed dosing, and body surface area normalized dosing demonstrated that body surface area normalized dosing minimized exposure variability best followed by body surface weight normalized dosing as second best; the FDA Clinical Pharmacology reviewer concluded that body weight normalized dosing is generally acceptable considering the flat exposure-response relationship of pembrolizumab in terms of efficacy and safety.

- Thorough QT study or other QT assessment

The Interdisciplinary Review Team for QT Studies Consult Review stated that no large change (i.e., > 20 ms) in the QTc interval was detected when pembrolizumab was administered up to 10 mg/kg Q3W, which was based on Applicant submitted ECG data for Parts A, B1, B2, C, and D of Trial P001.

- Other notable issues (resolved or outstanding)

Dose Selection

The FDA Clinical Pharmacology review summarized the Applicant's dosage selection of 2 mg/kg administered once every three weeks based on two types of pharmacokinetics and pharmacodynamics evaluations. The clinical biomarker (IL-2 release) and the translational PK/PD projection of clinical response based on preclinical activity of an anti-PD-1 antibody supported the recommended pembrolizumab dosage from the clinical pharmacology perspective.

Exposure-Response Analyses

The FDA Clinical Pharmacology review described the exposure-response relationship for ORR and for adverse events (adverse events of special interest and Grade 3-5 AEs or serious AEs) as flat across the range of pembrolizumab doses from 2 mg/kg to 10 mg/kg and from 1 mg/kg to 10 mg/kg, respectively.

Immunogenicity

The effect of anti-product antibodies (APA) on pK or on clinical safety or efficacy cannot be assessed based on the data in the BLA. The Applicant developed a bridging electrochemiluminescence assay for detection of APAs in human serum. Of the 153 patients administered pembrolizumab at 2 mg/kg Q3W, there were 97 patients who had a concentration of pembrolizumab in the last post-dose sample that was below the drug tolerance level of 25 ug/mL for the APA assay and none of these 97 patients had a post-dose sample which tested positive for APA. In the analysis of APA irrespective of pembrolizumab dosage, there were 129 of 449 patients who were evaluable for APA based on a concentration of pembrolizumab in the last post-dose sample below the drug tolerance level of the assay. As summarized in the FDA Clinical Pharmacology review, there was one post-dose sample that tested positive in the APA analysis across pembrolizumab dosages, from a patient who received pembrolizumab 10

mg/kg Q3W; this patient's samples tested positive on Day 83 and the patient did not experience any hypersensitivity events such as anaphylaxis, urticaria, or angioedema. This antibody was identified as a neutralizing antibody, but pembrolizumab concentrations measured in this patient on approximate Study Days 83, 168, and 252 were similar to those from patients who had received the same dosage of pembrolizumab and did not develop APAs.

6. Clinical Microbiology

The section is not applicable to the review.

7. Clinical/Statistical- Efficacy

I agree with the overall conclusions of the primary FDA Clinical Reviewer for efficacy, Dr. Jennie Chang, and of the primary FDA Statistical Reviewer, Dr. Emmanuel Sampene, pertaining to the efficacy data submitted in the BLA to support an indication for pembrolizumab for treatment of patients with unresectable or metastatic melanoma who had disease progression following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The following postmarketing requirement is recommended to fulfill the requirements under 21 CFR part 601, subpart E to verify and describe the clinical benefit of pembrolizumab:

Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of pembrolizumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab.

- **Efficacy Summary**

The Applicant submitted data and results of Trial P001 titled "Phase I Study of Single Agent pembrolizumab in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma", an ongoing, uncontrolled, open-label, multiple cohort trial evaluating multiple objectives including pharmacology endpoints and therapeutic exploratory endpoints in patients with solid tumors. Trial P001 comprises 5 parts (A, B, C, D, F) consisting of 10 cohorts (refer to Table Appendix B in this review).

The efficacy of pembrolizumab was primarily demonstrated in Part B2 of Trial P001, an international, multicenter, open-label, randomized (1:1), dose-comparative, activity-estimating cohort of pembrolizumab in a treatment refractory, unresectable or metastatic advanced melanoma population. Part B2 enrolled patients with unresectable or metastatic melanoma who met the Applicant's definition of ipilimumab-refractory disease, as follows: (1) progressive disease according to immune-response criteria (irRC)⁷ within 24 weeks following the last of at least two doses of ipilimumab (3 mg/kg or higher) and (2) a minimum of 4 weeks

⁷ Wolchok, JD, A Hoos, S O'Day, JS Weber, O Hamid, et al., 2009, Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria, Clin Cancer Res, 15:7412-7420.

from the last dose of ipilimumab. This cohort also required patients with BRAF V600 mutation-positive melanoma to have previously received a BRAF inhibitor or MEK inhibitor.

The Applicant required the following additional key eligibility criteria for patients to enroll in the ipilimumab-refractory disease cohort, primarily related to safety parameters with respect to prior ipilimumab: (1) resolution of ipilimumab-related AEs to Grade 0-1 and requirement of ≤ 10 mg/day of prednisone, or equivalent dose of another corticosteroid, for immune-related adverse events (irAEs) for at least 2 weeks prior to first dose of study drug, (2) no history of severe immune-related AEs from ipilimumab (i.e., CTCAE Grade 4 requiring steroid treatment), and (3) no history of CTCAE Grade 3 irAEs from ipilimumab requiring steroid treatment (>10 mg/day prednisone or equivalent dose) for >12 weeks. General exclusion criteria included known active central nervous system metastases (previously treated, clinically stable brain metastases not requiring steroids allowed), risk factors for bowel obstruction or bowel perforation, history of pneumonitis or interstitial lung disease, active or history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents, HIV positivity, active hepatitis B or hepatitis C, and prior treatment targeting the PD-1:PD-L1 pathway.

The primary endpoint of Part B2 is objective response rate based on Response Evaluation Criteria in Solid tumors (RECIST) version 1.1 by independent central review. As discussed with the Applicant at the pre-BLA meeting held on October 25, 2013, the primary efficacy population in the FDA review of this BLA was the modified intent-to-treat population (mITT), which consisted of all patients who received at least one dose of pembrolizumab. Secondary endpoints include disease control rate (DCR), response duration, PFS, and OS.

One hundred seventy-three patients were randomized (1:1) to receive pembrolizumab 2 mg/kg (n=89) or 10 mg/kg (n=84) as an intravenous infusion over 30 minutes once every 3 weeks until progressive disease (PD) by irRC or unacceptable toxicity. Tumor assessments were scheduled at Week 12 and then every 12 weeks thereafter.

Patients could continue to receive pembrolizumab following an initial response assessment of PD at the discretion of the investigator if the patient met pre-defined criteria, as follows: (1) absence of symptoms and signs indicating clinically significant PD, including worsening of laboratory values indicating disease progression; (2) no decline in ECOG performance status; and (3) absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention. The protocol required a repeat tumor assessment within 4 to 6 weeks after initial progression in order to confirm progressive disease.

Among the 173 patients enrolled, the median age was 61 years (36% age 65 or older); 60% were male; 97% were White; and 66% and 34% had an ECOG performance status 0 and 1, respectively, 17% had BRAF V600 mutation, 39% had an elevated lactate dehydrogenase (39%) at baseline, 82% were M1c category, 9% had brain metastases, and 73% had two or more prior therapies for advanced or metastatic disease.

Reviewer Comment: The FDA Clinical Reviewer of Efficacy for the BLA clarified with the Applicant the metastasis stage category (M0, M1a, M1b, M1c) for all 411 melanoma patients in Trial P001 based on discrepancies identified in the demographic and baseline characteristics datasets. The Applicant’s responses to the June 2, August 27, and August 28, 2014, FDA requests for information, and FDA review of the Applicants responses and datasets, accounts for the increase in the proportion of M1c disease listed above (and reported in labeling) compared with the proportion of patients with M1c listed in the FDA Clinical Review of the BLA.

The anti-tumor activity of pembrolizumab appeared similar with either dose. The ORR by RECIST 1.1 per BICR was 23.6% (95% CI: 15, 34) in the pembrolizumab 2 mg/kg arm and was 23.8% (95% CI: 15.2, 34.3) in the 10 mg/kg arm. The proportion of patients with ongoing responses and the durations of responses were also similar in each arm as summarized in Table 1.

Table 1: Overall Response Rates and Duration of Response by RECIST 1.1 as Assessed by Blinded Independent Central Review, Part B2

	2 mg/kg, N=89 n (%)	10 mg/kg, N=84 n (%)
Overall Response Rate (%) 95% CI	21 (23.6) (15.2, 33.8)	20 (23.8) (15.2, 34.3)
Complete Response	1 (1)	1 (1)
Partial Response	20 (22)	19 (23)
Duration of Response Median, months (range)	Not reached (1.4+, 8.5+)	Not reached (2+, 9+)
Ongoing Response (%)	86	90

Source: Modified from the FDA Statistical Review of BLA

Among the 21 patients in the pembrolizumab 2 mg/kg arm with an objective response, 3 (14%) had progression of disease 2.8, 2.9, and 8.3 months after initial response. The remaining 18 patients (86%) had ongoing responses with durations ranging from 1.4+ to 8.5+ months, which included 8 patients with ongoing responses of greater than 6 months, as listed in Table 2.

Table 2: Durations of Response, 2 mg/kg Arm, Part B2

Patient	Response Durations, months
11000315	1.4
19000279	2.8 ^a
21000369	2.8
19000380	2.8
10000253	2.9 ^a
19000338	3
21000324	4.7
20000318	5.1
20000322	5.1
16000346	5.6

Patient	Response Durations, months
10000341	5.6
11000307	5.9
10000274	8.3 ^a
20000290	8.3
16000306	8.3
1000284	8.3 ^b
10000255	8.4
15000294	8.4
21000287	8.4
23000269	8.5
23000280	8.5

Source: Modified from the FDA Statistical Review Addendum, Merck Communication to FDA August 26, 2014 (verified by FDA Statistical Reviewer with ADIOBOR.xpt, ADIORDRT.xpt, DS.xpt, and ADSL.xpt datasets).

^a Patients with progression of disease after initial response, all other responses were ongoing at the time of the data cutoff date

^b Response duration updated from that listed in the FDA statistical review addendum, from 2.8 months to 8.3 months, based on inclusion of the duration of PR which preceded the best response of CR.

In the analyses performed by the FDA statistical reviewer, the ORR was similar across subgroups based on key demographics and baseline disease characteristics. Although the numbers are relatively small, patients with BRAF V600 mutation-positive melanoma also experienced objective responses, 2/12 (17%) on the 2 mg/kg arm 3/16 (16%) on the 10 mg/kg arm, all partial responses.

Results of Parts B1 and D of Trial P001 provided supportive evidence of a treatment effect of pembrolizumab. Part B1, which enrolled a heterogeneous population consisting of ipilimumab naïve and ipilimumab-treated patients with unresectable or metastatic melanoma to receive one of three dosages of pembrolizumab, had the longest duration of follow-up (at least one year for all patients). In comparison, the duration of follow-up in Part B2 was at least 28 weeks for all patients, approximately half with at least 9 months of follow-up. Objective responses observed in patients treated in the three pembrolizumab dosage arms in Part B1 appear to be durable with median durations of response that were not reached in any arm and DOR ranging from 9+ to 60+ weeks, 11+ to 72+ weeks, and 8+, 76+ weeks in the pembrolizumab 2 mg/kg Q3W [ORR 41% (9/22)], 10 mg/kg Q3W [ORR 29% (16/56)], and 10 mg/kg Q2W arms [ORR 49% (28/57)], respectively. There were no formal comparisons of anti-tumor activity between dosages as patients were not randomized to the three pembrolizumab dosages. Responses were ongoing in 100%, 88%, and 89% of the objective responders in the 2 mg/kg Q3W arm, the 10 mg/kg Q3W arm, and the 10 mg/kg Q2W arm, respectively.

As summarized by the FDA Clinical Reviewer of Efficacy, Part D consisted of patients who were ipilimumab-naïve and had received not more than two prior systemic treatment regimens for melanoma. The BICR-assessed ORR per RECIST v. 1.1 was 33% (95% CI: 21, 48) in the 2 mg/kg arm (n=51) and 37% (95% CI: 24, 51) in the 10 mg/kg arm (n=52) with a median duration of response that was not reached in either arm. All (100%) responders in the 2 mg/kg arm and 89% of responders in the 10 mg/kg arm had an ongoing response with response durations ranging from 7+ to 36+ weeks and from 6+ to 39+ weeks, respectively, at the time of data cut-off.

Figures 1 and 2 (reproduced from the Trial P001 clinical study report) show the durations of response by RECIST as assessed by BICR for Part B1 and Part D of Trial P001.

Figure 1: Plots of Time to Response and Duration of Response by BICR per RECIST v. 1.1, Part B1

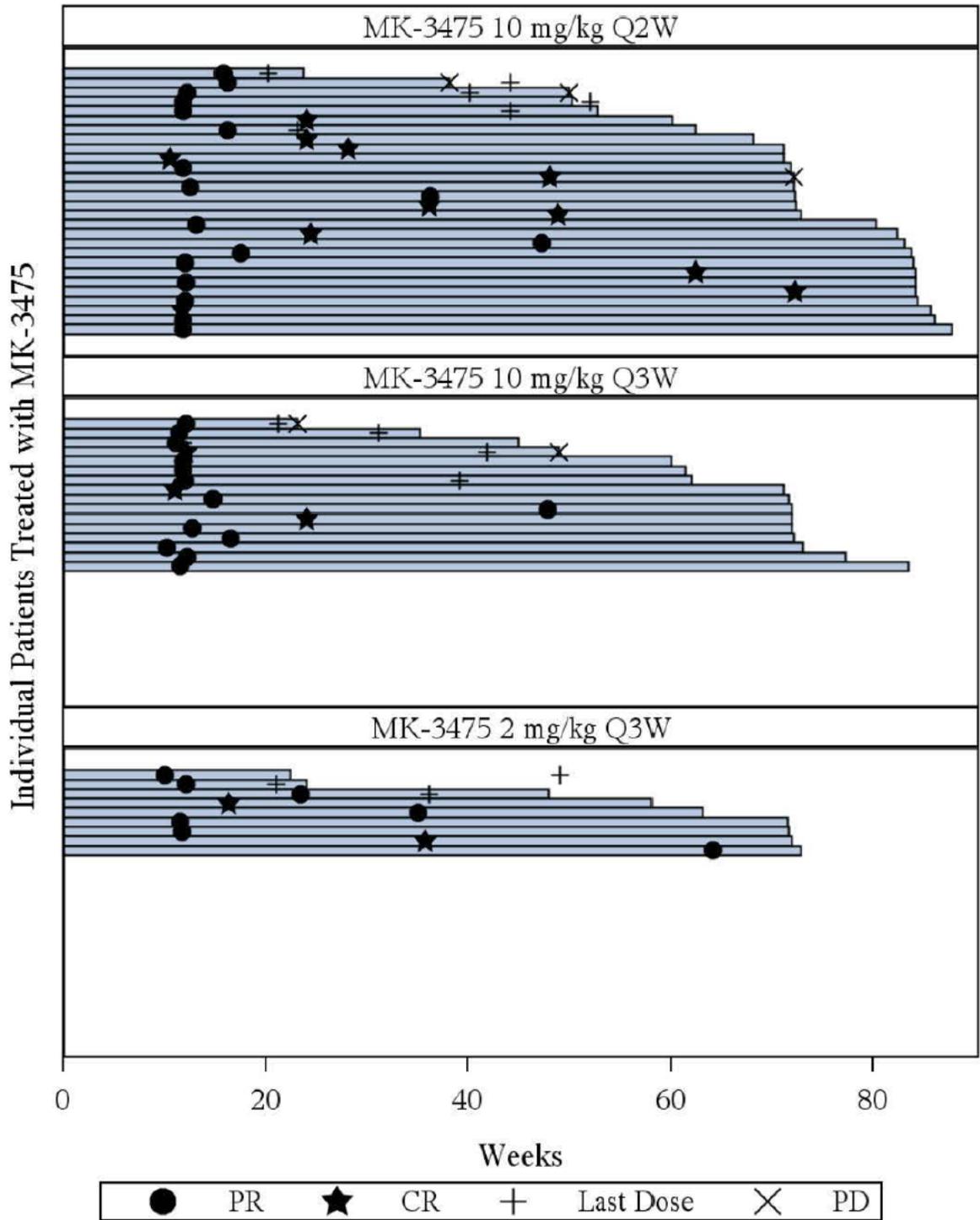
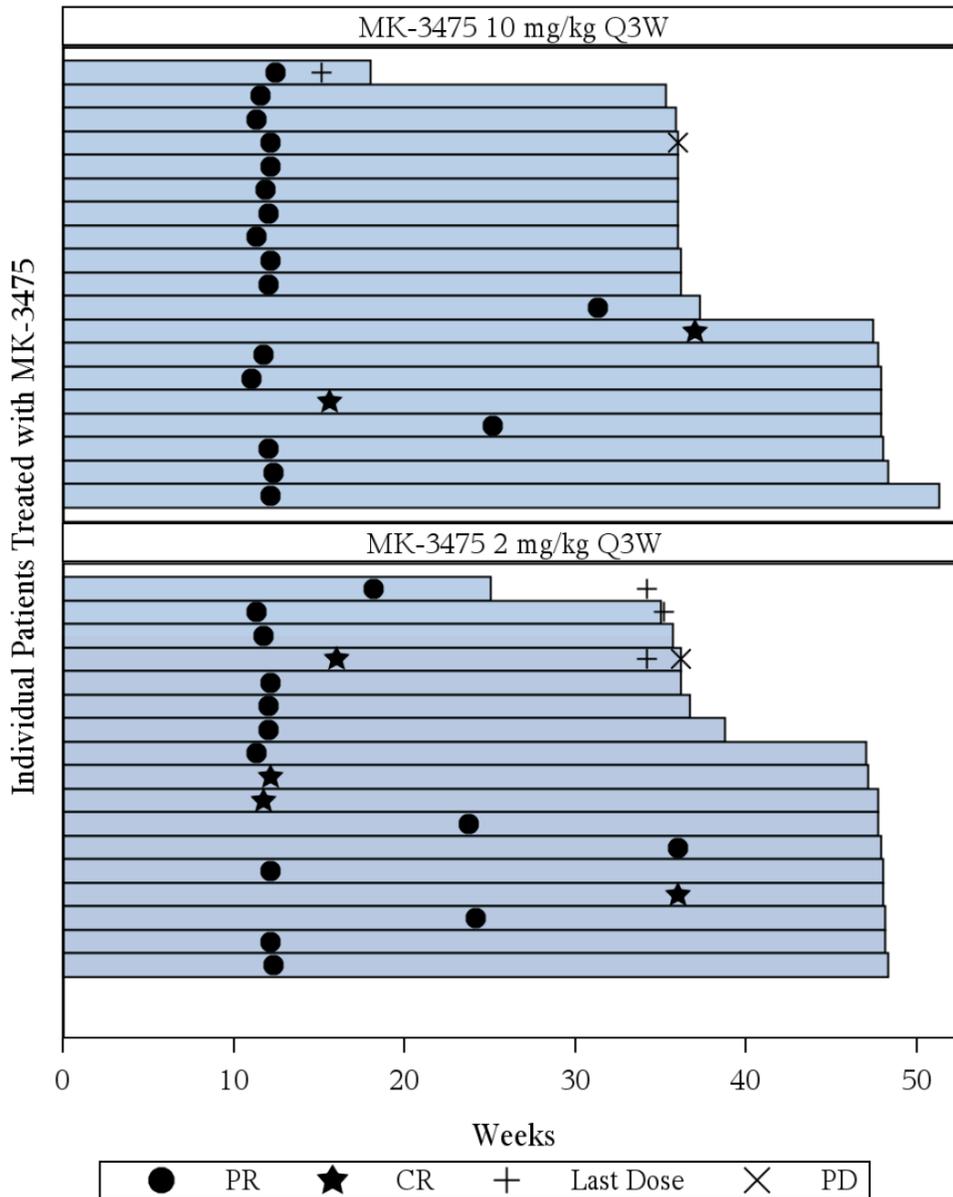


Figure 2: Plots of Time to Response and Duration of Response by BICR per RECIST v. 1.1, Part D



ORR by irRC as assessed by the investigator was a secondary endpoint of the trial. In Part B2, investigators assessed patients for response only by irRC thus no comparison was possible with ORR by RECIST as assessed by the investigators. However, the BICR assessed ORR by RECIST 1.1 and by irRC. The FDA clinical reviewer of efficacy summarized the analyses of ORR by irRC as assessed by BICR and compared to ORR by RECIST 1.1 by BICR. Based on the mITT population, the ORR by irRC was 19% (95% CI: 12, 29) on the 2 mg/kg arm and was 24% (95% CI: 15, 34) on the 10 mg/kg arm, which are similar to the ORRs by RECIST 1.1. Additionally, BICR-assessed ORRs by RECIST v. 1.1 and by irRC were similar across all parts of the trial when based on the mITT population. Of note, there was one patient (approximately 1%) on each arm of Part B2 who experienced PD by RECIST v. 1.1 but had a

confirmed PR by irRC as assessed by BICR; both patients were determined to have PD by RECIST at the Week 12 evaluation based on development of new lesions. On the 2 mg/kg arm, the patient developed two new asymptomatic lesions at the first tumor assessment concurrent with a 75% decrease in overall tumor burden; this reduction in tumor burden was durable for 5+ months.⁸

8. Safety

I agree with the overall conclusions of the primary FDA Clinical Reviewer for safety, Dr. Meredith Chuk, regarding the safety data submitted in the BLA. I agree that a REMS is not required for this application. However, this application requires a Medication Guide to communicate the serious risks of pembrolizumab and enhance its safe use.

The safety profile of pembrolizumab was primarily evaluated in Trial P001, an uncontrolled, open-label, multiple cohort trial in which 411 patients with unresectable or metastatic melanoma received pembrolizumab at either 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks (Melanoma ISS). The median duration of exposure to pembrolizumab was 6.2 months (range 1 day to 24.6 months). The data cutoff dates for the safety data in the original BLA submission was October 18, 2013, and in the safety update was December 31, 2013. The demographics and baseline characteristics of the safety population was similar to those described for the efficacy population with the exceptions that 54% of the safety population had prior exposure to ipilimumab and fewer than half of the patients had received two or more systemic therapies for advanced or metastatic disease.

The key safety findings are as follows (Melanoma ISS unless otherwise noted):

- Five fatal adverse events occurred in 1.2% of the patients: septic shock, cellulitis, pulmonary embolism, acute myocardial infarction, and increased LDH (one patient each).
- Serious adverse events occurred in 35% of patients, most commonly ($\geq 2\%$) renal failure, dyspnea, pneumonia, and cellulitis.
- Discontinuations due to adverse events occurred in 10% of patients. AEs leading to treatment discontinuation in more than one patient were pneumonitis (three patients), fatigue, pain, and renal failure (two patients each).
- Delays in pembrolizumab administration due to AEs occurred in 18% of patients. AEs leading to treatment delay in $\geq 1\%$ of patients were rash (1.7%), ALT increased (1.4%), AST increased (1.4%), pneumonitis (1.2%), anemia (1%), diarrhea (1%), and hypothyroidism (1%).
- Grade 3-5 treatment-emergent adverse events (TEAE) occurred in 38.9% of patients. Common ($\geq 2\%$) Grade 3-5 TEAEs were anemia (3.4%), fatigue (2.4%), dyspnea (2.4%), and cellulitis (2.2%).

⁸ Merck response dated August 26, 2014, to FDA information request dated August 25, 2014 (verified in ADIORDRT.xpt dataset by FDA reviewer of clinical efficacy)

- Common TEAEs ($\geq 20\%$) were fatigue (45%), rash (31%), nausea (29%), cough (29%), diarrhea (28%), pruritis (27%), arthralgia (25%), and constipation (20%).
- Common laboratory abnormalities (Part B2 2 mg/kg arm; n=89) representing an increase in Grade from baseline ($\geq 20\%$) were anemia (55%), hyperglycemia (40%), hyponatremia (35%), hypoalbuminemia (34%), hypertriglyceridemia (25%), increased AST (24%), and hypocalcemia (24%).
- Immunogenicity data was discussed in Section 5 of this Review.

Immune-mediated adverse reactions (imAR) were of special interest for this application based on the mechanism of action of pembrolizumab and the safety profile of a related FDA-approved product, ipilimumab. Overall, 26% of patients received corticosteroids (systemic or topical) during the study. The Applicant's database did not link concomitant medications to specific AEs, thus manual review was required to evaluate use of corticosteroids and outcomes for specific AEs. In the Applicant's analysis, 13% of patients received systemic corticosteroids and 5% received topical corticosteroids for an AE.

The FDA clinical review of safety identified the following clinically significant immune-mediated adverse reactions: pneumonitis (2.9%), hyperthyroidism (1.2%), colitis (1%), and nephritis, hepatitis, and hypophysitis ($<1\%$ each). Analyses of the timing of onset of imARs were limited for most imARs based on the relatively few cases; however, labeling of pembrolizumab includes median time to onset and the range for descriptive purposes. Immune-mediated adverse reactions were, in general, manageable with high-dose systemic corticosteroids followed by a corticosteroid taper. Hypothyroidism occurred in 8.8% of the patients but did not require initiation of corticosteroids in any patient; all but two patients received long-term thyroid hormone replacement. Additional clinically significant imARs were identified by the FDA clinical reviewer of safety during the labeling review based on analyses of the Melanoma ISS and of an extended safety database of approximately 2000 patients exposed to pembrolizumab; these were exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, adrenal insufficiency, myasthenic syndrome, optic neuritis, and rhabdomyolysis. Based on the mechanism of action of pembrolizumab, identification of additional imARs is expected during routine pharmacovigilance as well as analyses of randomized clinical trial data.

9. Advisory Committee Meeting

The application was not referred to an Oncologic Drug Advisory Committee (ODAC) as the safety profile is acceptable for treatment of patients with unresectable or metastatic melanoma that is refractory to ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor; the primary efficacy outcome measures are acceptable and similar to those used for previously approved products granted accelerated approval in patients with unresectable or metastatic melanoma; the application did not raise significant public health questions on the role of pembrolizumab in the treatment of patients for this indication; and outside expertise from

ODAC was not necessary because there were no controversial issues that would benefit from advisory committee discussion.

Consultations with Special Government Employees (SGEs) were not held during the review of this BLA. In total, eleven SGEs were recused following screening for conflicts of interest (COI). Preliminary screening of the eight SGEs in CDER and CBER identified by the review staff as having current expertise in melanoma resulted in recusals for all eight SGEs based on participation in clinical trial(s) of pembrolizumab. Preliminary screening of another SGE, one without specific expertise in melanoma but with expertise in developmental therapeutics and care of patients with treatment refractory disease resulted in a recusal based on participation in clinical trial(s) of pembrolizumab. Lastly, two SGEs underwent formal screening by the Division of Advisory Committee and Consultant Management for conflicts of interest, a physician with experience in general oncology and developmental therapeutics and a patient representative—both were recused.

10. Pediatrics

Pembrolizumab is exempt from the pediatric study requirements of the Pediatric Research Equity Act (PREA), i.e., to assess the safety and effectiveness of the product for the claimed indication(s) in pediatric patients, because FDA granted this product orphan designation for patients with Stage IIb to IV melanoma on November 19, 2012.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Financial Disclosures:** One investigator received \$50,000 in research grant money from Merck [REDACTED] (b)(6) Potential bias was minimized in the trial by use of multiple clinical investigators and study sites, review of primary endpoint data by an independent and adjudicated central vendor, and randomization.
- **Other GCP Issues:** None
- **DSI Audits:** The Office of Scientific Investigations inspected three sites: Dr. Wen-Jen Hwu (Houston, TX; Site 12), Dr. Anthony Joshua (Toronto, ON; Site 20), and Dr. Naiyer Rizvi (New York, NY; Site 19). A Form FDA 483 was issued to one site (Site 19) for failure to report AEs documented in source records in the electronic CRFs in seven patients. The Applicant performed internal audits in support of the quality and integrity of safety data submitted in the BLA. I agree with the conclusions of the FDA clinical reviewer of safety that the omission of safety events appears limited to Site 19 and this does not affect the overall safety assessment of pembrolizumab.

12. Labeling

- **Proprietary name:** In the FDA Proprietary Name Memorandum dated January 14, 2014, Dr. Otto Townsend, DMEPA, concluded that the proposed proprietary name, Keytruda, is acceptable
- **OSE /Division of Medication Error Prevention and Analysis (DMEPA):** DMEPA concluded the carton and container labeling was acceptable; DMEPA provided recommendations regarding the preparation and administration section of labeling.
- **Office of Prescription Drug Promotion (OPDP):** OPDP provided recommendations regarding text that may be considered promotion in Sections 5 and Section 12.1.
- **Patient Labeling:** The FDA Patient Labeling team participated in labeling discussions of the Prescribing Information and the Medication Guide. Refer to the FDA Patient Labeling BLA Reviews for their recommendations.
- **FDA Modifications to Labeling:** FDA communicated to the Applicant high-level comments and draft edits to the prescribing information regarding conformance to 21 CFR 201.56(a) and (d) and 201.57 in the Filing Communication dated April 29, 2014. The Applicant provided proposed edits to the label on May 23, 2014. FDA communicated proposed labeling to the Applicant on August 13, 2014, which was prior to the date stipulated by the 21st Century Review Process for this communication of September 26, 2014. FDA provided edits to all sections of the label for brevity and clarity. Final labeling was agreed upon at the time of this review. The following is a summary of Sections of the Prescribing Information containing substantial modifications compared to the version of the label submitted in the original BLA.
 - **Indications and Usage:** the indication was clarified to reflect the treatment refractory population evaluated in Part B2 of Trial P001, i.e., patients refractory to ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Addition of wording for products approved under accelerated approval regulations according to the Draft FDA Guidance for Industry “Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway.”
 - **Dosage and Administration:** information in the Dose Modification subsection more appropriate for the Warnings and Precautions Section was moved accordingly. DMEPA provided recommendations to the Preparation and Administration Section. This subsection was reformatted to clarify instructions for preparation, storage of reconstituted and diluted solutions, and administration.
 - **Dosage Forms and Strengths:** OBP proposed use of Single-dose vial rather than use of single-use vial on carton and container labeling. The term single-dose vial is the appropriate term for the pembrolizumab vial per United States Pharmacopeia 8/1/14 – 11/30/14 <659> Packaging and Storage Requirements. The Applicant’s proposal of the term *single-use vial* was retained based on potential concerns raised about the potential for misunderstanding the term

single-dose vial when multiple vials likely are required based on patient weight, acceptance of the term single-dose vial in labeling for recent FDA-approved injectable products, and absence of clear guidance from FDA on use of these terms. Note that FDA is planning to clarify the appropriate terminology in a Draft Guidance later this year for *Appropriate Package Type Terms for Injection Drugs or Biological Products in Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers*.

- Warnings and Precautions: added details on all immune-mediated adverse reactions including incidence, time to onset, duration, management, and outcome in accordance with FDA Guidance for Industry “Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format.” Addition of the subsections *Renal Failure and Immune-mediated Nephritis* and *Embryofetal Toxicity*.
- Adverse Reactions: narrowed the adverse reactions table to the 89 patients treated with pembrolizumab at 2 mg/kg in Part B2. Modified the adverse reactions table to include the incidence of adverse reactions irrespective of attribution in as this was an uncontrolled trial, unless the adverse reaction was clearly related to another cause as supported by the data. Added a laboratory abnormalities table consisting of abnormalities increased in toxicity severity grade from baseline and occurring above a threshold incidence, all Grades and Grades 3-4, consistent with current labeling practices. Immunogenicity section was narrowed to patients who received pembrolizumab 2 mg/kg and moved from a subsection of Clinical Studies to a subsection of Adverse Reactions.
- Drug Interactions: deleted (b) (4) (b) (4) (b) (4) as the BLA did not contain data on this population based on the patient selection criteria of Trial P001.
- Use in Specific Populations: revised from Pregnancy Category (b) (4) to Pregnancy Category D based on the predicted abortifacient risk and a teratogenic risk that has not been fully characterized as summarized by the FDA. Refer to DRISK Review of the BLA.
- Nonclinical Toxicology: added findings from studies in mice engineered with a deletion of PD-1 compared with wildtype mouse controls in models of infection, specifically M.tuberculosis infection and lymphocytic choriomeningitis viral infection, which both demonstrated decreased survival in mice lacking PD-1. Also added were findings of increased liver transaminases in an Applicant-conducted studied of chimpanzees with naturally occurring, chronic hepatitis B administered pembrolizumab.
- Clinical Studies: narrowed the description of the design and results of this section to Part B2 of Trial P001, the part of the trial supporting an accelerated approval of pembrolizumab. Added a description of the clinical criteria that must have been met by patients in the protocol to continue pembrolizumab after the first determination of disease progression until progression was confirmed on repeat imaging performed at 4 to 6 weeks. Added details of the one patient

on the 2 mg/kg arm of Part B2 who was identified as having PD by RECIST version 1.1 based on presence of two new lesions in the context of an overall 75% reduction in tumor burden.

- (b) (4) removed (b) (4)
- Patient Counseling Information: added information about immune-mediated adverse reactions as the most important risks of pembrolizumab, consistent with the Draft FDA Guidance, “Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.”

On August 7, 2014, Merck submitted a Medication Guide to the BLA. FDA provided modifications throughout the Medication Guide for brevity and clarity. Substantial modifications to the Medication Guide were: (1) addition of the potential risk of immune-mediated adverse reactions involving the kidney and other organs in the “What is the most important information I should know about KEYTRUDA” Section and (2) clarification of the indicated population in the “What is Keytruda” Section.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval (21 CFR part 601, subpart E)
- Risk Benefit Assessment

Patients with unresectable or metastatic melanoma who have progression of disease following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor have a serious and life-threatening disease with a high unmet medical need. Melanoma develops at a relatively early age which results in a substantial number of years of life lost per person⁹, and once metastatic carries a grim prognosis—the five year survival rate is historically less than 10% for patients.

In general, FDA-approved treatment options in use for treatment of metastatic melanoma are limited and include immunotherapy (interleukin-2, ipilimumab), chemotherapy (DTIC), and, if BRAF V600 mutation positive, BRAF inhibitors (vemurafenib, dabrafenib) and a MEK inhibitor (trametinib). Only ipilimumab and vemurafenib have been demonstrated in clinical studies to prolong overall survival compared with conventional therapy. There are no drugs approved specifically for patients refractory to ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor. Dacarbazine and interleukin-2 may be used in this setting but objective responses with either product are low (< 20%) and have not been studied in this treatment refractory population. Furthermore, treatment with interleukin-2 is associated with substantial on-treatment toxicity and is an appropriate therapeutic option only in a selected subgroup of patients.

⁹ Ekwueme, DU, GP Guy, C Li, SH Rim, P Parelkar et al., 2011, The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity-United States, 2000 to 2006, J Am Acad Dermatol, 65 (5 Suppl 1):S133-43.

The recommendation for approval of BLA 125514 (Keytruda) is primarily based on the results of Part B2 of Trial P001 which demonstrated a clinically relevant, albeit modest, ORR (24%; 95% confidence interval: 15, 34) with prolonged durations of response in a treatment-refractory patient population. Of the 21 patients with objective responses in the pembrolizumab 2 mg/kg arm of Part B2, 86% of the responses were ongoing as of the data cut-off date (range 1.5+ to 8.5+ months) and responses were ongoing for greater than 6 months in 8 of the 21 patients. Similar results were observed in the 10 mg/kg arm of Part B2. Exploratory subgroup analyses did not demonstrate that the anti-tumor activity of pembrolizumab was limited to a specific subpopulation. Analyses of ORR and DOR in additional melanoma cohorts of Trial P001 with longer durations of follow-up than in Part B2 are supportive of the durability of objective responses observed in the treatment refractory population.

The primary safety risks of pembrolizumab identified in the 411 patients with melanoma in Trial P001 are immune-mediated adverse reactions (imAR), a finding that is consistent with the mechanism of action of pembrolizumab and the safety profile of a related FDA-approved product, ipilimumab. The FDA clinical review of safety identified the following clinically significant imARs: pneumonitis (2.9%), hyperthyroidism (1.2%), colitis (1%), and nephritis, hepatitis, hypophysitis (<1% each). Hypothyroidism occurred in 8.8% of the patients but did not require initiation of corticosteroids in any patient but required long-term thyroid hormone replacement. Additional clinically significant imARs, (i.e., imARs that were serious, required treatment modification of pembrolizumab, or required management with corticosteroids) were exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, adrenal insufficiency, myasthenic syndrome, optic neuritis, and rhabdomyolysis.

Approximately 10% of patients experienced adverse events (AE) leading to treatment withdrawal. Delays in treatment for AEs occurred in 18% of patients; common ($\geq 1\%$) AEs leading to treatment delay were rash (1.7%), ALT increased (1.4%), AST increased (1.4%), pneumonitis (1.2%), anemia (1%), diarrhea (1%), and hypothyroidism (1%). Grade 3 to 5 AEs occurred in 38.9% of patients; the most common ($\geq 2\%$) were anemia (3.4%), fatigue (2.4%), dyspnea (2.4%), and cellulitis (2.2%). The most frequent ($\geq 20\%$) adverse reactions of pembrolizumab were fatigue (45%), rash (31%), nausea (29%), cough (29%), diarrhea (28%), pruritis (27%), arthralgia (25%), and constipation (20%).

The risk-benefit assessment of pembrolizumab is favorable for the treatment of patients with unresectable or metastatic melanoma and progression of disease following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor—a treatment refractory population with no satisfactory available therapy. FDA approval of pembrolizumab will be the first in the class of monoclonal antibodies blocking PD-1 or PD-L1 and will represent a new therapeutic option with a novel mechanism of action for treatment of the indicated population. In this treatment refractory population, pembrolizumab at a dose of 2 mg/kg administered once every 3 weeks demonstrated durable objective responses that are of sufficient magnitude—an approximate 25% ORR with ongoing responses in 18 of the 21 (86%) responding patients ranging from 1.5+ to 8.5+ months, including 8 patients with response durations of greater than 6 months—to be considered reasonably likely to predict clinical benefit. Pembrolizumab administered at the

10 mg/kg every 3 week dosage does not appear to offer additional benefit, supporting the Applicant's selection of 2 mg/kg Q3W as the recommended dosage. In general, immune-mediated adverse reactions, the major safety risk with pembrolizumab were manageable with high-dose systemic corticosteroids followed by a corticosteroid taper. It is uncertain whether the durable objective responses observed with pembrolizumab will translate into outcomes of clinical benefit, e.g., an improvement in survival or irreversible morbidity, and, therefore, as a condition of accelerated approval the Applicant must verify and describe the benefit of pembrolizumab. The Applicant identified two ongoing randomized control trials—one trial in ipilimumab-refractory patients and one in ipilimumab-naïve patients—each with co-primary endpoints of PFS and OS, which could potentially confirm the clinical benefit of pembrolizumab (Refer to FDA Clinical Review of the BLA for details).

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

I agree with the recommendations of the BLA review team, including DRISK, that a REMS is not required to ensure safe use of pembrolizumab.

- Recommendation for other Postmarketing Requirements and Commitments

The following postmarketing requirement is recommended to fulfill the requirements under 21 CFR part 601, subpart E to verify and describe the clinical benefit of pembrolizumab:

1. Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of pembrolizumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab.

The following postmarketing commitments are recommended:

2. To conduct an animal study that will measure the effect of PD-1 inhibition on the magnitude of the primary (first vaccination) and recall (second vaccination) antibody responses to antigen challenge (e.g., tetanus toxoid or KLH). This study will evaluate the effect of PD-1 inhibition on the primary immune response once steady state plasma levels have been achieved, and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing.
3. To develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the pembrolizumab drug substance release program. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided in the final study report.
4. To re-evaluate pembrolizumab drug substance lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

5. To re-evaluate pembrolizumab drug product lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.
6. To conduct a study to assess the endotoxin recovery at various time-points from three drug product lots spiked with control standard endotoxin (7.5 EU/mL and 10 EU/mL) in vials using the kinetic turbidometric assay.

Table Appendix A: FDA-Approved Therapies Indicated for the Treatment of Patients with Metastatic Melanoma

FDA Approved Drug ¹	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
DTIC (dacarbazine) ²	1975	Single-arm	ORR	ORR of 5-20%
Proleukin (interleukin-2) ²	1998	Multicenter single-arm	ORR	ORR 16% (CR 6%); DOR CR: 59+m (3 to 122+ m) CR or PR: 59+ m (1 to 22+m)
Yervoy (ipilimumab) ²	2011	Multicenter, randomized, blinded, active-controlled three-arm	OS ORR	Ipi vs. gp100: OS: HR 0.66 (95% CI: 0.51, 0.87) median 10 vs. 6 m BORR: 10.9% vs. 1.5% mDOR: not reached in either arm Ipi+gp100 vs. gp100: OS: HR 0.68 (95% CI: 0.55, 0.85) median 10 vs. 6 m BORR: 5.7% vs. 1.5% mDOR: 11.5 m vs. NR
Zelboraf ² (vemurafenib)	2011	Randomized, open-label active-controlled, two-arm	OS PFS ORR	Vemurafenib vs. DTIC mOS: NR vs. 7.9 m HR: 0.44 (95% CI: 0.33, 0.59) mPFS: 5.3 vs. 1.6 m HR: 0.26 (95% CI: 0.20, 0.33) cORR: Vemurafenib: 48.4% (95% CI: 41.6%, 55.2%) CR 0.9% PR 47.4% DTIC: 5.5% (95% CI: 2.8%, 9.3%) PR: 5.5%
Tafinlar ³ (dabrafenib)	2013	Randomized, open-label active-controlled, two-arm	PFS ORR	Dabrafenib vs. Dacarbazine mPFS: 5.1 vs. 2.7 m HR: 0.33 (95% CI: 0.20, 0.54) cORR: Dabrafenib: 52% (95% CI: 44%, 59%) CR 3% PR 48% Dacarbazine: 17% (95% CI: 9%, 29%) CR 0% PR 17%

FDA Approved Drug ¹	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
Mekinist ⁴ (trametinib)	2013	Randomized, open-label active-controlled, two arm	PFS ORR	<u>Trametinib vs. Chemotherapy</u> mPFS: 4.8 vs. 1.5 m HR: 0.47 (95% CI: 0.34, 0.65) cORR: Trametinib: 22% (95% CI: 17%, 28%) CR 2% PR 20% Chemotherapy: 8% (95% CI: 4%, 15%) CR 0% PR 9%
Tafinlar and Mekinist ⁵ (dabrafenib and trametinib)	2014 ⁶	Randomized, open-label, active-controlled, two arm portion of dose-escalation study	ORR	<u>Dabrafenib plus Trametinib vs. single-agent Dabrafenib</u> ORR 76% vs. 54% mDOR 10.5m vs. 5.6m mPFS: 9.4m vs. 5.8m HR: 0.39 (95% CI: 0.25, 0.62)

Reproduced from FDA Clinical Review of BLA 125514

Source: Proleukin (USPI); Yervoy (USPI); Zelboraf (USPI); Dacarbazine (USPI); Tafinlar (USPI); Mekinist (USPI).

Abbreviations in Table: m, months; BORR, best overall response rate; CR, complete response; cORR, confirmed objective response rate; DOR, duration of response; HR, hazard ratio; Ipi, ipilimumab; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response; +, response is ongoing.

¹ Hydroxyurea is also FDA-approved for treatment of melanoma but is of historical interest.

² BRAF V600 mutation status unknown.

³ Patient selection based on BRAF V600E mutation-positive tumors.

⁴ Patient selection based on BRAF V600E or V600K mutation-positive tumors

⁵ Patient selection based on BRAF V600E, V600K, or V600D mutation-positive tumors

⁶ Accelerated approval as per 21 CFR 314.510 of subpart H

Table Appendix B: Trial P001, Description of Cohorts

Part	Cohort	Purpose	Design	Population	MK-3475 Dose, mg/kg	Dosing Interval, weeks	Subjects, N
A	A	Dose tolerance	3+3 dose escalation	Refractory solid tumors	1, 3, and 10	2 ^a	10
	A1	Dose confirmation	Single-arm	Refractory solid tumors	10	2	7
	A2	Dose Titration	Parallel arm, randomized, intra-patient dose titration	Refractory solid tumors	0.005 to 10 ^b	3	13
B	B1	Dose exploration	Parallel arm, non-randomized	Melanoma (IPI-naïve or IPI-treated)	2 or 10	2 or 3	135
	B2	Dose comparison	Parallel arm, randomized	Melanoma (IPI-refractory)	2 or 10	3	173
	B3 ^d	Dose comparison	Parallel arm, randomized	Melanoma (IPI-naïve, IPI-treated, or IPI-refractory)	10	2 or 3	248
C		Activity-estimating	Single arm	NSCLC	10	3	38
D		Activity estimation, dose comparison	Parallel arm, randomized	Melanoma (IPI-naïve)	2 or 10	3	103
F	F1 ^d	Activity-estimation, dose comparison	Parallel arm, randomized	PD-L1 positive NSCLC (no prior treatment)	10	2 or 3	43 ^c
	F2 ^d	Activity estimation, dose comparison	Parallel arm, randomized	PD-L1 positive NSCLC (prior treatment)	10	2 or 3	200 ^c

Source: Modified, FDA Clinical and Clinical Pharmacology Reviews

Abbreviations in table: RR=response rate; PFS=progression free survival; OS=overall survival; IPI=ipilimumab; NSCLC=non-small cell lung cancer

^aDosing interval 28 days for cycle 1 for PK analysis and 14 days for cycle 2 and beyond

^b Three cohorts with separate cycle 1 inpatient dose titration followed by either 2 or 10mg/kg Q3W for Cycle 2 and beyond.

^c Enrollment ongoing

^d Submission of SAE line listings only

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/s/

MARC R THEORET
09/04/2014