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RESEARCH**

*APPLICATION NUMBER:*

**125514Orig1s000**

**SUMMARY REVIEW**

## Division Director Summary Review

<b>Date</b>	September 4, 2014
<b>From</b>	Patricia Keegan
<b>Subject</b>	Division Director Summary Review
<b>BLA #</b>	STN BL 125514
<b>Applicant Name</b>	Merck
<b>Date of Submission</b>	February 27, 2014
<b>PDUFA Goal Date</b>	October 28, 2014
<b>Proprietary Name / Established (USAN) Name</b>	Keytruda Injection/ pembrolizumab
<b>Dosage Forms / Strength</b>	lyophilized powder/ 50 mg pembrolizumab in single-use vials
<b>Proposed Indication(s)</b>	KEYTRUDA is indicated for the treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab.
<b>Recommended Action for NME:</b>	<i>Approval under the provisions of 21 CFR 601 Subpart E</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Regulatory Project Manager Review	Sharon Sickafuse
Medical Officer Review	Jennie Chang & Meredith Chuk
Statistical Review	Emmanuel Sampene
Pharmacology Toxicology Review	Shawna Weis
Quality (OBP) Review	Mark Paciga & Deborah Schmiel
Microbiology Review	Kavlati Suvarna & Reyes Candau-Chacon
Clinical Pharmacology Review	Runyan Jin, Hongshan Li & Jingyu Yu
OPDP	Carole Broadnax
Patient Labeling Team	Sharon Mills
OSI	Lauren Iacono-Connor
CDTL Review	Marc Theoret
OSE/DMEPA	Otto Townsend
OSE/DRISK	Carolyn Yancey
QT-IRT Consult	Justin Earp

OND=Office of New Drugs  
 OBP=Office of Biotechnology Products  
 OPDP=Office of Prescription Drug Promotion  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 OSI=Office of Scientific Investigations  
 DDRE= Division of Drug Risk Evaluation  
 DRISK=Division of Risk Management  
 CDTL=Cross-Discipline Team Leader

# Division Director Summary Review

## 1. Introduction

I recommend that this application be approved under the provisions of 21 CFR 601 Subpart E with the agreed-upon labeling, post-marketing requirements and commitments. All scientific review disciplines have recommended approval. The applicant (Merck) seeks accelerated approval (under 21 CFR 601 Subpart E) for Keytruda (pembrolizumab), for injection, based on demonstration of durable objective responses of sufficient magnitude and durability that it was reasonably likely to predict clinical benefit in patients with progressive disease following ipilimumab, and for those with BRAF V600E mutation-positive melanoma, progressive disease following a BRAF tyrosine kinase inhibitor. The indicated population has a serious, life-threatening disease and no satisfactory alternative therapy.

Pembrolizumab (also known as MK-3475) is a humanized monoclonal antibody of the IgG4/kappa isotype. Pembrolizumab inhibits the interaction between the programmed cell death-1 receptor (PD-1) and its ligands, programmed death ligand 1 (PD-L1) and PD-L2. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. The proposed mechanism of action of pembrolizumab is inhibition of the PD-1 checkpoint inhibitor by blocking ligand binding and activation. This in turn, results in recognition of self-antigens, leading to autoimmune disorders, and tumor antigens, which are attempting to escape immune surveillance.

The biologics license application (BLA) for pembrolizumab, STN BL 125514, relies on the results of a single, randomized (1:1), open-label, dose-ranging, multicenter cohort (Cohort B2) within a large, multi-stage, multiple cohort dose-finding, activity-estimating, safety and tolerability trial, Study PN001. This sub-study is comprised of 173 patients with advanced or unresectable melanoma, who had progressed on or within 24 weeks of receiving ipilimumab and, if their melanoma tumor was BRAF V600 mutation-positive, had also received a prior BRAF inhibitor, and were randomized and received at least one dose of study treatment. All patients were required to have evidence of active disease progression at the time of enrollment. Key exclusion criteria included the presence of autoimmune disease, requiring for therapeutic corticosteroids (> 10 mg prednisone/day), and severe autoimmune adverse drug reactions with prior ipilimumab therapy.

Among the 173 patients with progressive, unresectable or metastatic melanoma who were enrolled and treated in this sub-study (Cohort B2), 89 received pembrolizumab 2 mg/kg every 3 weeks (Q3W) as an intravenous infusion and 84 received pembrolizumab 10 mg/kg Q3W. Among the 173 patients enrolled, the median age was 61 years (36% age 65 or older); 60% male; 97% White; and 66% and 34% with an ECOG performance status 0 and 1, respectively. Disease characteristics were BRAF V600 mutation (17%), elevated lactate dehydrogenase (39%), M1c (82%), brain metastases (9%), and two or more prior therapies for advanced or metastatic disease (73%).

The trial met its primary endpoint of demonstrating an objective response rate of >10% based on the lower 95% confidence interval around the observed response rate of 24% (95% CI:15, 34) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review (IRC) which included both radiologists and oncologists. There were one complete response and 20 partial responses identified by the IRC; among these 21 responding patients, three (14%) patients have had progression of disease with durations of response of 2.8, 2.9, and 8.2 months. As of the data cut-off date of October 2013, the remaining 18 patients (86%) have ongoing responses with durations ranging from 1.4+ to 8.5+ months; this includes 8 patients with ongoing responses of 6 months or longer. One additional patient experienced a response according to the WHO immune-related response criteria IrRC).

Durable objective tumor responses were observed at a similar rate with both treatment regimens. Merck requested approval only for the lower dose administered in Cohort B2. The selection of this regimen as the recommended dose is appropriate since the anti-tumor activity was similar between the two arms in Cohort B with respect to both overall response rate and duration of response.

The safety database contained all adverse event information reported in 411 patients with unresectable or metastatic melanoma received who pembrolizumab administered as an intravenous infusion at doses of 2 mg/kg every 3 weeks or 10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks and were enrolled in Cohorts B1, B2, and D of Study PN001. This safety information was supplemented by complete safety information from sequential dose-escalation cohorts from Study PN001 and by the serious and unexpected adverse drug reactions reported in approximately 2000 patients enrolled completed or ongoing clinical trials of pembrolizumab.

Among the 89 patients receiving the “to-be-recommended” dose of pembrolizumab (2 mg/kg every three weeks), the most common adverse events (occurring at a per-patient incidence of  $\geq 20\%$ ) were fatigue, cough, rash, pruritus, nausea, decreased appetite, constipation, arthralgia, and diarrhea. Across the safety database of 411 patients, the median duration of exposure to pembrolizumab was 6.2 months. Pembrolizumab was discontinued for adverse reactions in 9% of these patients; the most common adverse reactions resulting in discontinuation of pembrolizumab were pneumonitis, renal failure, and pain. The incidence of serious drug adverse reactions was 36%; the most commonly reported serious adverse drug reactions were renal failure, dyspnea, pneumonia, and cellulitis. The most common severe or clinically significant adverse drug reactions were the induction of autoimmune disorders affecting multiple organs and tissues, resulting from the intended mechanism of action of pembrolizumab with “off-target” effects. Across the pooled safety database of 411 patients with melanoma, the most common and clinically significant autoimmune disorders were pneumonitis, hepatitis, colitis, hypophysitis, hyperthyroidism, and hypothyroidism; the most common was pneumonitis occurring in 2.9% of patients. Autoimmune disorders responded in many cases to interruption or termination of pembrolizumab and high-dose corticosteroid therapy; however these findings should be viewed cautiously in light of the limited experience in 411 patients. In addition, important adverse reactions include embryofetal toxicity based on

non-product specific literature evaluating the role of PD-1 in embryofetal development and the potential increased risks of uncontrolled infection due to immune dysregulation resulting from perturbation of PD-1 pathway. All of these risks are described in agreed-upon product labeling.

Issues considered during this review included the durability of the responses observed given the relatively modest response rate, the adequacy of the characterization of toxicity, the potential need for a REMS, need for a Medication Guide as part of the Risk Management strategy, and need for a Boxed Warning in physician labeling. These issues will be discussed in Sections 7 and 8 of this review.

During the review cycle of this application, it was determined that due to the serious unmet need for the treatment options for the melanoma patient population who have failed standard therapies, the Keytruda license application should be approved earlier than its PDUFA action date. However, the pre-approval inspection for one of the facilities, (b) (4) where in-process testing for Keytruda (b) (4) DS is performed, was scheduled for (b) (4), thus preventing an early action on Keytruda. Keytruda drug substance is manufactured at two sites, (b) (4) and FMC. Therefore the sponsor decided to withdraw the (b) (4) drug substance and drug product, and, consequently the (b) (4) testing site, from the pending BLA to allow the Agency to take early action on the pending BLA. As a result of this amendment, only FMC drug substance and drug product will be approved under this BLA. (b) (4)

## 2. Background

### *SEER database information on melanoma*

Cutaneous melanoma, arising from malignant transformation of melanocytes in the skin, is the most aggressive malignancy arising from the skin; based on trend analyses, the incidence of melanoma has been increasing over the past several decades. The National Cancer Institute estimates that in 2014 there will be 76,100 new cases of melanoma and 9,710 deaths due to melanoma in the United States.<sup>1</sup> While 84% of melanoma presents with localized disease which may be cured with surgical excision alone or with adjuvant interferon or investigational agents and has a 5-year survival rate of 98%, for the 4% who present with metastatic disease and receive systemic treatment, the 5-year survival rates is only 16%.

### *Available therapy for melanoma*

There are seven drugs that have been approved by the US FDA for the treatment of metastatic melanoma: vemurafenib, dabrafenib, trametinib, ipilimumab, aldesleukin, dacarbazine, and hydroxurea. Hydroxurea, which was FDA-approved in the 1970's, is no longer used or recommended in clinical practice guidelines for oncology. Dacarbazine and aldesleukin (interleukin-2) were approved by FDA for the treatment of metastatic melanoma in May 1975 and January 1998, respectively, based on evidence of durable objective tumor responses. Their

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<sup>1</sup> <http://seer.cancer.gov/statfacts/html/melan.html> (accessed September 2, 2014)

use for the initial treatment of metastatic melanoma has declined following approval of ipilimumab and vemurafenib.

Commonly used off-label treatments, whose use have also declined following approval of vemurafenib and ipilimumab, include temozolomide alone or in combination with other drugs, dacarbazine-based combination chemotherapy regimens, and interferon alone or in combination with chemotherapy, as well as investigational immunotherapy treatments. All currently used off-label treatment approaches are characterized by low objective tumor response rates (<20%) and no evidence of improved survival.

On March 25, 2011, FDA approved ipilimumab (Yervoy, Bristol Myers Squibb) for the treatment of unresectable or metastatic melanoma based on demonstration of improved survival [HR 0.66 (95% CI: 0.55, 0.85), p=0.0004] with median survival times of 9.95 months and 6.44 months for ipilimumab in the gp100 peptides and gp100 peptides (control), respectively. Approval was also supported by the high level results of Protocol CA 184024, a randomized trial of dacarbazine with or without ipilimumab, in which the high level results also demonstrated an improvement in overall survival [HR 0.85 (95% CI: 0.76, 0.93)] with a nominal p-value of 0.001, stratified log-rank test.

On August 17, 2011, vemurafenib (ZELBORAF, Genentech Inc.), an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E, was approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Approval was based on demonstration of a statistically significant improvement in overall survival [HR 0.44 (95% CI: 0.33, 0.59); p < 0.0001] and progression-free survival [HR 0.26 (95% CI: 0.20, 0.33); p < 0.0001] for patients in the vemurafenib arm as compared to those receiving dacarbazine.

On May 29, 2013, trametinib was approved for treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. Trametinib was not indicated for treatment of patients who have received prior BRAF-inhibitor therapy. Approval was based on demonstration of a statistically significant improvement in the progression-free survival among patients randomized to receive trametinib as compared to those receiving chemotherapy [HR 0.47 (95% CI: 0.34, 0.65)] with an increase in median PFS from 1.5 months in the chemotherapy arm to a median PFS of 4.8 months for the trametinib arm. The limitation of use was based on lack of antitumor activity (objective tumor responses) in patients with BRAF V600E mutation-positive melanoma who had received a BRAF inhibitor.

On May 29, 2013, dabrafenib was approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation, as detected by an FDA-approved test. This approval was based on a statistically significant and clinically meaningful improvement in PFS for dabrafenib as compared to dacarbazine [HR 0.33 (95% CI: 0.20, 0.54), p < 0.001] with a median PFS of 5.1 months for dabrafenib and 2.7 months for dacarbazine, respectively.

Dabrafenib was also approved with a limitation of use (not indicated for use in patients with wild-type BRAF melanoma) based on the potential risks of tumor promotion.

On January 10, 2014, dabrafenib and trametinib were approved for use in combination for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. This approval was based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for these drugs used in combination over either drug used alone.

#### *Pre-Submission Regulatory History*

- December 10, 2009: IND 110080 submitted for investigation of pembrolizumab
- August 21, 2012: “End of Phase 1” meeting held to discuss the submission of data from PN001 to support a request for accelerated approval. Merck stated that this application would be based data from up to 80 ipilimumab-refractory melanoma with a projected median follow-up of 7 months and an estimated objective response rate (ORR) of 30% in the high-dose arm (pembrolizumab 10 mg/kg every 3 weeks). Verification of clinical benefit would be based on the results of Studies PN002 and PN006. FDA stated that Merck should design adequate and well-controlled trial(s) designed to detect a response rate of sufficient magnitude and duration to be reasonably likely to predict clinical benefit. In addition, consider existing treatments in the determination of a desired target effect size of MK-3475 in trials designed to support accelerated approval.
- November 19, 2012: orphan drug designation for the treatment of Stage IIB - IV malignant melanoma.
- January 11, 2013: pre-Phase 3 meeting held to discuss 1) the proposed plans for retrospective testing of biomarkers (PD-L1 expression in tumors) for patients enrolled in Cohort B2 (ipilimumab-refractory subset) in Study PN001 to potentially support a marketing application for accelerated approval; 2) the design of study PN006 patients with ipilimumab (IPI) treatment-naïve, unresectable or metastatic cutaneous melanoma, intended to verify clinical benefit if accelerated approval is granted treatment of patients with ipilimumab-refractory melanoma (b) (4) and 3) to seek FDA concurrence with Merck’s proposed CMC, companion diagnostic plans, and nonclinical and clinical pharmacology development programs.
- January 17, 2013: Breakthrough Therapy Designation for the treatment of 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.
- April 2, 2013: CMC meeting held to discuss the manufacturing strategy with respect to comparability of the results and bridging data.
- April 17, 2013: FDA acknowledged Merck’s initial Pediatric Study Plan for pembrolizumab for treatment of unresectable or metastatic melanoma. FDA further stated that because pembrolizumab had an orphan drug designation for this indication, Merck was exempt from the requirement to submit a PSP for this indication.
- April 22, 2013: Type B meeting to discuss nonclinical, clinical pharmacology, and clinical development programs intended to support accelerated approval (under 21 CFR 601 Subpart E) of pembrolizumab based on demonstration of durable objective responses of sufficient magnitude and durability that it was reasonably likely to predict clinical benefit in patients with progressive disease following ipilimumab, and for those with BRAF

V600E mutation-positive melanoma, progressive disease following a BRAF tyrosine kinase inhibitor.

- June 11, 2013: CMC meeting held to discuss the adequacy of the comparability and stability plans for the manufacturing processes and drug product intended for commercial marketing in the proposed BLA.
- August 27, 2013: CMC meeting to discuss the Fab-arm exchange data, analytical strategy for HCP and potency assay, viral clearance strategy, process performance qualification strategies for drug substance and drug product, and reference material strategy for drug product intended for commercial marketing in the proposed BLA.
- October 24, 2013: Pre-BLA CMC meeting in which FDA advised that a rolling submission to allow initiation of review of complete components might be more efficient for review of the proposed BLA.
- October 25, 2013: Pre-BLA interdisciplinary meeting held to reach agreement on the content and format of proposed BLA under the PDUFA V program. The FDA agreed that the application could be filed without a REMS, noting that final determination of the need for a REMS would be based on review of the BLA. FDA stated that evaluation of efficacy would be based on response rate determined by independent review in the intent-to-treat population with adequate follow-up to ensure durability of responses.
- February 5, 2014: Expanded access protocol submitted for use of pembrolizumab for the treatment of patients with melanoma “with limited to now treatment options”. Treatment protocol was allowed to proceed on February 28, 2014.

#### *Regulatory History of the BLA*

- November 22, 2013: First module submitted for STN BL 125514; final module completing the BLA submitted February 27, 2014.
- April 3, 2014: Risk Management Plan submitted to the BLA.
- April 24, 2014: Application Orientation meeting held.
- April 30, 2014: 120-Day Safety Update Report (SUR) submitted.
- June 27, 2014: Mid-Cycle Communication Meeting held with Merck.

### **3. CMC/Biopharmaceutics**

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance and that there are no outstanding quality issues that preclude approval. Manufacturing site inspections were acceptable or pre-approval inspections for certain facilities were waived based on the compliance history of the firm. As noted in the Section 1 of this review, one of the manufacturing sites was withdrawn from the BLA in consultation with Merck to allow an early action to be taken on this application. Review issues regarding the proposed stability protocol, acceptance criteria and qualification/re-qualification of reference standards, and acceptance criteria for the potency assay were resolved during review of the BLA. Stability testing supports an expiry of 18 months at 2-8 C.

Agreed-upon post-marketing commitments for quality issues are described in Section 13 of this review.

## 4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

The BLA contained the results on *in vitro* assessments to support claims regarding the proposed mechanism of action, *in vivo* studies in several animal models of infection evaluating possible effects of inhibition of the PD-1 pathway on control of infection, and a one-month and a 6-month toxicology studies. Based on the proposed indication in patients with late stage cancer with short life expectancy, a carcinogenicity study was not required. In addition, given the class (monoclonal antibody), genotoxicity studies were not required. During pre-submission meetings, FDA advised Merck to that evaluation of reproductive toxicity could be performed through a non-product specific, literature based assessment. As stated in the nonclinical pharmacology/toxicology reviews, In accordance with ICH S6 and S9, Merck provided literature describing investigations of the effects of disruption of PD-1 signaling in mouse models of allogeneic pregnancy. Based on the information provided, Merck showed that inhibition of this signaling pathway, either through administration of an anti-PD-L1 antibody or through genetic disruption, can lead to increases in loss of allogeneic pregnancy, leading to the categorization of this drug under Pregnancy Category D.

The 1-month and 6-month toxicology studies were determined to provide drug exposure reaching or exceeding expected exposures in humans at the recommended dose and ex-vivo studies indicated receptor saturation. Despite this, the pathologic findings were muted, with only observation of monocytic and lymphocytic infiltration of various organs and tissues without overt evidence of organ dysfunction resulting from induction of autoimmunity.

PD-1 is an inhibitory receptor, which controls immune responses in healthy tissues to prevent autoimmunity and collateral tissue damage<sup>2,3</sup>. PD-1 is expressed or up-regulated on CD4<sup>+</sup> and CD8<sup>+</sup> T cells, natural killer (NK) T cells, B cells, as well as in monocytes and dendritic cells in the setting of lymphocyte activation. In healthy individuals, the role of this pathway is to prevent autoimmunity by promoting tolerance to self-antigens and to limit damage to normal tissues following activation of the normal immune response. PD-1 is also up-regulated in certain tumors and may play a role in escape from immune surveillance of tumors.

The BLA contains data demonstrating that pembrolizumab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor

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<sup>2</sup> Chen L . Co-inhibitory molecules of the B7-CD28 family in the control of T-cell immunity. *Nat Rev Immunol*2004;4:336–47.

<sup>3</sup> Grabie N, Gotsman I, DaCosta R, Pang H, Stavakis G, Butte MJ, et al. Endothelial programmed death-1 ligand 1 (B7-H1) regulates CD8<sup>+</sup> T-cell mediated injury in the heart. *Circulation*2007;116:2062–71

models, blocking PD-1 activity resulted in decreased tumor growth. In addition, ex vivo studies using human PBMCs demonstrated increased antigen responsiveness in the presence of pembrolizumab. Increases were noted not only following primary immune activation, but also in anamnestic responses to tetanus toxoid.

Data in the published literature demonstrates a correlation between PD-1 deficiency and exacerbation of viral and bacterial infections. Following infections with *M. tuberculosis* (TB) or lymphocytic choriomeningitis virus (LCMV), PD-1-deficient mice exhibited marked decreases in survival compared with wild-type controls. In addition, Merck provided the results of a study in chimpanzees that had been naturally-infected with hepatitis B virus (HBV). Treatment with pembrolizumab led to greater liver dysfunction, without evidence of increased viral load; complete resolution of liver dysfunction was not evidence by the end of the 4-week post-treatment recovery period. In clinical studies, there were cases of sepsis in patients with cancer receiving pembrolizumab; however whether the incidence is increased could not be determined due to lack of untreated controls. Merck also reported one case of a patient who experienced recurrence of a latent TB infection while receiving pembrolizumab.

## 5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The recommended dose of pembrolizumab 2 mg/kg administered as an intravenous infusion over 30 minutes every 21 days, is supported by the efficacy data from Cohort B2 of Study PN001, and is reasonably safe and supported by the dose-escalation studies carried out in Cohort A of Study PN001, which evaluated increasing doses at half-log increments (1, 3, and 10 mg/kg). Selection of the 2 mg/kg dose was based on desired pharmacodynamic effects (interleukin-2 release in a peripheral blood mononuclear assay) and clinical experience. The dosage regimen of 2 mg/kg Q3W provided similar objective response rates to the dose of 10 mg/kg Q3W, however continuing investigation of dose optimization is being evaluated in ongoing clinical trials, specifically cohort D, where preliminary results suggest that a more frequent schedule, e.g., Q2W, may be more efficacious than a Q3W schedule.

The application contained the results of a population pharmacokinetic (PK) analysis from sampling of 476 patients who received pembrolizumab at doses of 1, 3 or 10 mg/kg every two weeks (Q2W) or Q3W, assessment of anti-product antibodies from patients enrolled in Cohort B2 and Cohort D who received pembrolizumab at the dose of 2 mg/kg Q2W, and assessment of electrocardiographic effects across 500 patients enrolled in the clinical development program for pembrolizumab.

The population PK mean (95% confidence intervals (CI)) estimates for time to reach steady state concentrations were 129 (118, 142) days, half-life was 25.8 (23.6, 28.3) days, and volume of distribution at steady-state was 7.66 (7.09, 8.13) L. Based on the population PK analysis, there were no clinically important differences in pembrolizumab exposure based on age, gender, tumor type, tumor burden, mild or moderate renal impairment, or mild hepatic

impairment. Since pembrolizumab is a monoclonal antibody that is catabolized into amino acids by general protein degradation process, it is unlikely to have an effect on drug metabolizing enzymes or transporters in terms of inhibition or induction and its clearance is unlikely to be affected by renal or hepatic impairment. Therefore, post-marketing requirements to further evaluate for such effects were not necessary.

There was no evidence of an exposure-response relationship for either safety or efficacy across the dosage regimes of 2 mg/kg Q3W and 10 mg/kg Q3W, based on data from patients enrolled in Cohort B2. In an exploratory, retrospective assessment of data from Cohort B2, there was no indication that therapeutic corticosteroid treatment abrogated the treatment effect of pembrolizumab, i.e., affected the likelihood of achieving an objective response.

There was a limited assessment for product immunogenicity, which cannot exclude an incidence of anti-product antibodies (APA) of < 3%. There were no APA detected in 97 patients receiving pembrolizumab 2 mg/kg Q3W, using an electrochemiluminescence (ECL) based assay, based on samples obtained at appropriate time points (i.e., considering drug tolerance limits of the assay).

## **6. Clinical Microbiology**

I concur with the conclusions reached by the microbiology reviewer that there are no outstanding sterility issues related to product manufacture that preclude approval.

## **7. Clinical/Statistical-Efficacy**

A substudy of a single trial established efficacy in support of this BLA, Study PN001, also known as 3475-001, titled “Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma.” The trial was submitted in the original IND submission for IND 110080 on December 9, 2010 as a dose-finding, safety, and tolerability trial. It was subsequently amended 8 times through the data cut-off date for this BLA; this included amendments to allow for estimation of anti-tumor activity for based on objective tumor responses in multiple cohorts of patients with homogeneous cancers/extent of prior treatment as well as to further explore other dosing regimens and evaluate the role of PD-1 tumor expression as a predictor of treatment effects. The key features of this ongoing study, as described in the interim clinical study report (CSR) provided in the BLA, are summarized in tabular format below, abstracted from the CSR.

	Cohort	Disease Indication	MK-3475 Dose	Dose Frequency	IPI status	Enrollment Status	Allocation method	PD-L1 Status	Total N <sup>2</sup>
Part A	A	Solid Tumors	1, 3 and 10 mg/kg	Q2W	NA	Completed	Non-randomized	NA	10
	A1	Solid Tumors	10 mg/kg	Q2W	NA	Completed	Non-randomized	NA	7
	A2	Solid Tumors	2 or 10 mg/kg <sup>1</sup>	Q3W	NA	Completed	Randomized	NA	13
Part B	B1	Melanoma	2 or 10 mg/kg	Q2W or Q3W	Naïve or Treated	Completed	Non-randomized	All comers	135
	B2	Melanoma	2 or 10 mg/kg	Q3W	Refractory	Completed	Randomized	All comers	173
	B3 <sup>3</sup>	Melanoma	10 mg/kg	Q2W or Q3W	Naïve or Treated or Refractory	Completed	Randomized	All comers	248
Part C		NSCLC	10 mg/kg	Q3W	NA	Completed	Non-randomized	All comers	38
Part D		Melanoma	2 or 10 mg/kg	Q3W	Naïve	Completed	Randomized	All comers	103
Part F <sup>3</sup>	F1	NSCLC	10 mg/kg	Q2W or Q3W	NA	Ongoing	Randomized	Positive	43
	F2	NSCLC	10 mg/kg	Q2W or Q3W	NA	Ongoing	Randomized	Positive or Negative	200

Efficacy data in support of this BLA are derived primarily from Cohort B2 of Study PN001. This portion of the protocol was included under amendment 5 to the protocol, with substantive amendments made to 1) increase the sample size, 2) alter the allocation to the two dosing regimens to achieve equal allocation, and 3) identify assessment of objective response rate by an independent review committee, according to RECIST v 1.1 as the primary study endpoint for this cohort.

#### Protocol Design of PN001, Cohort B2

In its final iteration, the primary objective was determination of the best overall response rate (ORR) by independent central radiologic review and integrated medical oncologist disease assessment based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The key secondary efficacy objectives included estimation of duration of response, estimation of progression-free survival (PFS) and overall survival (OS). Supportive objectives included determination of the best overall response and response duration according to RECIST v1.1 by investigators and determination of best overall response rate according to immune-mediated response criteria (irRC) by investigators and by the independent review committee.

Key inclusion criteria for Cohort B2 were a histologic diagnosis of unresectable or metastatic melanoma, disease progression while receiving or within 24 weeks of the last dose of an adequate treatment course of ipilimumab (defined as at least two doses of ipilimumab of  $\geq 3$  mg/kg three weeks apart); disease progression on or following prior treatment with a tyrosine kinase inhibitor of BRAF (with or with a MEK inhibitor) for patients with BRAF V600 mutation-positive melanoma; and an ECOG performance status of either 0 or 1. Key exclusion criteria were a history of autoimmune disease; any medical condition requiring immunosuppressive therapy; and a history of severe autoimmune adverse reactions with ipilimumab (defined as any Grade 4 adverse reaction requiring treatment with corticosteroids or any Grade 3 adverse reaction requiring corticosteroid treatment with  $> 10$  mg/day prednisone for more than 12 weeks).

Patients were randomized to receive pembrolizumab at a dose of 2 mg/kg or 10 mg/kg as an intravenous infusion over 30 minutes every 3 weeks. Treatment was to continue until disease

progression<sup>4</sup> or unacceptable toxicity; however patients with asymptomatic disease progression were allowed to continue pembrolizumab at the investigator's discretion despite evidence of increasing tumor volume or new lesions for another 4 to 6 weeks if the patient was "clinically stable". Clinically stable was defined as

- Absence of symptoms and signs indicating clinically significant PD (including worsening of laboratory values) indicating disease progression;
- No decline in ECOG performance status; and
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

If repeat imaging showed 4-6 weeks later an objective response or stable disease, clinically stable patients were allowed to continue pembrolizumab with resumption of tumor imaging studies for disease assessment every 12 weeks. Assessment of tumor status was performed every 12 weeks. Patients who discontinued pembrolizumab prior to IRC-determined disease progression were to continue imaging assessments until documentation of disease progression, initiation of a new anti-cancer therapy, or death.

The sample size of 80 to 84 patients per treatment group in Cohort B2 was based on ability to detect a clinically meaningful response rate through exclusion of ORR of less than 10% based on the lower bound of the 95% confidence interval, assuming the observed ORR would be  $\geq 30\%$ . In addition, a comparison between the two treatment groups was planned; the sample size was sufficient to detect with approximately 85% power, an absolute difference of 15% in ORR between the treatment groups. Given the revisions to the protocol, including changes in allocation to treatment group, and the protocol violations (treatment of two patients randomized to 2 mg/kg at the 10 mg/kg dose), no formal comparisons of ORR were conducted between the two treatment groups.

### *Efficacy Results*

A total of 173 patients were enrolled and randomized in Cohort B2 of Study PN001 between August 28, 2012 and April 5, 2013 across 15 clinical study sites internationally (12 clinical sites in the US and one site each in Australia, Canada, and France).

With regard to efficacy data, the data cut-off date was October 18, 2013. Bioresearch monitoring of three clinical study sites, selected for high accrual rates and with either higher or lower than average objective response rates (as compared to the study population overall), as well as a sponsor-site inspection were conducted. As a result of these inspections, the clinical data were considered to be reliable.

There were 90 patients randomized to receive pembrolizumab 2 mg/kg every three weeks and 83 patients randomized to receive pembrolizumab 10 mg/kg every three weeks who received at least one dose of study drug; for purposes of data analysis, results are provided according to treatment received rather than treatment assigned, with data from one patient randomized to receive 2 mg/kg who actually received pembrolizumab 10 mg/kg. This patient is included in the 10 mg/kg group for efficacy analyses.

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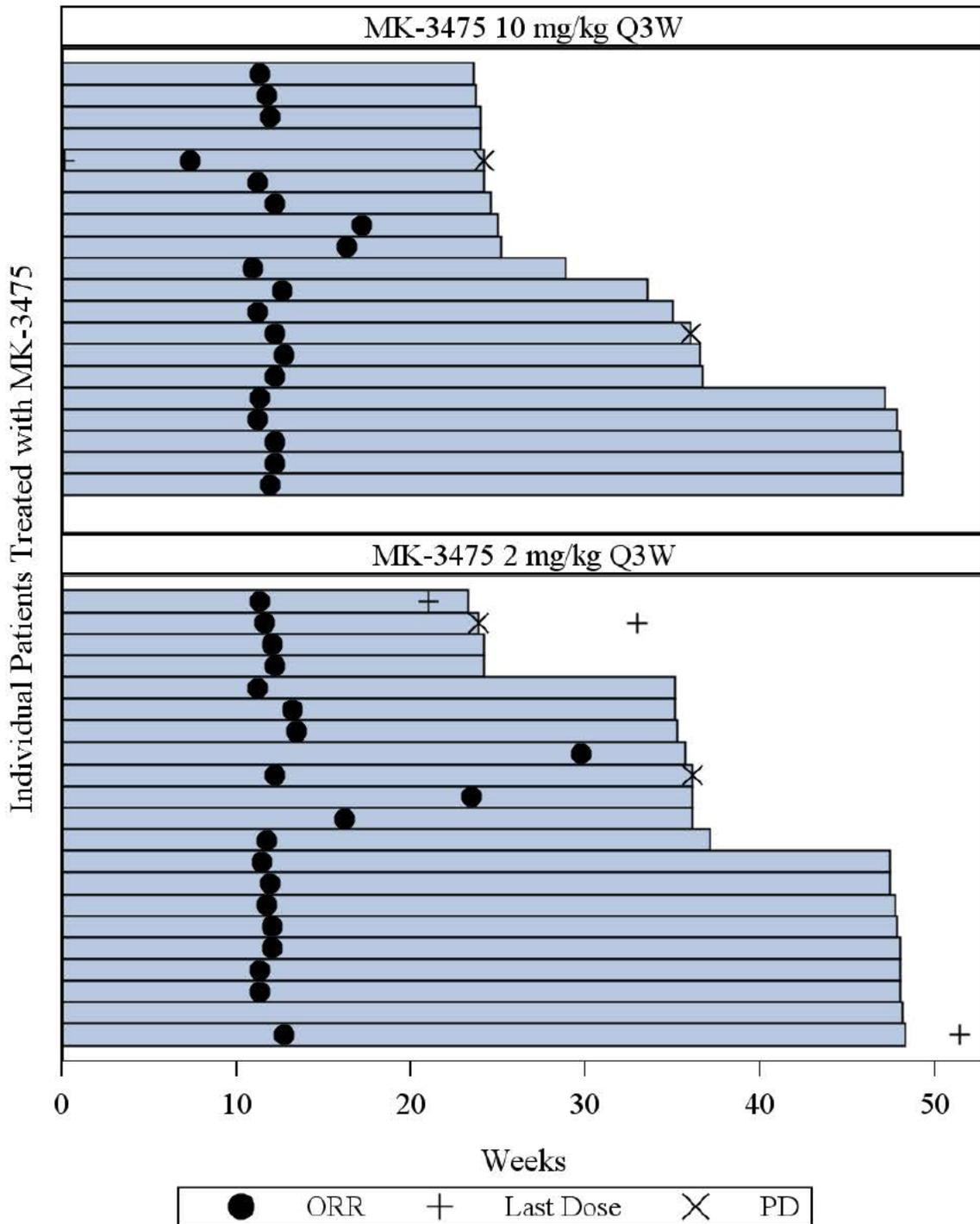
<sup>4</sup> Wolchok JD, et al. *Clin Cancer Res.* 2009;15:7412-20.

Approximately three-quarters of the patients were accrued from US sites. The median age of the study population was 61 years, with 36%  $\geq$  65 years of age, 60% were male, the majority of the study population (97%) was White; and 66% had an ECOG performance status 0. A minority (17%) of the patients had BRAF V600 mutation-positive melanoma, 39% had elevated lactate dehydrogenase (LDH) levels at baseline, 82% had stage M1c at study entry, 9% had CNS metastases, and 73% had two or more prior lines of systemic treatment for unresectable or metastatic disease. Demographic and baseline tumor characteristics were generally similar across the two arms, although there was numerically higher proportion of males (54% vs 68%), lower proportion with BRAF mutation-positive melanoma (13.5% vs. 21.4%), higher proportion with only one prior treatment (33% vs. 23%), and higher proportion with normal LDH (55% vs. 66%) in the 2 mg/kg arm compared with the 10 mg/kg arm.

The results for the primary analysis (ORR by the independent review committee according to RECIST 1.1) are presented in the table below. With limited patient follow-up, the median duration of response has not been reached as of the data cut-off date; this information is represented graphically (abstracted from the CSR). For the majority of patients with responses, evidence of a response was present at the first on-study tumor assessment at 12 weeks. Among the 21 patients who received pembrolizumab 2 mg/kg every three weeks and achieved an objective response, three (14%) have had progression of disease with durations of response of 2.8, 2.9, and 8.2 months.

There was an additional single patient in each treatment group who achieved a response according to the immune-related response criteria as determined by the independent review committee, indicating that this type of mixed response is uncommon. In the 2 mg/kg treatment group, the patient with an irRC response developed two new asymptomatic lesions at the first tumor assessment concurrent with a 75% decrease in overall tumor burden; pembrolizumab was continued; with a durable reduction in tumor burden that is ongoing as of the data cut-off (5+ months). The investigator-determined response rate was similar to independently-determined response rate when using RECIST; investigators identified a higher response rate than the independent review committee when using irRC, however the investigators did not use an “as-treated” population, which likely inflated the investigator-determined response rate by irRC (see Statistical Review). The Agency’s experience with this novel response criteria is limited; however these data suggest that ORR based on RECIST and irRC will yield similar results.

Outcome Measure	Pembrolizumab 2 mg/kg Q3W (n=89)	Pembrolizumab 10 mg/kg Q3W (n=84)
Best Overall Response Rate (95% Confidence Interval)	23.6% (15.2; 33.8)	23.8% (15.2; 34.3)
Complete Response Rate	1.2% (n=1)	1.2% (n=1)
Partial Response Rate	22.5% (n=20)	22.6% (n=19)
Median Duration of Response (Range in months)	Not Reached (1.4+; 8.5+)	Not Reached (1.8+, 6.2+)



compared to those whose tumors did not have these mutations, however the response rates observed in those with BRAF mutation-positive melanoma (17% in both the 2 mg/kg and 10 mg/kg treatment groups) indicate sufficient activity to consider that these patients should be included in the indicated population.

Although the number of events are small, there was no suggestion that progression-free survival or overall survival were different in the two treatment groups.

## 8. Safety

### *Size of the database,*

The size of the safety database was sufficient to identify adverse drug reactions occurring at an incidence of at least 3% and is consistent with ICH Guidelines for drugs that are not administered chronically (safety experience in 300-600 patients). The safety database contained all adverse event information reported in 411 patients with unresectable or metastatic melanoma enrolled in Cohorts B1, B2, and D of Study PN001. Across this safety database, patients received pembrolizumab at doses of 2 mg/kg every 3 weeks (n=162), 10 mg/kg every 3 weeks (n=192) or 10 mg/kg every 2 weeks (n=57).

This safety information was supplemented by complete safety information from sequential dose-escalation cohorts from Study PN001 and by the serious and unexpected adverse drug reactions reported in approximately 2000 patients enrolled in the following completed or ongoing clinical trials of pembrolizumab:

- PN001 (n= 20 patients with various advanced cancers and 38 patients with lung cancer, respectively, enrolled in Cohorts A1-A3 and C):
- PN001 (n= 248 patients with melanoma and 243 patients with NSCLC, respectively, enrolled in Cohorts B3 and F):
- PN002 (n=496 patients with melanoma and disease progression after ipilimumab):
- PN006 (n=87 patients with melanoma and no prior ipilimumab exposure):
- PN010 (n=12 patients with lung cancer); and
- PN012 (n=12 patients with various advanced cancers).

### *Major safety concerns related to labeling*

Across the safety database of 411 patients, the median duration of exposure to pembrolizumab was 6.2 months. The incidence of adverse events were generally similar between patients receiving 2 mg/kg and 10 mg/kg Q3W and higher among patients receiving 10 mg/kg Q2W. While difficult to make definitive conclusions, based on identification of the unique basis for patient disposition, where the highest reason may have been “unknown”, it appears that more patients across the overall safety database (n=411; 12% vs. 17%) or Cohort B2 (n=173; 13% vs. 20%) discontinued treatment for adverse events in the 10 mg/kg Q3W as compared to the 2 mg/kg Q3W regimen.

The most common adverse reactions resulting in discontinuation of pembrolizumab were pneumonitis, renal failure, and pain. The incidence of serious drug adverse reactions was 36%;

the most commonly reported serious adverse drug reactions were renal failure, dyspnea, pneumonia, and cellulitis.

Among the 89 patients receiving the “to-be-recommended” dose of pembrolizumab (2 mg/kg every three weeks), the incidence of serious, non-fatal adverse reactions was 30%, the most common serious adverse reactions were pneumonia and dyspnea, and the most common adverse events (occurring at a per-patient incidence of  $\geq 20\%$ ) were fatigue, cough, rash, pruritus, nausea, decreased appetite, constipation, arthralgia, and diarrhea. In Cohort B2, patients who received 10 mg/kg Q3W were more likely to discontinue treatment for adverse drug reactions (20% vs. 13%) as compared patients treated at 2 mg/kg Q3W.

Most serious or clinically important adverse drug reactions were exaggerated pharmacologic effects, resulting from inhibition of the ligand binding to PD-1 resulting in recognition of normal tissues as foreign; these adverse reactions manifested as autoimmune disease. These were described in the Warnings and Precautions section of product labeling.

- Immune-mediated pneumonitis occurred 2.9% of the 411 patients in the safety database. Among the 173 patients receiving pembrolizumab in Cohort B2 of Study PN001, 2.1% of patients developed Grade 2 or 3 immune-mediated pneumonitis.
- Immune-mediated colitis occurred in 1% of the 411 patients in the safety database. Among the 173 patients receiving pembrolizumab in Cohort B2 of Study PN001, 0.7% developed Grade 2 or Grade 3 immune-mediated colitis.
- Hepatitis (including autoimmune hepatitis) occurred in 0.5% of the 411 patients in the safety database. Among the 173 patients enrolled in Cohort B2, the incidence of hepatitis was 0.2%.
- Immune-mediated hypophysitis occurred in 0.5% of the 411 patients in the safety database and in 0.2% of the 173 patients enrolled in Cohort B2.
- Nephritis occurred in 0.7% of the 411 patients in the safety database; this included one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%). One of these presented as a delayed event, at 5 months after the last dose of pembrolizumab. No cases of renal failure occurred in Cohort B2.
- Immune-mediated hyperthyroidism occurred in 1.2% of the 411 patients in the safety database and in 0.7% of patients enrolled in Cohort B2. Hypothyroidism occurred in 8.3% of the 411 patients in the safety database and in 0.2% of the patients in Cohort B2. The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks-19 months). Two of the four patients recovered thyroid function and were able to discontinue thyroid hormone replacement therapy. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.
- Other clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients enrolled in Cohort B2, including exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and adrenal insufficiency. Across 2000 patients enrolled in clinical studies with pembrolizumab, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: myasthenic syndrome, optic neuritis, and rhabdomyolysis.
- Embryofetal toxicity [see Nonclinical Pharmacology/Toxicology section (Section 4) of this review] was added to the Warnings and Precautions section of the labeling based on the

literature assessment indicating an increased risk of fetal loss in patients with PD-1 pathway inhibition.

*Final labeling recommendations*

FDA's assessment and modifications to the proposed physician product labeling is summarized in Section 12 of this review. Merck did not propose to include a Boxed Warning in product labeling. During review of the BLA, in particular labeling review, the clinical review considered whether to include a Boxed Warning, noting that a product with similar immune-mediated adverse reactions (ipilimumab) has a Boxed Warning. The review team concluded, and I concur, that based on lower incidence and lesser severity of immune-mediated adverse reactions with pembrolizumab and the experience gained in the medical oncology community with use of these drugs, a Boxed Warning was not necessary to ensure safe use. Further, a Boxed Warning is not necessary to ensure an adequate risk assessment for the indicated population, which has no satisfactory alternative therapies and for whom these risks would be deemed acceptable.

*REMS:*

I concur with the conclusions reached by the clinical review team and DRISK consultants that that a REMS is not required for pembrolizumab. Merck submitted a proposed Risk Management Plan consisting of product labeling and routine pharmacovigilance monitoring in the BLA. The serious risks which may have required a REMS to ensure safe use consist of treatment-emergent autoimmune disease affect multiple organ systems. Merck argued that, unlike ipilimumab, for which a REMS was required for similar adverse drug reactions, the overall incidence and the incidence of serious and fatal autoimmune adverse reactions are lower with pembrolizumab than ipilimumab and the medical oncology community has gained significant experience in the early recognition and management (drug interruption and corticosteroid immunosuppression) of autoimmune adverse reactions. Based on review of the BLA and this rationale, the clinical team considered the need for a REMS as well as other measures that might mitigate serious risks. The review team informed Merck in the post-Mid-cycle communication to submit a Medication Guide in order to communicate information to patients on the risks of serious autoimmune adverse drug reactions and when to contact healthcare providers. With the additional measure to mitigate potential risks, the clinical review team and DRISK consultants agreed that a REMS would not be required to ensure safe and effective use of pembrolizumab.

*PMRs and PMCs:*

There are no post-marketing requirements to evaluate adverse drug reactions of pembrolizumab; however there is an agreed-upon post-marketing commitment to further investigate the effects of PD-1 pathway inhibition on the primary and anamnestic responses to vaccination in an animal model. Such studies may provide insight on recommendations for the timing of vaccinations or inform risk management strategies in patients requiring vaccinations while receiving pembrolizumab. See Sections 4 and 13 of this review.

## 9. Advisory Committee Meeting

The BLA for pembrolizumab was not referred to an advisory committee although it is for a new molecular entity. The application did not raise significant public health questions on the role of the pembrolizumab for this indication and outside expertise was not necessary as there were no controversial issues that would benefit from an advisory committee discussion. The endpoints used to support this accelerated approval is described in the 1996 Reinventing Government (ReGo) Initiative and has been used commonly for approvals in patients with cancers for which there is no available therapy. In addition, the toxicity profile of this drug is similar to that of ipilimumab; as compared to that application, no new issues of safety were identified.

The clinical review staff made extensive attempts to seek clearance of Special Government Employees for individual advice; however clearance could not be obtained for two individuals with no evidence of potential conflicts of interest. Several other individuals were considered but not screened due to conflicts (e.g., investigator for Study PN001, other pembrolizumab trials, or for another product being investigated for treatment of recurrent melanoma).

## 10. Pediatrics

Orphan Drug Designation was granted for pembrolizumab on November 19, 2012 for the treatment of Stage IIB - IV malignant melanoma. Therefore, this application is exempt from the requirements of PREA for the approved indication.

## 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

## 12. Labeling

- Proprietary name: Merck was notified that the name was conditionally acceptable in a January 27, 2014 letter from FDA. Upon completion of the BLA review, the Office of Medication Error Prevention and Risk Management and the review team for this BLA confirmed that the proposed proprietary name, KEYTRUDA, was acceptable from based on lack of promotional claims and low potential for medication errors.
- Physician labeling: All major issues with physician labeling were resolved. Major issues considered during negotiations on Merck's proposed physician labeling include the following:
  - Indications and Usage: Indication statement revised to reflect the population studied, for which there is no satisfactory alternative therapy. Added statement to reflect that this is an accelerated approval; effects on survival and clinical symptoms not demonstrated.

- Dosage and Administration: Revised for brevity and clarity with regard to when to discontinue treatment based on unacceptable toxicity, specifically, continued requirements for therapeutic corticosteroids for more than 12 weeks. Moved information on management of adverse reactions to Section 5; replaced with cross-reference to relevant section. Edited for brevity and readability (new subsections under preparation for administration).
- Strengths and Dosage Forms: Revised to include essential information and conformance with FDA guidances and regulations.
- Contraindications: no modifications.
- Warnings and Precautions: Revised to provide a succinct description of adverse reactions and their outcomes, a numerical estimate of the risks, specific instructions for monitoring as appropriate, and actions taken with the drug. Subsections re-ordered to describe most common and/or serious risks first. Deleted section on (b) (4) and incorporated this information into relevant subsections to monitor for specific risks. Added new subsections on Embryofetal Toxicity based on literature review and risk of fetal loss and on Renal Failure/Immune-mediated nephritis based on adverse reaction information in the BLA.
- Adverse Reactions: revised to include additional demographic, baseline entry information, and exposure data on patients enrolled in Cohort B2 and included this information in tabular listing rather than (b) (4).  
 (b) (4) Removed redundant information already described under Section 5 of product labeling. Inserted tabular listing of laboratory abnormalities. Added separate subsection to describe risks of anti-product antibodies (immunogenicity).
- Drug Interactions: removed (b) (4) due to lack of data to support this direction.
- Use in Specific Populations: Changed Section 8.1 to Pregnancy Category D based on animal data alone; revised sections 8.1 and 8.3 in accordance with current labeling policy and added new subsection (8.7) on Men and Women of Reproductive Potential as per recommendations of Maternal Health Team. Modified subsection on hepatic impairment to describe available data with references to more detailed information in Section 12 of the package insert.
- Overdosage: none.
- Description: removed vague or promotional statements.
- Clinical Pharmacology: Edited for brevity and included subsections to enhance legibility. Subsection on Mechanism of action edited to remove statements not supported by data provided in the BLA; limited detail on PD-1 to essential information necessary to understand mechanism of action.
- Nonclinical Pharmacology/Toxicology: under section 13.2, replaced information on (b) (4) and replaced with information on decreased survival in animal models of infection and PD-1 deficiency/inhibition.
- Clinical Studies: expanded description of study to provide information on key eligibility criteria (inclusion and exclusion) and greater detail on treatment plan. Removed information on (b) (4).  
 (b) (4) Removed redundant tabular listing

- of outcomes, since this is described in text. Provided additional information to provide better context for duration of responses. Deleted information on (b) (4), as non-essential. Deleted subsection on immunogenicity/anti-product antibody development and moved this information to Adverse Reactions section of labeling.
- (b) (4) deleted this section as non-essential, per FDA policies/guidances on labeling.
  - How Supplied: editorial changes only.
  - Patient Counseling: expanded this section to include counseling on aspect other than pregnancy/risks to fetus.
- Carton and immediate container labels: Deviations from 21 CFR Parts 201, 610, and US Pharmacopeia were identified and resolved during the review of the BLA. Carton and immediate container (vial) labeling submitted on August 14, 2014 are deemed acceptable.
  - Patient labeling/Medication guide: Patient labeling was submitted in the original BLA. The clinical review team requested that a Medication Guide be submitted to mitigate risks to patients, based on the potential serious risks of autoimmune adverse drug reactions, in order to ensure that patients were provided materials describing these risks and advising patients of actions to take in the event of new or worsening signs or symptoms. The agreed-upon Medication Guide conforms to applicable regulations, is written at an appropriate reading level, and does not contain promotional information. All recommendations from the Patient Labeling Team were considered in reaching agreement on final labeling.

### **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action  
I concur with the findings of all other scientific review disciplines that this product may be approved based on their individual scientific assessments. I recommend that this application be approved under the provisions of 21 CFR 601 Subpart E, based on demonstration of a durable objective response rate that is clinically meaningful in magnitude, where the benefits of this product are not outweighed by its risks, for patients who have progressive melanoma and who have received FDA-approved therapy, such that there is no satisfactory alternative treatment.
- Risk Benefit Assessment  
The indicated patient population has a serious and life-threatening disease with an estimated 5-year survival of 16%, and as specified in the indication statement, have no satisfactory alternative therapy as they were no longer responding to ipilimumab or BRAF inhibitor therapy and other FDA-approved drugs have lower reported response rates. The data provided in the BLA demonstrate a clinically important objective response rate of 24%, which appears to be very durable, and thus is likely to predict a true clinical benefit to patients, which may include prolongation of progression-free survival or improvement in overall survival. The observed adverse reaction profile is notable for treatment-induced autoimmune disorders affecting multiple organ systems; these adverse reactions were

managed with suspension of pembrolizumab and initiation of therapeutic, high-dose, corticosteroids. The incidence of fatal autoimmune events appears to less than 1%. Common adverse reactions of pembrolizumab were fatigue, cough, rash, pruritus, nausea, decreased appetite, constipation, arthralgia, and diarrhea. These common adverse reactions were generally neither severe nor serious (requiring hospitalization or resulting in death). Given the serious, and ultimately fatal, outcomes with metastatic melanoma, these risks do not outweigh the potential benefit of tumor shrinkage lasting for several months.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)  
I concur with the recommendations of the DRISK consultants and the clinical review team that a REMS is not required for this product to ensure safe and effective use. The applicant has stated, and I concur, that the risks of serious autoimmune adverse drug reactions can be appropriately mitigated through communication of the incidence of such risks and recommended dose modifications as described in the approved product labeling, based on the low incidence of fatalities and hospitalization for such adverse drug reactions observed in the clinical safety database of 411 patients with unresectable or metastatic melanoma. At FDA's request, a Medication Guide was submitted to provide patients with access to information regarding the risks of potentially serious autoimmune adverse drug reactions and to provide uniform guidance to patients regarding when to contact healthcare providers for symptoms or signs suggestive of autoimmune disorders.
- Recommendation for other Postmarketing Requirements and Commitments

#### Post-Marketing Requirement Under 21 CFR 601 Subpart E

- 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.

There are two potential trials, in which enrollment is completed, which may be able to fulfill this requirement: Study PN002 and Study PN006. The co-primary endpoints in these studies are overall survival and progression-free survival.

#### Post-marketing Commitments Under 506(B):

- 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.

Post-marketing Commitments Not Under 506(B):

- 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.
- 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.
- 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.
- 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.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PATRICIA KEEGAN  
09/03/2014