

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125514Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: July 25, 2014

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)

Team Leader: Doris Auth, Pharm. D., DRISK

Acting Division Director: Cynthia LaCivita, Pharm. D., DRISK

Subject: Evaluation to determine whether a REMS is necessary to ensure that the benefits of pembrolizumab outweigh the risks

Drug Name: KEYTRUDA® (pembrolizumab, MK-3745) for Intravenous Infusion

Therapeutic Class: Humanized monoclonal anti-programmed-cell death-1 (PD-1) antibody

Dosage and Form: 50 mg lyophilized powder of MK-3475 in a 15 mL single-use vial; Administered as 2 mg/kg intravenously over 30 minutes every 3 weeks

Application Type/Number: BLA 125-514/Supplement Number (SN) 00/04/05/16/24

Office of New Drugs: Division of Oncology Products - 2

Applicant: Merck Sharp & Dohme Corporation (Merck)

OSE RCM #: 2014-22 MASTER RECORD - Milestone Meetings  
2014-23 Risk Management Plan

## 1 INTRODUCTION

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for pembrolizumab (Keytruda™), a new molecular entity (NME) proposed for the treatment of unresectable or metastatic melanoma in adult patients who have been previously treated with ipilimumab (IPI). Submission of this Rolling Original Biologic License Application (BLA) 125-514 to the Division of Oncology Products-2 (DOP-2) was completed on February 27, 2013.<sup>1</sup> The applicant submitted a risk management plan (RMP) to this BLA that does not include a proposed REMS.

## 2 BACKGROUND

Pembrolizumab (MK-3475) is a humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) kappa isotype directed to the programmed cell death-1 (PD-1) receptor. MK-3475 is designed to block the interaction between the PD-1 receptor and its ligands, PD-1 and PD-2. According to the applicant, the PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance.<sup>2</sup> The applicant describes MK-3475 as a high affinity antibody against PD-1 (including PD-1 and PD-2) on the antigen presenting tumor cells. By inhibiting the PD-1 receptor from binding to its ligands, MK-3475 activates tumor-specific cytotoxic T-lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity.<sup>3</sup>

The applicant states that MK-3475 is catabolized by protein degradation processes; typical small molecule metabolic pathways (eg, cytochrome P450 enzymes (CYPs), glucuronosyltransferases) do not contribute to its clearance. MK-3475 is eliminated through catabolism with minimal renal secretion. The systemic clearance of MK-3475 is 0.22L/day and the terminal half-life is ~26 days.<sup>4</sup>

### Proposed Formulation and Strength

The proposed formulation and strength of pembrolizumab is 50 mg supplied as lyophilized powder in a 15 mL vial intended for single use only. The proposed to-be-marketed dose of pembrolizumab is 2 mg/kg, administered intravenously (IV), over 30 minutes every 3 weeks (Q3Ws).

### Non-Clinical Support

According to the applicant, non-clinical data in Cynomolgus monkeys did not report safety concerns with repeat administration. Due to the mechanism of action, the applicant

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<sup>1</sup> BLA 1250514, Pembrolizumab in Global Submit (GS); SN-004, Module 2.0, Common Technical Document Summaries, Subsection 2.7 Clinical Summary (with Biopharmaceutical Studies); SN-005, Module 2.0 Common Technical Document Summaries, Subsection 2.2 Introduction, Subsection 2.5 Clinical Overview, Subsection 2.7 Clinical Summary; SN-016, Module 1.16, RMP

<sup>2</sup> BLA 125-514/SN-016, Pembrolizumab, GS, Module 1.16 RMP, Table 3, p 9/85.

<sup>3</sup> BLA 125-514/SN-005, Pembrolizumab, GS, Module 2.0, Subsection 2.5 Clinical Overview, p 8/119.

<sup>4</sup> BLA 125-514/SN-005, Pembrolizumab, GS, Module 2.0, Subsection 2.5 Clinical Overview, p 16 /199.

concludes that pembrolizumab may increase the risk of abortion and stillbirths if administered during pregnancy and proposes pembrolizumab as Pregnancy Category (b) (4).<sup>5</sup> There are no adequate and well-controlled studies of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab.

The potential risk of developing immune-mediated (IM) adverse reactions (AR) is a known risk associated with use of pembrolizumab as demonstrated in the clinical trials.

### **Unresectable or Metastatic Melanoma**

Melanoma is the most lethal form of skin cancer. According to literature cited in this application (see footnotes), melanoma accounts for less than 5% of skin cancer cases and over 75% of skin cancer deaths.<sup>6</sup> In the United States (US), the incidence of melanoma increased at 2.6% per year between 1985 and 2009. In 2013, approximately 77,000 new melanoma cases will be diagnosed and approximately 9,500 deaths will occur in the US secondary to melanoma. Internationally, approximately 160,000 new cases of melanoma are diagnosed per year with over 70% diagnosed in Australia, Europe, or North American.<sup>4</sup>

### **Armamentarium of Therapy for Malignant Melanoma**

The currently recommended treatment options for newly diagnosed unresectable or metastatic melanoma patients include IPI, BRAF<sup>7</sup> inhibitors (vemurafenib or dabrafenib), or the MEK inhibitor trametinib (with or without dabrafenib) for patients with BRAF-mutant disease, and high-dose interleukin-2 (IL-2).

For patients whose disease has progressed after IPI, vemurafenib, dabrafenib, or trametinib for those with BRAF-mutant disease, there are few remaining treatment options. Dacarbazine was a commonly used chemotherapy treatment before the availability of IPI and BRAF/MEK inhibitors; however, dacarbazine is associated with a low level of clinical activity, even in treatment naïve patients. A meta-analysis of the effects of the addition of IL-2 to dacarbazine or other chemotherapy indicated that while response rates (as well as hematologic toxicity rates) were increased with the addition of these agents, there was no improvement in duration of response or survival.<sup>8</sup>

See the **Appendix**, to this review, **Section A, Table 1**. Comparator Products.

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<sup>5</sup> See **Section 4, Discussion**, for the Agency's a different conclusion on the Pregnancy Category.

<sup>6</sup> BA Shoo, M Kashani-Sabet, Melanoma arising in African, Asian Latino, and Native American Populations. *Seminars Cutan Med Surg* 28:96-102, 2009.

<sup>7</sup> B-Raf: BRAF is a human gene that makes a protein called B-Raf. The gene is also referred to as a proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, while the protein is more formally known as serine/threonine-protein kinase B-Raf. The B-Raf protein is involved in sending signals inside cells, which are involved in directing cell growth. In 2002, it was shown to be faulty (mutated) in some human cancers. Ref: DH Bignell et al. Mutations of the BRAF Gene in Human Cancer. *Nature*, 2002, Jun 27; 417 (6892):949-54.

<sup>8</sup> Abstract # 3702: European Cancer Organization (ECCO) 2013 Meeting. A meta-analysis of randomized, controlled trials in metastatic melanoma establishes progression-free survival as a surrogate for overall survival, by KT Flaherty, SJ Lee, R Dummer, A Hauschild, GV Long, P Lorigan, C Robert, D Schadendorf

## Risk Management Plan

As cited in the **Introduction** of this review, the applicant submitted a proposed RMP for pembrolizumab that includes a pharmacovigilance plan (PV) and does not include a proposed REMS. See **Section 3.1 Clinical Safety**, in this review, for details of the risks associated with use of MK-3475.

## Concerns from the Division of Oncology Products - 2

- The DOP-2 Mid-Cycle Communication Meeting (June 27, 2014) with the applicant included request for the applicant to submit detailed information in the BLA with respect to management and outcomes of immune-related adverse events (IM-AEs) treated with corticosteroids. The DOP-2 requests these data to support evidence-based recommendations (in labeling) for treatment of IM-AEs associated with use of pembrolizumab.
- The DOP-2 informed the applicant of the potential need for a Medication Guide in order to communicate safety information to patients about the serious complications of IM-AEs associated with use of pembrolizumab.<sup>9</sup>

### 2.1 Regulatory History

The regulatory history specific to BLA 125-514 for pembrolizumab follows:

- November 19, 2012: FDA granted Orphan Drug Designation for MK-3475, a humanized IgG4 mAb to PD-1 receptor, for treatment of Stage IIB-IV malignant melanoma (under IND 110-080).
- January 17, 2013: FDA designated MK-3475 as Breakthrough Therapy for the treatment of unresectable or metastatic melanoma that is refractory to IPI treatment *and* for the treatment of unresectable or metastatic melanoma in patients who have not received prior IPI therapy.
- August 23, 2013: The applicant submitted request for a Proprietary Name Review of Keytruda™. The Agency accepted Keytruda™ on October 3, 2014.
- October 25, 2013: The Agency held a Pre-BLA Meeting with the applicant and reached agreement for the proposed content of Original BLA 125-514. The FDA agreed with Merck's proposal not to include a proposed REMS in the initial BLA submission. It was noted that during the review of the BLA, the FDA may identify safety information that would require Merck to prepare a REMS, if necessary to ensure that the benefits of the drug outweigh the risks.
- November 13, 2013: The FDA accepted submission of portions of the application submitted to IND 110-080 for the forthcoming Rolling BLA for MK-3475.
- November 22, 2013: The applicant initiated submission of Rolling BLA 125-514 to the FDA and completed submission of all Modules to this BLA on February 27, 2014.

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<sup>9</sup> See Information Request/Advice, MID-CYCLE COMMUNICATION Letter issued to the applicant on June 16, 2014 with details of DHP's update on review of this application.

- April 3, 2014: The applicant submitted a RMP to this BLA without a proposed REMS.
- April 30, 2014: The applicant submitted the 120-Day Safety Update Report (SUR) to this BLA.
- June 27, 2014: The Agency held the Mid-Cycle Communication Meeting with the applicant to provide updates on review of their application.

## 2.2 Materials Reviewed

- February 17, 2014: BLA 125-514/SN-04 Pembrolizumab: Summary of Biopharmaceutical Studies and Literature References
- February 27, 2014: BLA 125-514/SN-05 Pembrolizumab: Proposed Labeling, Common Technical Document Summaries, Clinical Study Reports
- April 3, 2014: BLA 125-514/SN-16 Pembrolizumab, RMP.
- April 30, 2014: BLA 125-514/SN-24 Pembrolizumab, 120-Day Safety Update Report
- June 13, 2014: BLA 125-514, Pembrolizumab Mid-Cycle Clinical slides by Jennie Chang, Pharm. D., Efficacy Reviewer; Meredith Chuk, M. D., Safety Reviewer; and Marc Theoret, M.D., Team Leader, CDTL; Emmanuel Sampene, Ph.D, Statistics Reviewer, and Kun He, Ph.D., Team Leader, Statistics.
- June 27, 2014: DOP-2 Mid-Cycle Communication Meeting Minutes
- July 1, 2014: BLA 125-514, Pembrolizumab, Interdisciplinary Review Team for Thorough QT Studies Consultation: Thorough QT Study Review by Justin Earp, Ph.D., Jiang Liu, Ph.D., Moh Jee NG, Ph.D., and Qianyu Dang, Ph.D.

## 3 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

The clinical development program for MK-3475 (pembrolizumab), proposed for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab (IPI), consists of a Phase (P) 1, Study P001 and two ongoing, randomized studies (P002 and P006) with active comparators. Brief details on each study follow:

- **Study P001** forms the basis for this BLA and is a P1, multi-center, multi-cohort, open-label (OL) study evaluating safety tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of MK-3475 in patients with locally advanced or metastatic (advanced) melanoma (IPI-naïve or previously treated with IPI), non small cell lung cancer (NSCLC), or carcinoma. Study P001 was initially designed as a standard dose-escalation trial in patients with advanced melanoma, the first in-human study of MK-3475. Study P001 evolved into a Phase 2-like sub-study in melanoma and NSCLC patients based on expansion of cohorts in other cancers.<sup>10</sup>

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<sup>10</sup> This part of Study P001 is now called **Part A** (solid tumors). Several patients with melanoma were enrolled and had objective response to MK-3475, so the study was expanded to evaluate efficacy in melanoma in **Part B** (now **Part B1**- Melanoma). Through amendments, P001 evolved into four Phase 2-like melanoma sub-studies known as **B1, B2, B3 and D**. **Part C** includes NSCLC and **Part F** includes NSCLC (no prior treatment) and NSCLC (previous systemic treatment).

See the **Appendix**, to this review, **Section B**, for a description of patient cohorts within Study P001 and of the Parts in the Study P001 Protocol. For purposes of the MK-3475 clinical development program, “Cohort” refers to the types of melanoma patients (3 cohorts of melanoma patients in Study P001)<sup>11</sup> and “Part” refers to a section of the Study Protocol, P001, as an example, Part B2.

- **Study P002** is a randomized (R), P2 study comparing two MK-3475 dose levels, 2 mg/kg and 10 mg/kg Q3 Weeks (W), to the physician’s choice of chemotherapy in patients with unresectable and metastatic (advanced) melanoma, who have progressed after treatment with IPI and a BRAF (or MEK) inhibitor in patients with BRAF-mutant melanoma. The population in P002 is designed to be the same as the population in P001, Part B2.
- **Study P006** is a R, P3 study comparing MK-3475 10 mg/kg Q2W or Q3W versus (vs) IPI in patients with advanced melanoma who have not been previously treated with IPI. The population in P006 is designed to be the same as the population in P001, Part D. Efficacy data from Study P002 and P006 are not included in this BLA.

### **Study Population and Demographics**

The majority of patients were Caucasian (98% in the 2 mg/kg Q3W group and 96% in the 10 mg/kg Q3W) and 32% to 46% were female with a median age range from 59 to 63 years of age. Baseline disease stage shows 100% of patients with metastatic disease and 8 to 10% of patients with brain metastases. At baseline in the 2 mg/kg Q3W treatment group (n=89) and 10 mg/kg Q3W treatment group (n= 84), 20% and 35% of patients were BRAF mutation positive, respectively.

### **Efficacy**

The primary endpoint was overall response rate (ORR) to demonstrate anti-tumor activity of MK-3475 in all melanoma cohorts. The primary measure for assessment of tumor response was best overall response (BOR) assessment based on independent central radiologic review of disease assessments based on Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.<sup>12</sup>

According to the DOP-2 clinical reviewer<sup>13</sup>, in P001, MK-3475 (Part B2) achieved 23.6% ORR (95% CI 15.2 - 33.8) in patients with locally-advanced, metastatic melanoma refractory to IPI treated with MK-3475 at 2 mg/kg Q3W. The 10 mg/kg Q3W treatment group achieved ORR of 23.8% (95% CI 15.2 - 34.3), almost identical to the 2 mg/kg Q3W treatment, indicating no improvement in efficacy with a 5-fold higher dose of MK-

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<sup>11</sup> IPI-refractory pts; IPI-naïve pts; and IPI-Naive and IPI-treated pts (See the **Appendix, Section B**).

<sup>12</sup> RECIST is a set of published rules that define when cancer patients improve (respond), stay the same (stable) or worsen (progression) during treatments. The original criteria were published in February 2000 by an International collaboration including the European Organization for Research and Treatment of cancer (EROTC), National Cancer Institute of the US and the NCI of Canada Clinical Trials Group. RECIST 1.1 was published in January 2009 as an update to the original criteria (2000). The majority of clinical trials evaluating cancer treatments for objective response in solid tumors are using RECIST.

<sup>13</sup> The DOP-2 Clinical Reviewer for Efficacy is Jennie Chang, Pharm. D.; the Clinical Reviewer for Safety is Meredith Chuk, MD. As of this DRISK review, the DOP-2 reviews are *pending*.

3475 beyond the 2 mg/kg Q3W dose-regimen. Eighty-six (86%) of patients have ongoing responses.

### 3.1 Clinical Safety

The safety profile for MK-3475 is derived from 411 patients (pooled analysis of melanoma patients from Parts B1+B2+D) of P001, a small number of patients in Part A (solid tumors), and patients in Part C (NSCLC) that received the same treatment arm(s).

#### Exposure

Exposure for all patients with advanced melanoma who received MK-3475 (P001, Part B1, B2, and D) is shown in the **Appendix, Section B, Table 2**. A total of 411 patients were treated at 2 mg/kg Q3W (n=162), 10 mg/kg Q3W (n=192), and 10 mg/kg Q2W (n=57). The key dataset in support of patients previously treated with IPI is Part B2.

The safety and tolerability is assessed on the AEs and laboratory results reported during the treatment period up to the data cut-off of October 18, 2013 for 479 patients from P001 (Parts A, A1 and A2, B1, B2, C, and D) treated with MK-3475 for a mean number of a days on treatment, 213 days (range 1 - 680 days, ~ 23 months).

The duration of exposure was similar between the Q3W dose groups but longer for the 10 mg/kg Q2W dose group. The longest mean duration of exposure is in the 10 mg/kg Q2W group as all of these patients were initially enrolled in P001, Part B1 (IPI-naïve and IPI-treated melanoma patients, non-randomized dose assignments) in which enrollment was completed prior to initiation of cohort B2 (IPI-naïve and IPI-treated melanoma patients randomized to 2 mg/kg Q3W and 10 mg/kg Q3W) and cohort D (IPI-naïve patients randomized to 2 mg/kg Q3W and 10 mg/kg Q3W).

#### Safety Analyses

The safety analyses of Part B2 shows that both the 2 mg/kg Q3W and 10 mg/kg Q3W doses are tolerable when administered every 3 weeks to an advanced melanoma population. Few patients (6.7% for the 2 mg/kg Q3W group and 10.7% for the 10 mg/kg Q3W group) discontinued MK-3475 due to an adverse event (AE).

The applicant reports that drug-related AEs were balanced between IPI-refractory (~82%) and IPI-naïve (~86%) patients as were Grade 3-5 AEs. Grade 3-5 AEs occurred in 38.2% and 42.9% of IPI-refractory patients compared to 31.4% and 38.5% of IPI-naïve patients in the 2 mg/kg Q3W and 10 mg/kg Q3W doses respectively.

In the pooled melanoma cohorts (B1+B2+D), a total of 411 patients, a similar safety profile was demonstrated across safety data from additional randomized and non-randomized melanoma cohorts in P001.

The discontinuations due to adverse events (AEs) were infrequent in the 2 mg/kg Q3W and 10 mg/kg Q3W groups, 6% and 9%, respectively, and were numerically higher in the 10 mg/kg Q2W group.<sup>14</sup> The same was observed for drug-related AEs where the

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<sup>14</sup> The 10 mg/kg Q2W group had a numerically higher incidence of serious adverse events (SAEs), drug-related SAEs, Grade 3-5 SAEs, and drug-related Grade 3 -5 SAEs; however, the 10 mg/kg Q2W dose is not proposed for marketing.

discontinuation rate was 3.7% and 2.1% in the 2 mg/kg Q3W and the 10 mg/kg Q3W groups compared to 12.3% in the 10 mg/kg Q2W group.

AEs that resulted in treatment interruptions in  $\geq 2\%$  of patients were: upper respiratory infection (4%), urinary tract infection (4%), increased alanine aminotransferase (ALT) (4%), decreased appetite (4%), hyponatremia (4%), rash (4%), and hypothyroidism (7%), all in the 10 mg/kg Q2W treatment group.

There were few AEs that resulted in discontinuation in Part B2 (IPI-refractory), 7% for the 2 mg/kg Q3W group and 11% for the 10 mg/kg Q3W group. AEs that resulted in study drug discontinuation were: hyperthyroidism and hypophysitis (same patient), pancreatitis, fatigue, autoimmune hepatitis, partial seizures, and pneumonitis. Some of these events are likely related to progressive disease, for example, “metastases to the central nervous system” and “metastases to the meninges”.

In the combined Parts B1+B2+D, there were 36 of 411 (9%) of patients who discontinued due to an AE: 7% for 2 mg/kg Q3W and 11% for 10 mg/kg Q3W. Drug-related AEs resulting in discontinuation were: interstitial lung disease, hemolytic anemia, hematochezia, pneumonitis, rhabdomyolysis, increased ALT, pleural effusion, renal failure, decreased appetite with fatigue, and myopathy with peripheral sensory motor neuropathy, partial seizures, hyperthyroidism and hypophysitis, autoimmune hepatitis and pancreatitis.

### **Grade 3-5 AEs and SAEs with Discontinuation**

SAEs occurred in 27.5% and 32.7% of IPI-naïve patients compared to 8.3 and 14.6% of IPI-refractory patients. Relatively few patients discontinued treatment due to an AE, but the applicant reports these were numerically higher in the IPI-refractory group (1.9% and 2.0% vs. 6.7% and 10.7% in the 2 mg/kg and 10 mg/kg Q3W treatment groups, respectively). No IPI-naïve patients stopped treatment due to a drug-related AE and few patients (1.2% and 5.6%, 2 mg/kg and 10 mg/kg Q3W respectively) discontinued treatment due to drug related in the IPI-refractory

### **Common Adverse Events**

#### **(Part B2, IPI-Refractory)**

The most common adverse events (AEs) in Part B2 (IPI-refractory) were: fatigue (45%), nausea (27%), cough (29%), pruritus (26%), rash (21%), constipation (21%), decreased appetite (21%), diarrhea (21%), arthralgia (21%), dyspnea (18%), vomiting (16%) and anemia (16%). These AEs do not trend with a particular organ system class (SOC) and are not unexpected for an advanced melanoma population, with the exception of immune-mediated adverse events (IM-AEs). There was no clear dose-relationship observed with the common AEs. For Parts B1+B2+D in all patients with melanoma, 2 mg/kg Q3W or 10 mg/kg Q3W, there was a similar safety profile as observed in Part B2.

### **Serious Adverse Events**

#### **Grade 3-5 Adverse Events (Part B2, IPI-Refractory)**

The applicant reports that in Part B2 (IPI refractory), Grade 3-5 AEs occurred in 40.5% of patients no specific AE occurring in more than 6.7% of patients in either treatment group (2 mg/kg and/or 10 mg/kg Q3W). There were no Grade 5 AEs in this cohort. The

most frequently reported Grade 3 -5 AEs (for at least >2% of patients) were: anemia (3.4%), pneumonia (4.5%), dehydration (3.4%), dyspnea (2.2%) and fatigue (6.7%). Grade 3-5 SAEs did not cluster in any particular system organ class (SOC) and were not unexpected for an advanced melanoma population, with the exception of potentially immune-related AEs.<sup>15</sup>

The greatest numerical difference in Grade 3-5 AEs between 2 mg/kg vs 10 mg/kg Q3W was observed in the Gastrointestinal (GI) Disorders body system where the overall incidence was higher in the 10 mg/kg Q3W group (10.7%) vs the 2 mg/kg Q3W group (1.1%). Both diarrhea and constipation were higher in the 10 mg/kg Q3W group. The difference in GI AEs was not observed in Part D.

#### **Grade 3-5 (Parts B1+B2+D)**

The Grade 3-4 AEs in  $\geq 2\%$  were: anemia (3.4%), fatigue (2.4%), dyspnea (2.4%), and vomiting (2%). There were no reported Grade 5 AEs.

#### **Grade 3-5 Drug-Related Adverse Events (Part B2, IPI-Refractory)**

The Grade 3-4 AE was fatigue (3%) with all events in patients in the 2 mg/kg Q3W dose group (5.6% of patients, 2 mg/kg Q3W). There were no reported Grade 5 drug-related AEs.

#### **Grade 3-5 Drug-Related Adverse Events (Parts B1+B2+D)**

Seven (2%) Grade 4 drug-related AEs were reported in the melanoma cohort (Parts B1+B2+D). These drug-related adverse events include acute renal failure, blood creatinine phosphokinase (CPK) increased, and aspartate aminotransferase (AST) increased in cohort B1; hypophysitis and autoimmune hepatitis in Part B2; and blood uric acid increased and peripheral ischemia in Part D.

#### **Deaths**

There were a total of 7 deaths due to Grade 5 AEs from all Parts in Study P001 (B1+B2+D), Part A, and Part C that are reported up to 90 days after the last dose.<sup>16</sup>

- 4 of 7 deaths occurred in the 10 mg/kg Q2W group (Q2W dosing is not proposed for marketing)
- 5 of 7 patients had advanced melanoma
- 2 of 7 patients had NSCLC
- Serious infections (Cryptococcal fungemia, septic shock, cellulitis/sepsis, bilateral pneumonia) occurred in 4 of 7 patients with MK-3475 therapy.
- Progression of malignant melanoma was thought to be causally related in at least 2 of the 7 deaths.

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<sup>15</sup> BLA 125-514, GS, Module 2.7.4, Summary of Clinical Safety, p 67/3293.

<sup>16</sup> There were 144 deaths in Parts A, B1, B2, C, and D from P001 up to the data-cutoff of October 18, 2013. The applicant and FDA Clinical Reviewer report that the majority of the deaths are causally attributed to underlying advanced malignancy.

See **Appendix**, to this review, **Section C, Table 3** for brief summary of each death (by cancer diagnosis and study cohort).

### **Potential Immune-Mediated Adverse Reactions and Adverse Events of Special Interest**

The most important safety concerns in this application are the IM-AEs in melanoma patients (n = 411). There were 23% IM-AEs, all grades, 3.6% IM-AEs Grade 3 - 4. The most important IM-AEs are: rash (6%), hypothyroidism (4%), pneumonitis (2.7%), colitis (1.2%) including diarrhea, hypophysitis (0.5%), hepatitis (0.5%) including AST/ALT elevation, and uveitis (0.5%). Renal failure/renal failure acute was observed in 4% of patients; auto-immune nephritis was observed in 0.2% of patients (one patient).

The adverse events of special interest (AEOSI) were similar to the IM-AE profile in Part B1+B2+D. There were 12% AEOSI and 7% Grade 3 to 4 AEOSI. There were no reported Grade 5 events. There was no significant difference in the incidence of IM-AEs or AEOSI between the IPI-naïve and IPI-exposed groups across the melanoma patients.

- In Part B2, the most common IM-AEs in  $\geq 2\%$  of patients were: rash (2%), arthralgia (2%), hypothyroidism (2%), and diarrhea (2%). There were similar incidences across the 2 mg/kg Q3W and 10 mg/kg Q3W in IPI-refractory advanced melanoma patients. Most of the IM-AEs in Part B2 were Grade 1-2 with an overall incidence of Grade 3-4 IM-AEs of 2% (1 IM-AE (0.6%) was Grade 4). There were no Grade 5 events.
- In Part B2, there was one (1) case of drug-related autoimmune hepatitis (Grade 4) in the 2 mg/kg Q3W treatment group. There was 1 case each of drug-related pancreatitis (Grade 3) and drug-related rash (maculopapular) Grade 3 reported in the 10 mg/kg treatment group. The IR-AE profile was similar to the AEOSI profile for Grade 3-5 events.
- In Parts B1+B2+D (all melanoma patients), the highest incidence of IM-AEs was reported in the Skin and Subcutaneous Tissue Disorder SOC (12%) (rash, pruritus and vitiligo) followed by Endocrine Disorder (4%) and Musculoskeletal disorder (5%) SOCs. The Endocrine Disorder and the Skin and Subcutaneous Tissue Disorder SOCs are driven by hypothyroidism and arthralgia occurring in 3% and 2% of patients, respectively. Respiratory, Thoracic, and Mediastinal Disorders SOC is driven by pneumonitis and General Disorders and Administration Site Conditions SOC is driven by a higher incidence in influenza-like illness. There were no Grade 5 IM-AEs in the all melanoma patient group (Parts B1+B2+D).

### **Infusion-Related Reactions**

There were two (2) patients among 479 for which an infusion related AES was reported. One (1) patient had MK-3475 treatment interrupted after an infusion related reaction at Cycle 10 and was able to restart MK-3475 without additional infusion related reactions in 7 subsequent infusions. A second patient experienced a mild infusion related reaction at Cycle 3. Both patients were taking MK-3475 at the data cut-off date (October 18, 2013.)

### **QT Changes in Electrocardiograms**

The electrocardiogram (ECG) data was submitted by the applicant for Parts A, B1, B2, C and D of study P001. In the P1, OL, dose-escalation study with MK-3475, 479 patients

received 1 mg/kg Q2W, 2 mg/kg Q2W, 3 mg/kg Q3W, 10 mg/kg Q2W, and 10 mg/kg Q3W. Based on comments from the Thorough QT Study Review, no large change (i.e., > 20 ms) in the QTc interval was detected when MK-3475 was administered up to 10 mg/kg Q3W. See the Thorough QT Study Review in DARRTS. There is no QT-related language in the applicant's proposed label.

### **Thyroid Test Abnormalities**

The most common thyroid abnormalities were either subclinical (asymptomatic with elevated thyroid stimulating hormone) hypo- or hyperthyroidism (17% in the 2 mg/kg Q3W treatment group and 16% in the 10 mg/kg Q3W treatment group). Clinically overt hypo- or hyperthyroidism was less frequent, 7% and 4%, respectively, with the same MK-3475 treatment groups, as above. There did not appear to be a dose-dependent response in the incidence of thyroid abnormalities when comparing 2 mg/kg vs 10 mg/kg Q3W treatment groups. Hypothyroidism occurred more commonly than hyperthyroidism and was clinically managed with thyroid replacement hormone.

There was a numerically higher incidence of thyroid abnormalities (46%) in the 10 mg/kg Q2W treatment group. It is unclear if the difference in the Q2W vs Q3W dosing regimen, the sample size, or the treatment duration could be causally attributed to these differences (non-randomized comparison).

### **Immunogenicity**

The presence of circulating MK-3475 levels interfered with the analytical assay detection of anti-drug antibodies (ADA) and complicated interpretation of the immunogenicity assessments.<sup>17</sup> There were 123 of 449 (27%) of patients with post-dose samples in which the MK-3475 concentrations were below a level to confirm a negative immunogenicity status. There were 324 patients (72%) in which the ADA status is inconclusive due to the presence of circulating MK-3475 above the drug tolerance level of the assay.<sup>17</sup>

The applicant acknowledges there were two (2) patients with a single sample that tested positive in the screening assay and the confirmatory test, yielding a positive immunogenicity status. It is not possible to comment further on the potential of MK-3475 and the formation of ADA.

### **120-Day Safety Update Report**

There were no new safety signals or clinically meaningful changes in the frequency of reported AEs in the 120-Day SUR (dated April 30, 2014). The applicant reports all Grades of IM-AEs were reported for 23.4% (23% in the initial filing) of patients, most commonly as: skin and subcutaneous tissue disorders SOC (12.4%), musculoskeletal and connective tissue disorders SOC (4.9%), endocrine disorders SOC (4.9%), general disorders SOC (3.6%), and respiratory, thoracic and mediastinal disorders SOC (3.4%).

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<sup>17</sup> Applicant acknowledges this challenge (BLA 125-514, GS, Module 2.1.7 Immunogenicity, p 203/3293) and the Agency cites this specific concern in the Mid-Cycle Communication Letter to the applicant (see the Chemistry, Manufacturing and Controls comments in Comment #7). See **Section 4, Discussion**, for comments on the issue of immunogenicity/ADA assay validation and levels of MK-3475 in patient samples.

## 4 DISCUSSION

Pembrolizumab (MK-3475), a NME, is in the pharmacologic class of a humanized monoclonal anti-programmed-cell death-1 (PD-1) antibody proposed treatment of unresectable or metastatic melanoma in adult patients previously treated with IPI. The proposed pembrolizumab dosing regimen, via IV administration, appears to be tolerated and achieved clinical efficacy (ORR 23.6%) in patients with locally-advanced metastatic melanoma, refractory to IPI, treated with 2 mg/kg Q3W (proposed to-be marketed dose).

The most important safety concerns associated with use of MK-3475 are the risk of immune-mediated adverse events (IM-AEs), defined as clinically significant adverse events of any organ system that are associated with MK-3475 exposure. The risk of IM-AEs are predicted with MK-3475 therapy based on the formulation, its mechanism of action, and the reported experience with immunotherapy, particularly, IPI that has a similar mechanism of action. The IM-AEs reported with use of MK-3475 are pneumonitis, colitis, hypophysitis, autoimmune hepatitis, rash, hypothyroidism, uveitis, and autoimmune nephritis. Renal failure/acute renal failure is also reported in one patient exposed to MK-3475 therapy.

The DOP-2 has requested detailed information from the applicant on the management and outcomes of IM-AEs treated with corticosteroids. These data are requested to potentially support evidence-based recommendations in labeling for the treatment of IM-AEs associated with use of pembrolizumab.

The DOP-2 requires the applicant to revise the proposed Pregnancy Category <sup>(b)</sup><sub>(4)</sub> to D based on the Agency's precedence with other oncology products for small molecules and/or other therapeutic biologic products that are assigned Pregnancy Category D. The Agency acknowledges that there is no clinical human experience with human fetal/newborn outcomes. As of this review, the applicant has not conducted animal reproduction studies with MK-3475.

As cited in the **Introduction** of this review, the applicant submitted a RMP for pembrolizumab proposed for the treatment of unresectable or metastatic melanoma in patients previously treated with IPI. The DOP-2 did not require the applicant to submit a proposed REMS for pembrolizumab in this BLA.

The applicant proposes to manage the reported risks with pembrolizumab with routine postmarketing pharmacovigilance and labeling that includes a Prescriber Patient Information (PPI) focused on key serious risks reported with use of pembrolizumab. The DOP-2 has informed the applicant of the need for a Medication Guide in order to communicate safety information to patients on risk management of serious complications of IM-AEs associated with use of pembrolizumab.

The rationale for the conclusion that a REMS is not required for pembrolizumab follows:

- Yervoy (ipilimumab) Injection, approved by the FDA in 2011, is associated with severe and fatal IM-AEs (due to T-cell activation and proliferation) including risks of IM enterocolitis (including gastrointestinal perforation), fatal IM hepatitis (including hepatic failure), fatal IM toxicities of skin (including toxic epidermal necrolysis), fatal nervous system toxicity, and endocrinopathies. Most reported cases occurred early during IPI exposure; however, some cases occurred weeks to months after

discontinuation of IPI.<sup>18</sup> IPI has a REMS with a communication plan that includes robust educational materials.<sup>19</sup>

- In comparison to IPI, the reported safety profile for pembrolizumab in advanced melanoma patients includes fewer and less severe IM events and fewer fatalities causally attributed to an IM-AE with pembrolizumab. The IPI labeling includes a Box Warning; whereas, the proposed pembrolizumab labeling does not include a Box Warning.
- Among 15 severe to fatal IM-AEs with IPI (3 mg/kg for 4 doses, via IV infusion, in previously treated patients with unresectable or metastatic melanoma, n=131 patients in Study 1), there were: 7 enterocolitis (including intestinal perforation)\*<sup>20</sup>; 1 hepatotoxicity\*, 2 dermatitis\*; 1 neuropathy\*; and 4 endocrinopathy (all 4, hypopituitarism). For patients treated with pembrolizumab there were 7 fatalities causally attributed to MK-3475 therapy in this BLA. Five (5) of these 7 deaths are causally attributed to serious infections including Cryptococcal fungemia, septic shock, and bilateral pneumonia.
- The target providers for pembrolizumab are the same target providers for IPI: oncologists, surgical oncologists, oncology nurses, oncology pharmacists, infusion nurses, cancer treatment infusion nurses, and health system pharmacists. The target providers for pembrolizumab, should it be approved, are familiar with the severe to fatal IM-AEs that may occur with a therapeutic protein (see risks cited with IPI) and their clinical management. The 3-Year Yervoy REMS Assessment Review written by Julia Ju, Ph.D., (on July 3, 2014) reports that the prescriber knowledge survey results demonstrated a good understanding of the serious risks associated with use of IPI.<sup>21</sup>
- If pembrolizumab is approved, the DOP-2 will require that a Medication Guide be included in labeling, to communicate the serious risks associated with use of pembrolizumab in patients with advanced malignant melanoma.

## 5 CONCLUSION

The DRISK and DOP-2 concur that the benefit-risk profile of pembrolizumab (MK-3475), for the treatment of unresectable or metastatic malignant melanoma in patients who have been previously treated with IPI, is acceptable and, based on the clinical development program (Parts B1+B2+D), a REMS is not necessary to ensure that the benefits outweigh the risks, at this time. The DOP-2 should consult the DRISK, if additional safety information is identified that warrants re-evaluation of the risk management measures for pembrolizumab proposed as IV administration.

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<sup>18</sup> BLA 125-514 MK-3475 (submission dated June 30, 2014) MK-3475 IM-AE Identification, Evaluation and Management Guideline for Investigators, p 1/13.

<sup>19</sup> REMS for Yervoy, Communication Plan Educational Materials: Dear Healthcare Provider Letter, Immune-Mediated Adverse Reaction Management Guide, Patient Wallet Card, and Nursing Immune-Mediated Adverse Reaction Symptom Checklist.

<sup>20</sup> \* Includes a fatal outcome; See the approved YERVOY labeling for additional safety details.

<sup>21</sup> The 3-Year Yervoy REMS Assessment reports a mean correct score for prescriber knowledge on the survey questions as 83.5% (95% CI, 82.2% - 84.8%).

**APPENDIX:**

**Section A:** See **Table 1**, Comparator Products (on the next page).

Table 1. Comparator					
Product	KEYTRUDA Pembrolizumab	YERVOY Ipilimumab	ZELBORAF Vemurafenib	TAFINLAR Dabrafenib	MEKINIST Trametinib
Administration	Intravenous Infusion	Intravenous Infusion	Oral Tablet	Oral Capsule	Oral Tablet
BLA/NDA	BLA 125-514	BLA 125-377	NDA 202-429	NDA 202-806	NDA 204-114
NME Approval Date	Pre-approval review	25-Mar-11	17-Aug-11	29-May-13	29-May-13
Class	Humanized Monoclonal Anti-PD-1 Ab**	Human CTLA-4 blocking Ab ***	Kinase Inh bitor	Kinase Inh bitor	Kinase Inhibitor
Indication	Proposed indication: Tx of unresectable or metastatic melanoma in pts who have been previously treated with ipilimumab	Tx of unresectable or metastatic melanoma	Tx of unresectable or metastatic melanoma with BRAF V600E mutation	Tx of unresectable or metastatic melanoma with BRAF V600E mutation	As a single agent and in combo w/dabrafenib for tx of unresectable/metastatic melanoma w/BRAF V600E or V600K mutations
Boxed Warning	None Proposed	Yes	No	No	No
Labeled Risks: Warnings & Precautions	Immune-mediated (IM) Adverse Reactions (ARs); I-M Pneumonitis; I-M Hepatitis; I-M Thyroid Disorders; Lab Tests, Monitoring	IM ARs; I-M Enterocolitis; I-M Hepatitis; I-M Dermatitis; I-M Neuropathies; I-M Endocrinopathies; Other I-M ARs, including Ocular Manifestations	New Primary Malignancies; Hypersensitivity Reactions; QT Prolongation; Hepatotoxicity	New Primary Malignancies; Tumor Promotion in BRAF Wild-Type Melanoma; Hemorrhage; Venous Thromboembolism; Cardiomyopathy; Ocular Toxicities; Serious Febrile Reactions; Serious Skin Toxicity; Hyperglycemia; G6PD Deficiency; Embryofetal Toxicity	New Primary Malignancies; Hemorrhage; Venous Thromboembolism; Cardiomyopathy; Ocular Toxicities; Interstitial Lung Disease; Serious Febrile Reactions; Serious Skin Toxicity; Hyperglycemia; Embryofetal Toxicity
PPI	Proposed PPI	N. A.	N. A.	N. A.	PPI
Medication Guide	No	Yes	Yes	Yes	No
REMS	None Proposed	Yes (Communication Plan Only)	No	No	No
* DACARBAZINE discontinued marketing per sponsors Quad Pharms (NDA) and Abraxis (ANDA). Decreased clinical activity since IPI, BRAF/MEK inhibitors approved.					
** Human monoclonal anti-programmed cell death (PD)-1 ant body (Ab); *** Human cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking Ab; Abbreviations: Ab-antibody; Combo-combination; N.A.-Not Applicable; NME-New Molecular Entity; PPI-Patient Package Insert; pts-patients; tx-treatment; w-with;					

## Section B.

### MK-3475 Clinical Trial Experience for BLA 125-514 Efficacy Results

- Uncontrolled, Open-Label Study P001 (Total = 411 Advanced Melanoma Patients)
  - 3 Cohorts of Melanoma Patients
    - **PIVOTAL, Part B2** (n = 173 pts)
      - ❖ IPI-Refractory Patients
      - ❖ Randomized to 2 mg/kg Q3W and 10 mg/kg Q3W
    - **SUPPORTIVE, Part D** (n = 103 pts)
      - ❖ IPI-Naive Patients
      - ❖ Randomized to 2 mg/kg Q3W (n = 51) and 10 mg/kg Q3W (n = 52)
    - **SUPPORTIVE, Part B1** (n = 135 pts)
      - ❖ IPI-Naive and IPI-treated Melanoma Patients
      - ❖ Non-randomized Dose Assignments
- **Cohort C** (n = 38 pts) NSCLC patients, ongoing study

**Table 2.**

Drug Exposure in Pooled Cohorts, All Melanoma Patients (Parts B1+B2+D)

	MK-3475 2 mg/kg Q3W	MK-3475 10 mg/kg Q3W	MK-3475 10 mg/kg Q2W	Total
	N = 162	N = 192	N = 57	N = 411
Study Days on Therapy (Days)				
Mean	196.31	197.12	314.51	213.08
Median	190	170	296	188
Number of IV Administrations				
Mean	10.04	10.04	20.93	11.55
Median	9.50	9.00	19.00	10.00

Revised from Applicant's Table 2.7.4:7 (Section 2.7.4.1.2.2, p 26/3293) in BLA 152-514, GS, Module 2.5 Clinical Overview.

**Section C.**

**Table 3.** Deaths (Grade 5 SAEs) in MK-3475 Clinical Development Program

MK-3475 Dose Group	Summary Description
2 mg/kg Q3W	49-year old female with <b>Melanoma</b> (Part B2, IPI refractory), 39 days after exposure, extended safety follow-up, septic shock, Grade 5, fatal.
10 mg/kg Q3W	63-year old female with <b>NSCLC</b> (Part C), 42 days after exposure, extended safety follow-up, hypoxia, Grade 5, fatal.
	52-year old female with <b>NSCLC</b> (Part C), 17 days after exposure, safety follow-up, acute respiratory failure, malignant neoplasm progression, Grade 5, fatal.
10 mg/kg Q2W	76-year old male with <b>Melanoma</b> (Part A), 276 days after exposure, extended safety follow-up, Cryptococcal fungemia, Grade 5, fatal.
	69-year old male, <b>Melanoma</b> (IPI-naïve, Part B1), 50 days after exposure, safety follow-up, pleural effusion, sepsis, deep vein thrombosis, cellulitis, intestinal perforation/intra-abdominal abscess/progressive disease in pelvic wall and bowel, Grade 5, fatal.
	94-year old male, <b>Melanoma</b> (IPI-naïve, Part B1), 99 days after exposure, safety follow-up, bilateral pneumonia, complications from bronchoscopy, pneumothorax, intubated, acute myocardial infarction, Grade 5, fatal.
	77-year old female, <b>Melanoma</b> (previously received IPI, Part B1), 39 days after exposure, safety follow-up, pulmonary embolism, cord compression, resection of progressing melanoma, respiratory arrest, Grade 5, fatal.
BLA 125-514 Pembrolizumab, Module 2.0, Subsection 2.1.4 Deaths due to AEs All Cohorts, p 174/3293.	

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/s/  
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CAROLYN L YANCEY

07/25/2014

REMS Review Final for NME, BLA 125-514 KEYTRUDA (pembrolizumab) for treatment of unresectable or metastatic melanoma previously treated with ipilimumab.

CYNTHIA L LACIVITA

07/25/2014

Concur