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RESEARCH**

*APPLICATION NUMBER:*

**125514Orig1s000**

**MEDICAL REVIEW(S)**

Clinical Review  
Meredith K. Chuk and Jennie Chang  
BLA 125514  
Keytruda (pembrolizumab, MK-3475) for the treatment of patients with refractory unresectable or metastatic melanoma

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## CLINICAL REVIEW

Application Type	Efficacy
Application Number(s)	125,514
Priority or Standard	Priority
Submit Date(s)	February 28, 2014
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Reviewer Name(s)	Meredith K. Chuk (safety) Jennie Chang (efficacy) Marc Theoret, Team Leader
Review Completion Date	August 2, 2014
Established Name (Proposed) Trade Name Therapeutic Class Applicant	Pembrolizumab (MK-3475) Keytruda Monoclonal antibody Merck Sharp & Dohme Corp.
Formulation(s) Dosing Regimen	Lyophilized powder 2mg/kg IV every 3 weeks
Indication(s)	Treatment of patients with unresectable or metastatic melanoma who progressed after treatment with ipilimumab, and a BRAF <sup>(b) (4)</sup> inhibitor <sup>(b) (4)</sup>
Intended Population(s)	≥18 years of age

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

According to the review of the clinical data, the reviewers recommend accelerated approval (21 CFR part 601, subpart E) of MK-3475 at a dose of 2mg/kg every 3 weeks in patients with unresectable or metastatic melanoma who have progressed after treatment with ipilimumab, and a BRAF <sup>(b) (4)</sup> inhibitor <sup>(b) (4)</sup>.

The confirmed overall response rate for 89 patients receiving 2mg/kg of MK-3475 every 3 weeks in Part B2 of trial P001 was 24% (95% CI: 15.2, 33.8) by blinded independent central review (BICR). The median duration of response was not reached with 86% of patients who obtained a response maintaining that response at the time of data cut-off (response durations ranging from 1.4+ to 8.5+ months).

The safety profile is consistent with an immunologically mediated anti-cancer therapy and is acceptable in light of the serious and life-threatening nature of advanced, refractory melanoma.

### 1.2 Risk Benefit Assessment

Patients with advanced melanoma who have progressed following therapy with ipilimumab, and a BRAF or MEK inhibitor if indicated, represent a patient population with an extremely poor prognosis, for which there is an unmet medical need. The median overall survival for patients with metastatic melanoma is historically less than one year. FDA-approved therapies for patients with unresectable or metastatic melanoma which may be used in this population include dacarbazine and interleukin-2 (IL-2) and are expected to be of limited effectiveness based on low overall response rates observed with both products and, with IL-2, the potential for substantial toxicity in a treatment refractory setting.

The recommendation for accelerated approval of MK-3475 is primarily based upon the results of Part B2 in trial P001. Trial P001 is a multicenter, international, open-label, multi-cohort study of MK-3475 in patients with advanced melanoma and carcinoma. In Part B2 of P001, 173 patients with advanced melanoma refractory to ipilimumab, and a BRAF and or MEK inhibitor if indicated, were randomized to either 2 or 10mg/kg of MK-3475 administered intravenously once every three weeks (q3w) until disease progression or unacceptable toxicity. The BICR-assessed, confirmed overall response rate (ORR) per RECIST v. 1.1 was 23.6% (95% CI: 15.2, 33.8) in the 2 mg/kg q3w arm and 23.8% (95% CI: 15.2, 34.3) in the 10 mg/kg q3w arm. The median duration of

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response was not reached in both arms (range 1.4+ to 8.5+ months); however, objective responses were ongoing in 86% in the 2 mg/kg arm and in 90% in the 10 mg/kg arm at the time of data cut-off. The treatment effect of MK-3475 in Part B2 appeared consistent across subgroups based on demographics and baseline disease characteristics. In addition, objective responses were reported in patients with and without BRAF V600 mutations. Of importance, similar ORRs were observed and objective responses remained durable in other cohorts of P001 with a longer duration of follow-up—cohorts consisting of an ipilimumab-naïve and prior ipilimumab treated population of patients with unresectable and metastatic melanoma who received MK-3475 at three dosage regimens (2mg/kg q3w, 10 mg/kg q3w, and 10 mg/kg q2w).

The median progression free survival (PFS) was 5.5 months (95% CI: 3.0, 9.0) in the 2 mg/kg arm and 3.5 months (95% CI: 3.0, 6.0) in the 10 mg/kg arm [HR=0.84 (95% CI: 0.57, 1.23, p-value=0.36)] by BICR using RECIST v. 1.1. The median overall survival (OS) was 13 months (95% CI: 10.3, not reached) in the 2 mg/kg arm, and not reached (NR) in the 10 mg/kg arm (95% CI: NR) [HR 1.04, (95% CI: 0.6, 1.82), p=0.88].

The primary safety risks of MK-3475 are immune-mediated adverse events. Approximately 23% of all melanoma patients treated with MK-3475 on trial P001 (Melanoma ISS) and 16% of patients on the randomized Part B2 treated with MK-3475 2mg/kg every 3 weeks (Part B2-2q3) experienced an immune-related adverse event. The most common immune-mediated adverse events in more than 2% of patients in the Melanoma ISS were rash, hypothyroidism, vitiligo, pruritus, arthralgia, diarrhea, and pneumonitis. Five percent of all immune-mediated events were Grade 3 or 4. Colitis, hepatitis, hypophysitis, nephritis, and hyperthyroidism were also seen but at a lower frequency. Identification of additional immune-related adverse reactions is expected through routine pharmacovigilance as detection of low-frequency adverse events is limited in a relatively small safety database. Importantly, immune-related adverse reactions appear manageable with corticosteroids and no patients required additional immune-modulating agents; however, optimal corticosteroid management of immune-related adverse events is uncertain based on limitations of data collection concerning management of immune-mediated adverse events with corticosteroids.

The most common adverse events ( $\geq 20\%$ ) observed in Part B2-2q3 were fatigue, cough, rash, pruritus, nausea, and decreased appetite. The 2 mg/kg dose of MK-3475 in Part B2 appeared tolerable with 7% of patients requiring treatment withdrawal and 16% requiring dose delays. Grade 3 or 4 AEs occurred in 38% of patients, the most common were fatigue (6%), pneumonia (4%), anemia (3%), and dehydration (3%). Of note, 30% of patients in Part B2-2q3 and 35% in the Melanoma ISS experienced an SAE. The most common SAEs in  $\geq 2\%$  of patients in the Melanoma ISS were renal failure/acute renal failure (2.9%), dyspnea (2.4%), pneumonia (2.2%), and cellulitis (2.2%). The Applicant reported lower incidences of serious adverse events based on

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attribution to MK-3475 (i.e., drug-related); however, attribution of adverse events is difficult in single-arm trials, particularly in heavily pre-treated patient populations.

The risk benefit assessment is favorable for the use of MK-3475 in patients with unresectable or metastatic melanoma who have progressed after treatment with ipilimumab (IPI), and a BRAF or MEK inhibitor if indicated. Unresectable or metastatic melanoma that is refractory to ipilimumab and a BRAF or MEK inhibitor is a serious and life-threatening disease, and there are no FDA-approved therapies with proven clinical benefit for this refractory patient population. MK-3475 has shown substantial evidence of anti-tumor activity with a clinically significant confirmed overall response rate, evidence of durability of the responses, and an acceptable toxicity profile. The anti-tumor activity and safety appeared similar in both the 2mg/kg and 10mg/kg arms of Part B2, which supports the recommended dose of 2 mg/kg every 3 weeks. This ORR of 23.6% with evidence that responses are durable indicates that MK-3475 has anti-tumor activity that provides meaningful therapeutic benefit to this patient population. However, the relationship between the overall response rates and ultimate outcomes of clinical benefit, including overall survival, is uncertain and, therefore, the applicant is required to verify and describe the benefit of MK-3475 under the accelerated approval regulations.

The reviewers do not recommend a risk evaluation and mitigation strategy (REMS) given the current safety profile of MK-3475 and the experience of the medical community in managing immune-related adverse reactions from another FDA-approved immune-modulating agents, ipilimumab. Risk management based on labeling, including a non-REMS patient medication guide, will be employed to ensure the safe and effective use of MK-3475.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no safety issues identified at this time requiring Risk Evaluation and Mitigation Strategies (REMS); however, a medication guide for MK-3475 describing the risks of immune-related side effects for patient education for safe and effective use will be required.

### 1.4 Recommendations for Postmarket Requirements and Commitments

21 CFR part 601, subpart E describes accelerated approval of biologic products for serious and life-threatening illnesses based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity that provide meaningful therapeutic benefit to patients over existing therapies. Accelerated approval is “subject to the requirement that the applicant study the biologic product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.” The

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recommendation for accelerated approval for MK-3475 rather than regular approval for treatment of patients with unresectable or metastatic melanoma who are refractory to ipilimumab, and BRAF <sup>(b) (4)</sup> inhibitor <sup>(b) (4)</sup>, is based upon the following:

- There is uncertainty as to the relation of overall response rate (ORR) and duration of response (DOR) to ultimate outcomes of clinical benefit, including overall survival (OS) in this clinical trial with a small number of patients and limited follow-up.
- Confirmatory trials are ongoing to define the clinical benefit of MK-3475:
  - **Trial P002:** Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma
    - This is a multicenter, randomized (1:1:1) active-controlled trial of MK-3475 at 2mg/kg every 3 weeks vs. 10mg/kg every 3 weeks vs. investigator choice chemotherapy in approximately 510 patients with ipilimumab-refractory melanoma. The study is double-blinded for the MK-3475 arms and open label for the chemotherapy control arm. Patients are stratified by ECOG score, LDH levels, and BRAF mutation status. The primary endpoints are PFS by independent review using RECIST 1.1 and OS. Secondary endpoints are ORR and duration of response. The study has 88-92% power to detect a difference in median PFS of 3.6 vs. 2 months (HR=0.55), and 85% power to detect a difference in median OS of 9.2 vs. 6 months (HR=0.65), and a 95% power to detect a difference in median OS of 10 vs. 6 months (HR=0.6). The study has an overall one-sided alpha of 0.025. The study completed enrollment in November 2013.
  - **Trial P006:** A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma
    - This is a multicenter, open-label, randomized (1:1:1) controlled trial between MK-3475 10mg/kg every 2 weeks vs. 10mg/kg every 3 weeks vs. ipilimumab 3mg/kg every 3 weeks x 4 doses in approximately 645 patients with advanced untreated melanoma. The co-primary endpoints are OS and PFS by independent review using RECIST 1.1. Secondary endpoints include ORR. The study has 95% power to detect a difference in median PFS of 6 vs. 3 months (HR=0.5) and 85% power to detect a difference in median OS of 14.3-15.7 vs. 10-11 months (HR=0.7). The overall one-sided alpha for the study is 0.025. The study completed enrollment in March 2014.

The reviewers recommend the following postmarketing requirement for MK-3475:

MK-3475 is being approved under subpart E (accelerated approval); therefore, confirmatory trial(s) are required to verify and describe the clinical benefit of pembrolizumab in the proposed population, i.e., patients with unresectable or metastatic melanoma. These patients have a serious and life-threatening condition with an unmet medical need. The Applicant must 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.

## 2 Introduction and Regulatory Background

In 2014, it is estimated that there will be 76,100 new melanoma cases and 9,710 deaths from melanoma in the U.S. (American Cancer Society: Cancer Facts and Figures 2014). According to Surveillance, Epidemiology and End Results (SEER) data, between 2004 and 2010, approximately 84% of patients were diagnosed with localized disease, 9% with regional disease, and 4% with distant metastatic disease. While patients with localized disease have an excellent long-term prognosis, patients who are diagnosed with or develop metastatic disease have a median overall survival of less than one year and represent a patient population with an unmet medical need (Howlader N, et. al. 2014).

Alterations in the immune system have been shown to play a role in the pathogenesis of melanoma. One method of exploiting these pathways is to block inhibitory signals of T-cell activation in an attempt to enhance the endogenous anti-tumoral immune response (Shimanovsky A, 2013). The programmed death-1 (PD-1) pathway, including PD-1 and its ligands PD-L1 and PD-L2, functions to maintain tolerance, prevent the development of autoimmunity, and protect normal tissues during an infectious/inflammatory response. Interruption of this pathway, which can be upregulated in a variety of tumors, attempts to restore innate anti-tumor immune response (Topalian S, 2012).

### 2.1 Product Information

MK-3475 is a humanized monoclonal antibody of the IgG4/kappa isotype that binds to PD-1 and blocks the interaction between PD-1 and PD-L1 and PD-L2. MK-3475 is supplied as a lyophilized powder in single dose vials.

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### 2.2 Tables of Currently Available Treatments for Proposed Indications

Until 2011, widely-used FDA-approved therapies for metastatic melanoma included dacarbazine and interleukin-2. Response rates for these two therapies were low, between 5 and 20%; however, duration of response for interleukin-2 in an analysis of eight clinical trials with 270 patients for the 6% of patients who experienced a complete response was not reached, but reported to be greater than 59 months (Atkins MB, 1999; Proleukin, USPI).

In 2011, ipilimumab and vemurafenib were approved on the basis of prolongation of overall survival in patients with unresectable or metastatic melanoma.

On March 25, 2011, FDA approved ipilimumab (IPI), a recombinant human IgG1 immunoglobulin monoclonal antibody which binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), for the treatment of unresectable or metastatic melanoma based primarily on the results of the MDX010-20 trial. This was a multicenter, placebo-controlled, double-blind clinical trial that randomized (3:1:1) 676 HLA-A2\*0201 positive patients with previously treated unresectable Stage III or IV malignant melanoma to receive (a) IPI 3 mg/kg intravenously (IV) every 3 weeks up to 4 doses in combination with gp100 peptide subcutaneously every 3 weeks up to 4 doses, (b) IPI 3 mg/kg IV every 3 weeks up to 4 doses plus gp100 placebo every 3 weeks for 4 doses, or (c) placebo IV every 3 weeks up to 4 doses plus gp100 peptide subcutaneously every 3 weeks up to 4 doses. Patients randomized to the IPI-containing arms had a significantly longer median overall survival (mOS) than the gp100 vaccine arm:

- mOS of 10.2 months in the IPI monotherapy arm compared to 6.4 months in the gp100 arm, HR=0.66 (95% CI: 0.51, 0.87; p-value=0.0026 stratified log-rank test)
- mOS of 10 months in the IPI monotherapy plus gp100 arm compared to 6.4 months in the gp100 arm, HR=0.68 (95% CI: 0.55, 0.85; p-value=0.0004, stratified log-rank test)

The IPI prescribing information (Yervoy USPI) includes a boxed warning based on the risk of severe and fatal immune-mediated reactions due to T-cell activation and proliferation including enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and ocular manifestations, among others. The most common adverse reactions ( $\geq 5\%$ ) at a dose of 3 mg/kg were fatigue, diarrhea, pruritus, rash, and colitis.

On August 17, 2011, FDA approved vemurafenib, an inhibitor of some mutant forms of BRAF serine-threonine kinase, including BRAF V600E, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. FDA approval was based primarily on the results of the NO25026 trial, a Phase 3, open-label, active-controlled trial that randomized (1:1) 675 patients with previously untreated unresectable or metastatic melanoma to receive vemurafenib

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960 mg orally twice daily (n=337) or DTIC 1000 mg/m<sup>2</sup> IV on Day 1 every 3 weeks (n=338) (Zelboraf USPI). PFS and OS were co-primary endpoints of this trial. Vemurafenib demonstrated a clinically meaningful prolongation of PFS from a median of 1.6 months [95% CI: 1.5, 1.7] with DTIC to 5.3 months (95% CI: 4.8, 6.6) with vemurafenib with a HR of 0.26 (95% CI: 0.20, 0.33; p-value <0.0001). The NO25026 trial also demonstrated a statistically significant increase in OS of the vemurafenib arm compared to the DTIC arm with a HR of death of 0.44 (95% CI: 0.33-0.59; p<0.0001). At the time of the final OS analysis, the median OS for the vemurafenib arm had not been reached (95% CI: 9.6, NR), while the median OS for the DTIC arm—censoring those patients on DTIC who crossed over to vemurafenib—was 7.9 months (95% CI: 7.2, 9.6). The primary safety risks of vemurafenib include new primary malignancies, hypersensitivity reactions, dermatologic reactions, QT prolongation, liver laboratory abnormalities, photosensitivity, and ophthalmologic reactions. The most common Grade 1-4 treatment-emergent adverse events (AEs) in vemurafenib-treated patients were: arthralgia (49%), rash (36%), alopecia (33%), fatigue (32%), nausea (30%), photosensitivity reaction (30%), diarrhea (25%), pruritus (21%), headache (21%), hyperkeratosis (19%), pyrexia (18%), skin papilloma (18%), and decreased appetite (16%).

On May 29, 2013, two more products were approved by the FDA for use in patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma based on an improvement in PFS: dabrafenib was approved for patients with a BRAF V600E mutation and trametinib was approved for patients with a BRAF V600E mutation and for patients with a BRAF V600K mutation.

Dabrafenib is a small molecule ATP-competitive inhibitor of BRAF and is therapy targeted to the melanomas that contain BRAF V600E mutations. The safety and efficacy of dabrafenib was demonstrated in an open-label, multi-center, randomized active-controlled trial conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. The trial demonstrated a statistically significant increase in mPFS in the patients treated with dabrafenib compared to dacarbazine [5.1 months (95% CI: 4.9, 6.9) compared with 2.7 months (95% CI: 1.5, 3.2); HR=0.33 (95%CI: 0.20, 0.54; p-value < 0.0001)]. The most common AEs (>20%) were hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia and palmar-plantar erythrodysesthesia syndrome. New primary cutaneous malignancies, tumor promotion in BRAF wild-type melanoma, serious febrile drug reactions, hyperglycemia, uveitis, and iritis were noted as toxicities (Tafinlar USPI).

Trametinib is an allosteric inhibitor of MEK in the MAP kinase pathway. The safety and efficacy of trametinib was evaluated in an open-label, international, multi-center, randomized, active-controlled trial in 322 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. The trial demonstrated a statistically significant increase in mPFS in the patients treated with trametinib compared to those

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treated with chemotherapy [4.8 months (95% CI: 4.3, 4.9) compared to 1.5 months (95% CI: 1.4, 2.7); HR=0.47 (95%CI: 0.34, 0.65; p-value < 0.0001)] (Mekinist USPI). Common AEs (>20%) were hypertension, rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform. Cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, and serious skin toxicity were noted as toxicities.

On January 8, 2014, FDA granted accelerated approval to dabrafenib and trametinib for use in combination in the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test based on confirmed ORR and duration of responses. The safety and efficacy of the combination were based on the results of trial BRF113220 in which 162 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma were randomized (1:1:1) to (a) trametinib 2 mg orally once daily with dabrafenib 150 mg orally twice daily (150/2, n = 54), (b) trametinib 1 mg orally once daily with dabrafenib 150 mg orally twice daily (n = 54), or (c) dabrafenib 150 mg orally twice daily (n = 54). The investigator-assessed confirmed ORR was 76% (95% CI: 62%, 87%) on the 150/2 combination arm and 54% (95% CI: 40%, 67%) on the single-agent dabrafenib arm. The median DOR was 10.5 months (95% CI: 7, 15) for objective responders on the 150/2 combination arm and 5.6 months (95% CI: 4, 7) on the single-agent dabrafenib arm. The median PFS was 9.4 months for the 150/2 combination arm and 5.8 months for the single-agent dabrafenib arm [HR 0.39, 95% CI (0.25, 0.62)]. Common AEs with the combination were generally consistent with single-agent dabrafenib or trametinib use. Pyrexia occurred at a higher incidence with the combination than with single-agent dabrafenib and accounted for the greatest number of SAEs. Unexpected AEs, such as thromboembolic events (8%) and major hemorrhagic events (6%) occurred at a higher incidence with the combination compared to dabrafenib monotherapy.

**Table 1** lists the FDA-approved therapies for metastatic melanoma and the clinical basis for approval.

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**Table 1: Table of FDA-Approved Therapies Indicated for the Treatment of Patients with Metastatic Melanoma**

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

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

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

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

<sup>1</sup> Hydroxyurea is also FDA-approved for treatment of melanoma but is of historical interest.

<sup>2</sup> BRAF V600 mutation status unknown.

<sup>3</sup> Patient selection based on BRAF V600E mutation-positive tumors.

<sup>4</sup> Patient selection based on BRAF V600E or V600K mutation-positive tumors

<sup>5</sup> Patient selection based on BRAF V600E, V600K, or V600D mutation-positive tumors

<sup>6</sup> Accelerated approval as per 21 CFR 314.510 of subpart H

### 2.3 Availability of Proposed Active Ingredient in the United States

MK-3475 is not available in the U.S.

### 2.4 Important Safety Issues With Consideration to Related Drugs

Human cytotoxic T-lymphocyte antigen 4 (CTLA-4), like PD-1, functions as a negative regulator in immune responses. Ipilimumab, a human CTLA-4 blocking antibody is FDA-approved for the treatment of unresectable or metastatic melanoma. The ipilimumab prescribing information includes a boxed warning based on the risk of severe and fatal immune-mediated reactions due to T-cell activation and proliferation including enterocolitis, hepatitis, dermatitis, neuropathies, and endocrinopathies. The most common adverse reactions ( $\geq 5\%$ ) at a dose of 3 mg/kg were fatigue, diarrhea, pruritus, rash, and colitis (Yervoy USPI).

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Nivolumab, a monoclonal antibody against PD-1, is currently in clinical development for a variety of tumors, including melanoma, non-small cell lung cancer, and renal cell carcinoma. Important adverse events that have a potential immune-mediated etiology and have been described in patients treated with nivolumab are rash, diarrhea, thyroid abnormalities, increase in ALT, and pneumonitis (Nivolumab Investigator Brochure, 2013).

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following summarizes the presubmission regulatory activity for MK-3475:

- *December 10, 2009*: IND 110080 submitted
- *August 21, 2012*: End of Phase 1 meeting
  - The Applicant requested FDA feedback on whether tumor response rate in the expanded cohorts of melanoma patients in the Phase 1 trial (P001) could support a review under accelerated approval. FDA stated that the magnitude and durability of response and risk profile would determine the suitability of a BLA submission for accelerated approval.
  - FDA provided guidance on the design of the proposed trials to confirm the clinical benefit of MK-3475 including the proposed endpoints and statistical method.
  - FDA stated that if the clinical development program for MK-3475 includes the development of a companion in vitro diagnostic (IVD) device for PD-L1 expression, the sponsor for the companion IVD device and Merck should submit information about the proposed companion IVD device in a pre-Investigational Device Exemption (IDE) for review by the Center for Devices and Radiological Health (CDRH), as a consultative submission designed to ensure that appropriate validation studies are planned and carried out.
  - The Applicant asked if the preliminary anti-tumor activity of MK-3475 in melanoma patients meets the breakthrough therapy designation. FDA stated an amendment should be submitted to the IND requesting such a designation with the appropriate clinical information including a comprehensive summary of information that justifies this designation.
- *November 19, 2013*: Orphan drug designation granted for Stage IIB through Stage IV melanoma
- *January 11, 2013*: Type B Pre-Phase 3 Clinical meeting to discuss proposed plans for retrospective testing of PD-L1 biomarkers for patients enrolled in cohort

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B of P001; the design of trial P006 to be conducted in patients with IPI treatment-naïve, unresectable or metastatic melanoma, intended to verify clinical benefit if accelerated approval is granted treatment of patients with IPI-refractory melanoma (b) (4)

(b) (4) and to seek FDA concurrence with Merck's proposed CMC, companion diagnostic plans, and nonclinical and clinical pharmacology development programs. Major agreements reached during this meeting include:

- FDA agreed that the protocol submitted in the meeting package to demonstrate comparability between the old (b) (4) vs. the new (Brinny) Drug Product (DP) manufacturing processes was adequate in scope and design.
  - FDA stated that in order for pre-specified retrospective IHC testing to support accelerated approval for an indication in a subgroup of IPI-refractory melanoma patients expressing PD-L1, the following would be necessary:
    - The trial must meet its primary objective in the overall population
    - The clinical data would be derived from adequate and well-controlled clinical trials (preferably at least two trials)
    - The analysis plan is finalized prior to un-blinding of study results (with regard to biomarker result)
    - Appropriate tumor sample acquisition and handling procedures were used
    - Tumor samples were obtained in nearly all patients (90-100%)
    - The assay for the biomarker has acceptable analytical validation
  - FDA agreed that the proposed trial P006 in IPI-naïve patients could provide confirmatory evidence of therapeutic benefit if the product is approved under accelerated approval for IPI-refractory patients based on P001 and/or P002.
- *January 17, 2013*: Breakthrough Therapy Designation granted for the treatment of unresectable or metastatic melanoma that is refractory to and for those who have not received ipilimumab
  - *January 18, 2013*: Applicant requested a waiver for conducting pediatric studies under the Pediatric Research Equity Act due to orphan designation. Pediatric waiver granted by FDA on April 17, 2013.
  - *April 2, 2013*: Type B CMC meeting to discuss the overall commercial strategy to support the BLA.

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- The Applicant stated their plan was to file at the end of 2013 with several manufacturing sites (Drug substance: (b) (4) and MEDI, Fredrick, MD and Drug product: Briny, Ireland) using (b) (4) and (b) (4) at commercial launch with the eventual plan to (b) (4)
  - FDA recommended that the development goal should be to license one manufacturing process which should be the process used to provide material for pivotal clinical trials (b) (4).
  - The Applicant stated that they would need to (b) (4) request a CMC meeting in May to review analytical comparability and stability plans and data to support bridging and use of both manufacturing processes.
- *April 22, 2013*: Type B meeting to discuss nonclinical, clinical pharmacology, and clinical development programs
    - FDA agreed that an assessment of MK-3475's developmental and reproductive toxicology that does not include MK-3475-specific animal studies would be acceptable for the embryo-fetal toxicology assessment required for the drug's proposed indication but that the BLA submission should include relevant data and information that generally supports the scientific conclusion that blocking the PD-1/PDL1 signaling pathway during pregnancy would be expected to have a negative effect on fetal development. This explanation will be necessary to support an appropriate labeling statement for the product regarding use in pregnancy.
    - FDA agreed that the nonclinical pharmacokinetics and pharmacology program is adequate to support the registration of MK-3475 and future label claims regarding the mechanism of action of MK-3475 and that no additional studies are required.
    - FDA stated that either trial P002 or P006 could potentially serve as a confirmatory trial if results from trial P001 are accepted for accelerated approval, but that if trial P002 fails to meet its co-primary endpoint of demonstrating a statistically significant improvement in OS, the treatment effect demonstrated on PFS must be statistically robust and of sufficient magnitude to support a conclusion that it is of clinical benefit to patients, given the risks, and there must be no evidence of a detrimental effect on OS.

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- *June 11, 2013*: Type A CMC meeting to discuss the comparability and stability plans of (b) (4)
  - FDA agreed with the Applicant's proposed staged comparability strategy to support analytical comparability of (b) (4) and (b) (4) for use of (b) (4) (b) (4) in confirmatory studies, but stated that the final decision on acceptability will be a review issue. FDA further outlined requirements to support comparability of (b) (4) for commercial purposes.
- *August 27, 2013*: Type C CMC meeting to discuss the Fab-arm exchange data, analytical strategy for HCP and potency assay, viral clearance strategy, process performance qualification (PPQ) for Drug Substance (DS) and Drug Product (DP), and reference material strategy
  - FDA stated that they would not agree with retrospective PPQ data as a substitute for prospective PPQ data.
  - FDA stated that all available data comparing potency assay results should be included in the BLA; lot-specific data should be provided, in addition to statistical analyses of pooled data. The data submitted to the BLA should include stability data that compare the stability indicating properties of the cell based functional potency assay, the competitive ELISA, and the cell-based competitive ELISA under long term and accelerated storage conditions; and under stress conditions, e.g., temperature, pH, and light (UVA and UVB), in addition to forced oxidation, to support the use of only the competitive ELISA for the release and stability of the commercial DS and DP.
- *October 24, 2013*: Pre-BLA CMC meeting
  - FDA stated that the comparability plan for (b) (4) and (b) (4) appears sufficient, but that the major outstanding concern was the lack of stability data from commercial scale production batches.
  - FDA stated that they could not accept an incomplete CMC package and two options were available: the Applicant could proceed with an initial BLA submission for MK-3475 that contains a complete CMC package, including data from one PPQ batch, in December 2013 or submit the BLA components under Rolling Review with the data from the initial PPQ batch submitted in January/February 2014 as the final CMC component of a complete BLA.
- *October 25, 2013*: Pre BLA meeting
  - The Applicant proposed to submit a BLA for MK-3475 in late December 2013, for the proposed indication in melanoma patients previously treated with IPI, based predominantly on results of Part B2 in trial P001. The

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Applicant stated that approximately half of the cohort would have evaluable response data at 28 weeks at the time of the proposed BLA submission. The Applicant proposed to submit an efficacy update in February 2014 (data cutoff of October 18, 2013) of the 173 patient Part B2, when all patients will have at least 28 weeks of follow-up.

- FDA did not agree with the Applicant's proposal to provide partial efficacy results as the statistical analysis plan in Protocol Amendment 8 states that the efficacy analysis will be based on patients with at least 28 weeks of follow-up. FDA stated that data from the patient population in Part B2 of P001 with a data cutoff of October 18, 2013, for both efficacy and safety, will serve as the primary basis of the clinical review for the proposed indication. However, FDA stated that it was acceptable for Merck to submit a Clinical Study Report (CSR) in Module 5 with a data cut-off of July 26, 2013, for Parts B1, B2, D, as the initial clinical portion of a rolling BLA. Merck could then submit an updated CSR with an appendix for updated data from Part B2 with a data cut-off of October 18, 2013. For the last clinical portion of the rolling BLA, Merck could submit Sections 2.5, 2.7.1, 2.7.2, 2.7.3, and 2.7.4 in Module 2 and an Integrated Summary of Safety and Integrated Summary of Efficacy in Module 5 with data cutoffs of July 26, 2013, for Parts B1, and D, and October 18, 2013, for Part B2, to include side-by-side and pooled analyses.
- FDA did not agree with the Applicant's proposal to perform the primary efficacy analysis of ORR in the Full Analysis Set (FAS) population (patients who have measurable disease based on a centralized review), which included 88% of the study population. FDA stated that Merck may provide an analysis of ORR based on the FAS population; however, FDA's primary analysis of ORR will be based on the modified ITT population.
- FDA stated that trial P001 does not appear adequate in design to support (b) (4) and disagreed with the Applicant's rationale for (b) (4).
- FDA agreed with Merck's proposal not to include a REMS in the initial BLA submission; however FDA noted that the review of the BLA 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.

## 2.6 Other Relevant Background Information

None

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

The BLA submission contained all the required components of the electronic common technical document (eCTD). The submission was generally well organized; however, numerous information requests were sent to the Applicant during the review cycle. Examples of these were requests made to clarify discrepancies in the baseline demographics and characteristics as detailed in the efficacy analyses in Section 6, information to clarify non-standard presentation of data, requests for laboratory and vital sign safety analyses that were referenced in the CSR but not contained in the submission, and requests for additional safety analyses regarding mitigation of adverse events for use in product labeling. The discrepancies in the baseline demographics and characteristics do not appear to affect the efficacy or safety results and were not limited to one study site. The additional safety analyses did not substantially change the risk benefit profile of MK-3475.

The case report forms (CRFs) in Part B2 were audited by the clinical reviewer for efficacy (J. Chang) in 12 (7%) patients to verify that the data transmitted in the datasets were an accurate representation of the patient information documented in the CRFs, specifically, the information used to capture the efficacy data was verified.

Please refer to the review conducted by the Office of Scientific Investigations, in which other data quality issues at study sites were identified.

*REVIEWER COMMENT: No errors were identified in the transfer of the data relevant to efficacy from the CRFs to datasets for efficacy analyses.*

#### 3.2 Compliance with Good Clinical Practices

The applicant stated the following: “The clinical trials included in this application: P001 (safety and efficacy data) and P002, P006, P010 and P012 (serious adverse event data) were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.” (Source: BLA Module 2.5 Clinical Overview Section 1.7)

The Division of Oncology Products 2 (DOP2) consulted the Office of Scientific Investigation (OSI) on March 31, 2014, to perform an audit of three clinical trial sites

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(Site #12, Dr. Hwu, Site #20, Dr. Joshua, and Site #19, Dr. Rizvi) and the Applicant site to identify any issues that could affect the quality and interpretation of the data submitted with this application regarding clinical trial P001. The Division, in consultation with OSI, selected clinical sites for inspection based on enrollment characteristics, patterns of protocol violations reported for the sites, patterns of efficacy reporting, and patterns of serious adverse event (SAE) reporting.

OSI review revealed evidence of underreporting of adverse events at one clinical site (Site #19).

The following is an excerpt from the OSI review “With the exception of Site 19 (Dr. Rizvi), there was no evidence of underreporting of adverse events to the sponsor. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no major discrepancies. According to Merck’s response to the IR regarding inspectional observations at Site 19, they conducted a cumulative review of internal audits, Quality Control Visit’s, interim monitoring visits, investigator visit reports, as well as the recent FDA inspection findings at Site 19. Specifically, Merck conducted a review of all sites participating in the study (Part B2) and found that sustained incomplete reporting of AEs was limited to Site 19. Further, the sponsor noted that the deficiency at this site did not change the safety profile of the investigational drug, pembrolizumab. OSI concurs with Merck’s conclusion based upon available information, and acknowledges that the sponsor has already implemented corrective actions to mitigate these findings moving forward.”

### REVIEWER COMMENTS:

- *OSI issued an FDA form 483 to Dr. Rizvi’s site based on a failure to report safety information for 7 patients from trial P001. FDA issued an information request to Merck based on the information to assess their clinical trial monitoring process and assess the scope of the problem. Merck responded with an outline of their monitoring plan, their assessment of the issues at the site in question, information stating that their own inspections and re-review of the data did not reveal a pervasive nature of underreporting of adverse events at other sites or alter the risk-benefit assessment of MK-3475, and a plan for modifications to their existing risk-based clinical trial monitoring system.*
- *This reviewer agrees that the issues with safety reporting appear to be limited to the single site and that the omissions do not affect the overall safety assessment of MK-3475.*

### 3.3 Financial Disclosures (See also Appendix 9.4)

In accordance with 21 CFR 54, the Applicant submitted the following financial information:

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- A list of P001 trial investigators (BLA Section 1.3.4, Table 2) and FDA form 3454 certifying that the 279 investigators listed in Table 2 had no financial arrangements as defined in 21 CFR 54.2 (a, b, and f) that could affect the outcome of the trial.
- A list of P001 trial investigators (BLA Section 1.3.4, Tables 5) and FDA form 3455 stating that the one named individual in Table 5 has participated in financial arrangements or holds financial interests that are required to be disclosed. Table 5 states that (b) (6) received \$50,000 in research grant money from Merck to (b) (6). Funding period for this grant was (b) (6). Merck stated that the steps taken to minimize potential bias included:
  - Use of multiple clinical investigators and study sites
  - Review of primary endpoint data by an independent and adjudicated central vendor
  - Randomization of Melanoma Cohorts Part B2 and D

### REVIEWER COMMENT:

A subgroup analysis was conducted whereby efficacy data from patients from Part B2 enrolled at (b) (6) site were excluded. Efficacy was not impacted.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

There were no significant safety or efficacy issues identified related to Chemistry, Manufacturing, and Controls (CMC).

Refer to the FDA CMC BLA review for details.

### 4.2 Microbiology

There were no significant safety or efficacy issues related to product quality from a microbiology standpoint.

Refer to the FDA Product Quality Microbiology BLA review for details.

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### 4.3 Preclinical Pharmacology/Toxicology

The Applicant conducted 1- and 6-month repeat-dose toxicology studies in cynomolgus monkeys. There were no severe toxicities but there was a pattern of changes consistent with the immune-based mechanism of action of the drug. The following is excerpted from the FDA Pharmacology/Toxicology BLA review:

Pembrolizumab was evaluated in two repeat-dose toxicology studies in the cynomolgus monkey. There were no severe toxicities and no patterns of histopathological change that were suggestive of specific target organ toxicity in either study. Of note, there were considerably fewer background findings in the 6-month study than there were in the 1-month study, and the pattern of changes noted in treated animals (most of which were described as cellular infiltration) was generally consistent with a heightened pattern of immune surveillance, as expected from the pro-inflammatory mechanism of action of the drug.

There was no evidence of cytokine release when MK-3475 was evaluated by the Applicant in a cytokine release assay.

Given the role of the PD-1/PD-L1 pathway in suppressing the immune response, the Applicant evaluated the *in vitro* effect of MK-3475 on cytokine release following vaccination. They reported an approximately two and a half-fold increase in IFN $\gamma$ . The following is excerpted from the FDA Pharmacology/Toxicology BLA review:

Because of its known mechanism of action in limiting the immune response, there is concern that blocking PD-1 activity may exacerbate response to recall antigen stimulation. The Applicant evaluated pembrolizumab in cultures of peripheral blood cells derived from healthy volunteers that had been recently vaccinated with tetanus toxoid. When cells were re-stimulated with tetanus toxoid in culture there was an ~ 2-5X increase in the amount of IFN $\gamma$  produced in pembrolizumab-treated cultures (Pembrolizumab + TT) relative to control-treated cultures (TT alone). Because pembrolizumab may also increase the numbers of circulating and tissue responder-cells, patients who are vaccinated or re-vaccinated while undergoing treatment with pembrolizumab may experience an enhanced immune response resulting in vaccine-associated toxicity.

In addition to dis-inhibiting the immune response, there is data to suggest that blockade of PD-1 can skew the lymphocyte population toward a TH1 phenotype (Amaranth, et al., 2011) and also that it may lead to inappropriate containment of chronic infections such as tuberculosis. Data in TB-infected mice suggest that PD-1 deficiency is associated with a markedly reduced survival relative to wild-type mice. These data are of concern for the treatment of patients with chronic diseases such as TB. The Applicant has indicated that patients with chronic

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infections such as TB and hepatitis were excluded from clinical trials. Because of these outstanding concerns about long-term consequences following use of a PD-1 inhibitor on immune response and chronic infection, additional studies to investigate the pharmacology of pembrolizumab in these situations may be requested as post-marketing requirements.

Refer to the FDA Pharmacology/Toxicology BLA review for details.

### 4.4 Clinical Pharmacology

Refer to the FDA Clinical Pharmacology BLA review for details.

#### 4.4.1 Mechanism of Action

MK-3475 is a humanized monoclonal antibody of the IgG4/kappa isotype that binds to PD-1 and blocks the interaction between PD-1 and PD-L1 and PD-L2. Both PD-1 and PD-1 ligands are upregulated following initiation of an immune response and help to limit that response to avoid tissue damage. Upregulation of PD-1 ligands also occurs in some tumors and is thought to contribute to inhibition of active T-cell immune surveillance of tumors.

#### 4.4.2 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 479 patients with metastatic or unresectable melanoma or carcinoma who received doses in the range of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analysis in 479 patients, the mean [% coefficient of variation (CV%)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life ( $t_{1/2}$ ) is 26 days (24%). Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration ( $C_{max}$ ), trough concentration ( $C_{min}$ ), and area under the plasma concentration versus time curve at steady state ( $AUC_{ss}$ ) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 2 lists the clinical trials for which there is data in the BLA submission.

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The primary evidence to support the clinical efficacy of MK-3475 at a dose of 2mg/kg every 3 weeks in patients with unresectable or metastatic melanoma who are refractory to ipilimumab (IPI), and to BRAF or MEK inhibitors if indicated, is from patients in Part B2 of study MK3475-P001 “Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma” (hereafter referred to as P001). Data from Parts B1 and D provide additional information on the efficacy of MK-3475 in patients with melanoma.

The primary safety data used to characterize the safety profile of MK-3475 for patients with advanced melanoma is from Parts B1, B2 and D of trial P001, with an emphasis on patients in Part B2 who received 2mg/kg of MK-3475 every 3 weeks. Safety data from non-melanoma patients in Parts A and C of trial P001 and SAE line-listings for patients in Parts B3 and F of P001 and melanoma and non-melanoma patients in trials 002, 006, 010, and 012 were used to supplement the safety review.

**Table 2 Tabular Listing of Clinical Trials of MK-3475 in BLA submission**

Trial ID	Trial design/ Primary endpoint	Part	Cohort	Population	MK-3475 Dose (mg/kg)	Interval between doses (weeks)	Subjects (N)
MK3475-P001	Single arm/ Safety and RR	A	A	Refractory solid tumors	1, 3, and 10	2 <sup>a</sup>	10
			A1	Refractory solid tumors	10	2	7
			A2	Refractory solid tumors	2 or 10 <sup>b,c</sup>	3	13
		B	B1	Melanoma (IPI-naïve or IPI-treated)	2 or 10	2 or 3	135
			B2	Melanoma (IPI-refractory)	2 or 10 <sup>b</sup>	3	173
			B3 <sup>e</sup>	Melanoma (IPI-naïve, IPI-treated or IPI-refractory)	10 <sup>b</sup>	2 or 3	248
		C		NSCLC	10	3	38
		D		Melanoma (IPI-naïve)	2 or 10 <sup>b</sup>	3	103
		F	F1 <sup>e</sup>	NSCLC (no prior treatment)	10 <sup>b</sup>	2 or 3	43 <sup>d</sup>
			F2 <sup>e</sup>	NSCLC (prior treatment)	10 <sup>b</sup>	2 or 3	200 <sup>d</sup>

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Trial ID	Trial design/ Primary endpoint	Part	Cohort	Population	MK-3475 Dose (mg/kg)	Interval between doses (weeks)	Subjects (N)
MK3475-P002 <sup>e</sup>	Compare to chemo/ PFS and OS			Melanoma (IPI-refractory)	2 or 10 <sup>b</sup>	3	496
MK3475-P006 <sup>e</sup>	Compare to IPI/ OS			Melanoma (IPI-naïve)	10 <sup>b</sup>	2 or 3	87 <sup>d</sup>
MK3475-P010 <sup>e</sup>	Compare to docetaxel /OS			NSCLC	10 <sup>b</sup>	2 or 3	12 <sup>d</sup>
MK3475-P012 <sup>e</sup>	Safety and efficacy			PD-L1 positive advanced solid tumors	10	2	12 <sup>d</sup>

(Source: P001, CSR, ISS)

Abbreviations in table: RR=response rate; PFS=progression free survival; OS=overall survival;

IPI=ipilimumab; NSCLC=non-small cell lung cancer

<sup>a</sup>Dosing interval 28 days for cycle 1 for PK analysis and 14 days for cycle 2 and beyond

<sup>b</sup>Randomized

<sup>c</sup> 3 cohorts with separate cycle 1 inpatient dose titration followed by either 2 or 10mg/kg Q3W for cycle 2 and beyond

<sup>d</sup> Enrollment ongoing

<sup>e</sup> Data submitted consisted of SAE line listings only

## 5.2 Review Strategy

The FDA clinical BLA review consisted of two primary clinical reviewers, one primary reviewer of safety and one primary reviewer of efficacy. The primary clinical reviewer of safety was also responsible for synthesis and documentation of the overall conclusions of the application.

The BLA submission contained trial P001, a multicenter, open-label, multi-cohort trial entitled “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 clinical review of efficacy focuses on Part B2, the randomized, dose-comparative activity-estimating cohort of trial P001, in support of the proposed indication, including a detailed review and analysis of data including the clinical study report (CSR), case report forms (CRFs), and datasets in consultation with the FDA statistical review team.

The clinical review of safety focused on the clinical trial safety data from patients (N=89) in Part B2 who received 2mg/kg of MK-3475 every 3 weeks (hereafter referred to in this

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review as Part B2-2q3) with a detailed review and analysis of data including the CSR, CRFs, and datasets. Additional detailed review of safety data in patients with melanoma (N=411) in Parts B1, B2, and D of P001 (hereafter referred to in this review as the Melanoma ISS) was also completed. The safety review was supplemented by a general review of safety data from Parts A and C of trial P001, review of line listings of SAEs from ongoing studies with MK-3475, and review of the safety update provided by the Applicant.

The clinical review of safety and efficacy included the following:

- Review of the current literature on melanoma epidemiology and treatment, including other immune-mediated therapies
- Review of trial P001, including clinical study report, protocol, and protocol amendments
- Review and assessment of Applicant analysis of MK-3475 safety and efficacy in the clinical study report
- Review of datasets submitted as SAS transport files
- Review of patient narratives of serious adverse events and deaths
- Review of minutes of key meetings conducted during MK-3475 development
- Review and assessment of the Module 2 summaries including the Summary of Clinical Efficacy, and Summary of Clinical Safety, Integrated Summary of Efficacy, Integrated Summary of Safety, Risk Management Plan, and proposed labeling for MK-3475
- Review of reviews conducted by other teams including Pharmacology/ Toxicology, Clinical Microbiology, Clinical Pharmacology, Biostatistics, and CMC
- Review of consultation reports of Office of Scientific Investigations
- Requests for additional information from the Applicant and review of Applicant responses
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

### 5.3 Discussion of Individual Studies/Clinical Trials

#### *REVIEWER COMMENT:*

*Information in Section 5.3 of this review is based on protocol P001, Amendment 8, the amendment in effect at the time of data cut-off, and will focus on the melanoma population of the study with additional information included as needed for completeness. A listing of major changes of each amendment is included at the end of the protocol summary.*

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### Clinical Trial Title

Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Cancer (P001)

### Study Sites

The trial was conducted at 17 sites in 4 countries: United States (13), Australia (2), France (1), Canada (1).

### Objectives:

- Primary:
  - To evaluate and characterize the tolerability and safety profile of MK-3475 in adult patients with unresectable advanced carcinoma
  - To evaluate anti-tumor activity of MK-3475 in melanoma and NSCLC
  - To evaluate the extent of tumor response that correlates with the degree of biomarker positivity in the tumors of ipilimumab-naïve patients
  - To evaluate anti-tumor activity per RECIST 1.1 of MK-3475 in unselected melanoma patients refractory to ipilimumab and in melanoma patients refractory to ipilimumab with PD-L1 expressing tumors
  - To evaluate anti-tumor activity per RECIST 1.1 of MK-3475 in patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1
- Secondary:
  - To evaluate the response rate of unselected patients with melanoma refractory to ipilimumab and naïve to ipilimumab, patients with melanoma refractory to ipilimumab and naïve to ipilimumab whose tumors express PD-L1, and patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1, per immune-related response criteria
  - To characterize the PK profile of single agent MK-3475
  - To evaluate target engagement and modulation in peripheral blood (PD-1 receptor occupancy and modulation of receptor activity)
  - To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of MK-3475:
    - To evaluate the correlation between PD-L1 expression levels and anti-tumor activity of MK-3475 in patients with melanoma and NSCLC

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- To investigate other biomarkers (e.g., tumor infiltrating lymphocytes, PD-L2, PD-1; ribonucleic acid (RNA) signature profiles) that may correlate with tumor responses
- To evaluate differences in tumor tissue characteristics in biopsies taken during or post-treatment with MK-3475 versus baseline
- To evaluate response duration, progression-free survival and overall survival of melanoma patients treated with MK-3475
- To evaluate response duration, progression-free survival and overall survival of NSCLC patients who are treated with MK-3475

## Study Design

Trial P001 is an international, multi-center, open-label, dose-escalation study of MK-3475 in patients with advanced solid tumors with expansion cohorts in patients with advanced melanoma and NSCLC (see Table 2).

The study has 5 parts:

- Part A enrolled patients with refractory solid tumors.
  - *Cohort A* was a dose-escalation cohort and patients were treated at dose levels of 1, 3 and 10mg/kg of MK-3475 every 2 weeks in a 3+3 design.
  - *Cohort A1* was a PK expansion cohort at the maximum tolerated dose (MTD) or maximum administered dose in Cohort A.
  - *Cohort A2* was an intra-patient dose escalation cohort and patients received dosing as per the following table:

Cohort	MK-3475 Dose (mg/kg)			
	Day 1	Day 8	Day 22	C2 and beyond Q3W
A2-1	0.005	0.3	2	2
A2-2	0.02	0.3	2	2
A2-3	0.06	1	10	10

- Part B enrolled patients with advanced melanoma.
  - Patients in *Cohort B1* were either naïve or previously treated with ipilimumab and were non-randomly assigned to either 2 or 10mg/kg of MK-3475 either every 2 or 3 weeks.
  - Patients in *Cohort B2* were refractory to ipilimumab (see eligibility criteria below) and were randomized to receive either 2 or 10mg/kg of MK-3475 every 3 weeks.

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- Patients in *Cohort B3* were either naïve, treated or refractory to ipilimumab and were randomized to receive 10mg of MK-3475 every 2 or 3 weeks.
- Part C enrolled patients with advanced NSCLC who were treated with 10mg/kg of MK-3475 every 3 weeks.
- Part D enrolled patients with advanced melanoma who were naïve to ipilimumab treatment. Patients were randomized to receive either 2 or 10mg/kg every 3 weeks.
- Part F is ongoing and is enrolling patients with advanced NSCLC.
  - Patients in *Cohort F1* have NSCLC with high PD-L1 expression and no prior therapy and are randomized to receive 10mg of MK-3475 every 2 or 3 weeks.
  - Patients in *Cohort F2* have received prior therapy and are randomized to receive 10mg of MK-3475 every 2 or 3 weeks.

### Eligibility Criteria (summarized from protocol)

#### Inclusion criteria:

- Disease status:
  - *Part A*: melanoma or any type of carcinoma with progressive metastatic disease, or progressive locally advanced disease not amenable to local therapy.
  - *Part B*: melanoma with progressive locally advanced or metastatic disease not amenable to definitive local therapy with curative intent.
  - **Ipilimumab-naïve patients:**
    - Received no more than two prior systemic treatment regimens for treatment of melanoma.
  - **Ipilimumab-treated patients:**
    - Full resolution of ipilimumab-related adverse events (AEs) (including immune-related AEs) and no treatment for these AEs for at least 4 weeks prior to the time of enrollment.
    - Minimum of 12 weeks from the first dose of ipilimumab and >6 weeks from the last dose.
    - No history of severe immune-related AEs from ipilimumab (CTCAE Grade 4 or CTCAE Grade 3 requiring treatment for >4 weeks).
    - Unequivocal progressive disease (PD) following a dose of ipilimumab.

- **Ipilimumab-refractory patients:**
  - Received at least two doses of ipilimumab (minimum dose of 3 mg/kg).
  - Progressive disease after ipilimumab according to immune-response criteria (irRC).
  - Documented disease progression within 24 weeks of the last dose of ipilimumab.
  - Resolution of ipilimumab related AEs (including irAEs) to Grade 0-1 and  $\leq 10$  mg/day prednisone, or equivalent dose, for irAEs for at least 2 weeks prior to first dose of study drug.
    - No history of severe irAEs from ipilimumab (CTCAE Grade 4 requiring steroid treatment).
    - No history of CTCAE Grade 3 irAEs from ipilimumab requiring steroid treatment ( $>10$  mg/day prednisone or equivalent dose) for  $>12$  weeks.
    - Minimum of 4 weeks from the last dose of ipilimumab.
  - Have had prior treatment regimen that includes vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitors for patients with BRAF V600 mutant melanoma
- *Part C:* advanced or metastatic non-small cell lung cancer (NSCLC).
  - Progression after two prior systemic regimens.
  - Estimated life expectancy of at least 12 weeks.
- *Part D:* melanoma with progressive locally advanced or metastatic disease not amenable to definitive local therapy with curative intent.
  - Naïve to ipilimumab and have not received more than two prior systemic treatment regimens for treatment of melanoma.
- *Part F:* NSCLC.
  - Tumor amenable to biopsy.
  - Known EGFR and ALK translocation status.
  - Tumors that express PD-L1 for randomized patients in F1.
  - No prior systemic treatment and stage IV disease for patients in F1.
  - Progression after at least two prior systemic regimens for patients in F2.
  - PD-L1 positive patients in F2 must have progression after at least one prior systemic regimen, at least one of which must have been a platinum-containing doublet. PD-L1 negative patients in F2 must have received at least two prior lines of systemic therapy.
  - Radiographic progression on most recent prior therapy.

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- Patients who have received > 30 Gy prior thoracic radiation must wait at least 26 weeks before the first dose of MK-3475.
- Patients with a tumor at a critical anatomic location should have that tumor lesion radiated prior to treatment with MK-3475.
- Estimated life expectancy of at least 12 weeks.
- Disease measurement:
  - In Part A of the study, patients may have non-measurable disease.
  - In Parts B, C, D, and F of the study patients must have measurable disease as defined per irRC.
- Male or female ≥18 years of age.
- Performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
- Adequate organ function as indicated by the following laboratory values:

System	Laboratory Value
<b>Hematological</b>	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L <sup>1</sup>
<b>Renal</b>	
Serum creatinine	
<b>Hepatic</b>	
Serum total bilirubin	≤1.5 X upper limit of normal (ULN) ≤ 1.5 X ULN <b>OR</b> Direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN <b>OR</b> ≤ 5 X ULN for patients with liver metastases
<b>Coagulation</b>	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN (Only if not using anticoagulants <sup>2</sup> )
Activated Partial Thromboplastin Time(aPTT)	≤1.5 X ULN (Only if not using anticoagulants <sup>2</sup> )
1 Criteria must be met without a transfusion within 4 weeks of the blood draw 2 If patient is receiving anticoagulants, then value must be within therapeutic range for the condition the patient is being treated for.	

(Source: Protocol P001, Section 2.2, Amendment 8)

- Voluntary written informed consent.
- Agreement to newly obtained tumor biopsy for patients in Parts B, C, D and F.
- Negative urine or serum pregnancy test for female patients of childbearing potential and agreement to acceptable forms of birth control during the study.

### Exclusion criteria:

- Treatment with chemotherapy, radioactive or biological cancer therapy within 4 weeks prior to the first dose of study therapy (1 week for erlotinib, gefitinib, afatinib, or crizotinib), or related AEs that have not recovered to grade 1 or better.

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- Participation in a study of an investigational agent or device within 30 days of administration of MK-3475.
- Requirement for any other form of antineoplastic therapy while on study.
- Medical condition that requires chronic systemic therapy or requires immunosuppressive medication. Patients using physiological replacement doses of hydrocortisone, or its equivalent: up to 20mg hydrocortisone (or 5mg of prednisone) and 10mg hydrocortisone (or 2.5mg prednisone) in the evening, are eligible.
- Risk factors for bowel obstruction or bowel perforation.
- History of other malignancy within the last 5 years. (Exceptions are basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.)
- Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate if clinically stable for at least 4 weeks prior to study entry, have no evidence of new or enlarging brain metastases and are off steroids for at least 7 days from first dose of MK-3475.
- Previous severe hypersensitivity reaction to treatment with another monoclonal antibody.
- History of pneumonitis or interstitial lung disease.
- Active or history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. (Exceptions are vitiligo or resolved childhood asthma/atopy.)
- Prior treatment targeting PD-1: PD-L1 axis or CTLA-4 (with exception of ipilimumab in study Part B and Part C), or previous randomization in any MK-3475 trial.
- Active infection requiring therapy.
- Human Immunodeficiency Virus positivity, active Hepatitis B or Hepatitis C.
- History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate.
- Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial including use of illicit drugs and alcohol abuse.
- Symptomatic ascites or pleural effusion.
- Pregnancy or lactation.

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### Treatment Plan

MK-3475 was administered as a 30 minute IV infusion every 2 or 3 weeks depending on study cohort; the schedule of administration was once every 3 weeks for patients in Part B2. Study therapy for patients in all parts and cohorts continued until progressive disease (PD) (by investigator-assessed irRC for Parts B, C, D, and F and by RECIST 1.1 for Parts A, A1, and A2) or unacceptable toxicity. Tumor assessments were conducted every 8-12 weeks (12 weeks for patients in Parts B and D).

In Parts B, C, D, and F, patients could remain on study following PD as defined by RECIST 1.1 if they were experiencing clinical benefit. Patients were rescanned 4-6 weeks after initial progression in order to confirm progressive disease. The patient was eligible to remain on therapy and resume regularly scheduled imaging if the follow up scan did not confirm PD. The protocol specified that the following minimal requirements should be met in order for patients to remain on therapy following radiographic progression:

- Absence of symptoms and signs indicating clinically significant disease progression
- No decline in ECOG status
- Absence of rapid progression of disease or progressive tumor at critical anatomic sites (e.g. cord compression) requiring urgent medical intervention

Anti-MK-3475 antibodies and fresh or archival tumor specimens were collected for all patients. Detailed pharmacokinetic sampling was conducted for patients in Part A and limited sampling was done in patients in Parts B, C, D and F. Additional pharmacodynamics testing varied according to study cohort.

Toxicities were monitored and graded according to CTCAE version 4.0.

### Dose Modifications and Supportive Care Guidelines

The protocol specified that MK-3475 was to be held for the following drug-related events:

- Non-hematological toxicity  $\geq$ Grade 2, with the exception of Grade 2 fatigue and the adverse reactions listed under requirement of permanent discontinuation of study therapy.
- Grade 4 hematological toxicity

If study-drug-related toxicity did not resolve to Grade 0-1 within 12 weeks, study discontinuation was recommended with the exception of Grade 2 asymptomatic and controlled laboratory adverse events.

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The protocol specified that permanent discontinuation should be considered with the events listed below termed “Adverse Events Warranting Potential Dose Modification”. If patients were able to continue therapy after experiencing one of these reactions, they were to have their dosing interval increased by 1 week. If patients experienced a recurrence of the same SAE upon drug rechallenge, they were to discontinue MK-3475 permanently. If patients experienced the same severe AE, the investigator and sponsor would determine whether the patient would continue on study.

### Adverse Events Warranting Potential Dose Modifications:

- Severe or life-threatening adverse reactions:
  - Grade 4 toxicity (non-hematologic or hematologic)
  - Diarrhea with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, or gastrointestinal perforation
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal
    - For patients with liver metastasis who entered the study with Grade 2 elevation of AST/ALT, MK-3475 should be permanently discontinued if AST/ALT increases  $\geq$  50% relative to baseline and lasts  $\geq$  1 week)
  - Total serum bilirubin >3 times upper limit of normal
  - Steven-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous or hemorrhagic manifestations
  - Severe (i.e., CTCAE Grade 3 or 4) motor or sensory neuropathy, Guillain-Barre syndrome, or myasthenia gravis
  - Severe immune-related adverse events involving any other organs (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
  - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy
  - Grade 4 infusion reaction
  - Grade 2 clinical immune related adverse reactions which persist without improvement for >4 weeks
  - Inability to reduce corticosteroid dose for immune-related adverse events to  $\leq$  10 mg prednisone or equivalent per day

The protocol included specific supportive care guidelines were included in the protocol for infusion reactions, diarrhea, and pneumonitis (see Appendix 9.5).

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A document entitled “MK-3475 Event of Clinical Interest and Immune-Related Adverse Event Guidance Document” was provided to the investigators. Version 1 was provided to investigators in August 2012 and version 2 was provided in June 2013. The designation of adverse events as “Events of Clinical Interest” (ECI) with the current definition (see Appendix 9.6) was not instituted until version 2. Investigators were required to report any Grade 3-5 immune-mediated AE (irAE) as an ECI from version 1.

### **Monitoring Plan**

The monitoring plan and trial evaluations for patients in Part B2 are summarized in Table 3. All patients were followed for at least 30 days after their last dose of study drug or to resolution of toxicity to Grade 0-1, whichever occurred later, or until they initiated a new anti-cancer therapy. Patients who discontinued therapy without documented disease progression were to have imaging at protocol-defined intervals until disease progression, initiation of a new anti-cancer therapy, or death.

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**Table 3: Schedule of assessments in Protocol 001 for patients in Part B2**

<b>Part B: 3 Week Schedule</b>															
	Screening <sup>1</sup> (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
<b>Study Procedures</b>															
Informed Consent <sup>2</sup>	X														
Informed Consent for Future Biomedical Research (optional)	X														
Inclusion/Exclusion Criteria	X														
Demographics/Medical History/ Prior Medications <sup>3</sup>	X														
Vital Signs/Weight <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG <sup>5</sup>	X	X					X								
Review Adverse Events <sup>6</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential <sup>7</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel <sup>7</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters <sup>8</sup>	X														
Urinalysis <sup>7</sup>	X	X			X			X			X			X	X

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Pregnancy Test - Urine or Serum $\beta$ -HCG <sup>9</sup>	X														
Thyroid Function <sup>10</sup>		X	X		X		X		X		X				X <sup>10</sup>
Immunoglobulins <sup>11</sup>		X	X		X		X		X		X				X <sup>11</sup>
Auto-Antibodies <sup>12</sup>		X	X		X		X		X		X				X <sup>12</sup>
Anti-MK-3475 Antibodies <sup>13</sup>		X	X			X				X				X	X <sup>13</sup>
Pharmacokinetics <sup>14</sup>		X	X			X				X				X	X <sup>14</sup>
Lymphocyte Subtyping (FACS) <sup>15</sup>		X	X	X	X										
HIV, Hepatitis B and C <sup>16</sup>	X														
Proteomics and RNA Signature Profiling in Blood <sup>17</sup>		X	X	X		X		X							
BRAF Testing <sup>22</sup>	X														
Human leukocyte antigen (HLA) <sup>24</sup>		X													
Blood for Future Biomedical Research <sup>23</sup> (optional)		X													
<b>Efficacy Measurements</b>															
Tumor Imaging <sup>18</sup>	X					X <sup>18</sup>				X <sup>18</sup>				X <sup>18</sup>	X <sup>18</sup>
<b>Drug Administration</b>															
Study Drug Administration (30 min infusion)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Tumor Biopsies</b>															
Newly Obtained Tumor Biopsies <sup>20</sup>	X					X <sup>20</sup>				X <sup>20</sup>					
Archival Tumor Tissues <sup>21</sup>	X														

- 1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
- 2 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
- 3 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
- 4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
- 5 Electrocardiogram (12-lead ECG) should be performed at Screening, at the time of PK blood collection for PK (C<sub>max</sub>) within 30 minutes after the end of the first infusion of MK-3475, post dose at Cycle 6, and at the mandatory Safety Follow-up visit
- 6 Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. Study site should contact the patient mid-cycle (approximately 10 days post-dose) to assess for potential irAEs.

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- 7 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 36, urinalysis should be performed every 9 weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.
- 8 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
- 9 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.
- 10 Analysis of T3, FT4 and TSH will be performed by a central laboratory. Following Cycle 2, testing will be performed every other cycle.
- 11 Analysis of IgG and IgM will be performed by the local study site laboratory. Following Cycle 2, testing will be performed every other cycle.
- 12 Collected prior to dosing in Cycle 1 and Cycle 2, and then in every other subsequent cycle. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of  $\geq 40$ ), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.
- 13 Blood for anti-MK-3475 antibodies should be collected in Cycles 1, 2, 5, 9 and 13. Subsequently, testing should be performed approximately every 12 weeks for the first 12 months on the study, and approximately every 6 months thereafter. All samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for C<sub>trough</sub>.
- 14 Procedures for collection of samples are described in the Procedures Manual. Peak and trough samples will be collected at Cycles 1 and 2. A trough sample should be collected at Cycle 5. Subsequently, trough samples should be collected approximately every 12 weeks for the first 12 months on the study, then approximately every 6 months thereafter. All trough samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. The two peak samples in Cycles 1 and 2 should be drawn within 30 minutes after the end of the infusion.
- 15 Collected before start of infusion. FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.
- 16 Testing will be performed by the local laboratory at Screening. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies.
- 17 Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory.
- 18 Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 30 days prior to enrollment. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5) (see Section 2.4.1). Tumor imaging will be performed approximately every 12 weeks (or whenever clinically indicated) while the patient remains on study therapy regardless of Cycle/Day. Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. Refer to Section 3.3.1.3 of the protocol for additional information. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.
- 19 Ipilimumab-refractory patients must send pre-trial scans confirming investigator-determined PD (according to irRC) to the central imaging vendor. Details are provided in the Procedures Manual.
- 20 A newly obtained biopsy of at least one tumor lesion is mandatory at baseline (prior to Cycle 1/Day 1). A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1). Additional biopsy samples approximately at Week 12, Week 24, and at disease progression are highly desirable. When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions). Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator. The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling), but not artificially decrease the longest diameter of the lesion. Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.
- 21 Collection of archival tumor tissue for purpose of biomarker analysis is strongly encouraged. For patients enrolled with Amendment 07 and 08, collection of archival tumor tissue is mandatory and samples from fine needle aspiration will not be acceptable. An archival specimen is mandatory to be submitted within 3 weeks from the day a patient signs informed consent. Patients who do not have an archival specimen can only be enrolled after discussion with the sponsor. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

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- 22 Required at screening for patients without documented BRAF status. Analysis will be performed by a central laboratory.
  - 23 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.
  - 24 Collected in patients enrolled with Amendment 06, 07 and 08.
- (Source: Reproduced from Protocol P001, Amendment 8, Study flow chart for patients in B2)

## Statistics and Analysis Plan

The primary endpoint of Part B2 is tumor response rate (RR) as measured by RECIST 1.1 by blinded independent central review (BICR). Secondary endpoints include RR by immune-response criteria (irRC) by investigator, disease control rate (DCR), response duration and progression free survival (PFS) by RECIST and irRC, and overall survival (OS).

The following populations were defined for the analysis:

- All patients as treated (APaT) consists of all patients who received at least one dose of study treatment.
- Full analysis set (FAS) consists of patients with measurable disease at baseline who received at least one dose of study treatment.

The protocol states that the primary efficacy analysis will be based on the FAS population and all safety analyses and secondary efficacy analyses of PFS and OS will be based on the APaT population.

### Sample size calculations for RR in part B2:

The protocol states that with 80 ipilimumab-refractory patients at each dose level, Part B2 study has approximately 85% (or 96%) power to detect a 15% (or 20%) difference in RR between the two doses at the 10% type I error rate (one-sided) when the RR in the inferior arm is 10%. There are no historical data of the response rate of chemotherapies in patients who are refractory to ipilimumab; however, response rate of chemotherapies ranged from 5% to 10% in three recently completed phase 3 studies (ipilimumab in 1st line melanoma patients, and trametinib and vemurafenib in patients with BRAF V600E mutation). Therefore, the Applicant stated that it is reasonable to use 10% as the null hypothesis for testing the anti-tumor activity of MK-3475 against putative chemotherapies in this population. With 80 patients treated at a dose level, the study has 93% power to reject the null hypothesis at a type I error rate of 2.5% (one-sided) when the true response rate of MK-3475 is 25%. A p-value of 2.5% approximately corresponds to a 19% empirical response rate when sample size is 80.

Tumor response was assessed using radiographic and clinical data. Radiographic assessment was performed every 12 weeks while patient remains on study, with repeat imaging required approximately four weeks later for confirmation of response or progression. Radiographic modalities included CT scan and MRI.

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### Blinded Independent Central Review

The ORR primary endpoint was evaluated by BICR per RECIST version 1.1. The BICR comprises an independent radiology and oncology review, consisting of a minimum of three board-certified radiologists and one oncologist. As stated in the independent review charter, all patients underwent a primary radiology review by one independent radiologist (single read) according to RECIST 1.1 using the study imaging data to determine overall tumor response at each timepoint, and as directed by the Applicant, patients might have had a review by two radiologists (double read).

Following complete review by radiologists, each radiologist conducted a global assessment of response at all time points. If a disagreement arose between the two radiologists, the radiologic response assessment underwent adjudication by a third independent radiologist, who then selected the best representative assessment for the independent oncologist to review. In cases in which no adjudication was performed, the measurements from the first radiology read were submitted to the BLA.

For the last step of the independent review, a single independent oncologist assigned a response assessment for all patients in Part B2, after evaluating the data from the independent radiology review and available clinical data. Clinical data may have consisted of cytology and/or histology reports, clinical lesion reports, physical examination reports of palpable lesions, on-study intervention, such as surgery or palliative care, clinically assessed photographs and/or photography reports, and other relevant clinical data as determined by the Applicant.

#### REVIEWER COMMENTS:

- *FDA stated during the pre-BLA meeting that the primary efficacy analysis should be based on the APaT population and that efficacy analyses using the FAS population could be submitted as supportive analyses.*
- *In response to FDA information request received on May 8, 2014, the Applicant stated that all patients in cohorts Part B1, B2, and D were subjected to a double read and only patients in cohort Part A had a single read. In a follow-up response to the FDA information request received May 27, 2014, the Applicant stated that the purpose for the double read was to have a more robust approach for assessing response by independent radiology review.*
- *According to the Applicant's response to FDA information request received on March 21, 2014, the independent radiology review required adjudication in 91 (53%) patients in Part B2; 46 (51%) patients in the 2 mg/kg arm, and 45 (54%) patients in the 10 mg/kg arm.*

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### Protocol Amendments

The Applicant submitted 8 amendments to protocol P001. Key changes in each amendment were as follows:

- Amendment 1 (February 9, 2011):
  - Revision of DLT criteria as per FDA recommendations during initial review
- Amendment 2 (September 12, 2011):
  - Revision of Part B of the study to characterize the safety profile of MK-3475 at the recommended dose from Part A and evaluate the anti-tumor activity of MK-3475 in patients with melanoma. Protocol was revised to increase the sample size in Part B from 14 to 66 and limit enrollment to only patients with unresectable melanoma
- Amendment 3 (March 2, 2012):
  - Revision to Part A by adding 12 additional patients for additional PK characterization in an intra-patient dose-escalation cohort
  - Revision of Part B to increase sample size from 66 to 116 patients
  - Add Part C with 35 patients with NSCLC
- Amendment 4 (April 5, 2010):
  - Revision to guidelines for when study therapy should be held based on FDA recommendations (from Grade 3 non-hematologic toxicity to all drug-related non-hematologic toxicity greater than or equal Grade 2)
- Amendment 5 (August 13, 2012):
  - Revision of Part B to add 60 patients with melanoma who are ipilimumab-refractory
  - Addition of Part D with 88 patients with melanoma
  - Addition of Part E with 112 patients with NSCLC
- Amendment 6 (November 20, 2012):
  - Revision to Part B to add 100 patients with melanoma who are ipilimumab-refractory
  - Revision to Part E to increase sample size to 146
  - Addition of Part F with 120 patients with NSCLC
- Amendment 7 (March 29, 2013):
  - Revision of Part B to add 230 ipilimumab-naïve, treated or refractory patients
  - Remove Part E based on FDA comments to open a separate protocol for these patients.
  - Revision to Part F to include 270 patients with NSCLC

- Amendment 8 (August 2, 2013):
  - Primary measure for assessment of tumor response changed to RECIST 1.1 by blinded central review from investigator-assessed response by immune-related response criteria (irRC) based on FDA comments that response based on irRC is not a recognized regulatory endpoint.
  - Additional 20 biomarker negative patients added to Cohort F2.

## 6 Review of Efficacy

### Efficacy Summary

The BLA submission contained data from Trial P001, entitled “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 is an international, multicenter, open-label trial consisting of multiple cohorts including a dose-escalation evaluation of MK-3475 in patients with advanced solid tumors and expansion cohorts to estimate the anti-tumor activity of MK-3475 in patients with non-small cell lung cancer and melanoma. In support of the proposed indication, the efficacy review focuses on Part B2 of Trial P001, a randomized, dose comparative, activity-estimating cohort in patients with ipilimumab-refractory, unresectable or metastatic melanoma.

The original design of Part B2 was a randomized (2:1) trial of MK-3475 administered at two doses to 60 patients (40 patients at a dose of 2 mg/kg Q3W and 20 patients at a dose of 10 mg/kg Q3W). The randomization schema was modified to achieve a final 1:1 randomization, and the sample size in Part B2 was increased to add 100 IPI-refractory patients (total of 160 patients). The primary endpoint was confirmed, objective response rate (ORR) as assessed by blinded independent central review (BICR) using RECIST v. 1.1.<sup>i</sup> The immune-related Response Criteria (irRC) was used by the investigator to guide patient management on the trial, e.g., treatment discontinuation based on disease progression, and to determine overall response as a secondary endpoint of the trial.<sup>ii</sup>

The results in Part B2 showed that the ORR was 23.6% (95%CI: 15.2, 33.8) in the 2 mg/kg arm Q3W (hereafter referred as Part B2-2q3) and 23.8% (95% CI: 15.2, 34.3) in the 10 mg/kg arm Q3W (hereafter referred as Part B2-10q3) by BICR using RECIST v. 1.1. The median duration of response was not reached in both arms [range (1.4+, 8.5+ months) in the 2 mg/kg arm and (2+, 9+ months) in the 10 mg/kg arm)]. Responses were ongoing in 86% in the 2 mg/kg arm and 90% in the 10 mg/kg arm. Twenty-one patients in the 2 mg/kg arm had an objective response, and of these, three had progression of disease. The duration of responses among the remaining 18 patients ranges from 1.4+ to 8.5+ months, which includes eight patients with ongoing responses of 6 months or longer. Similar results were observed in the 10 mg/kg arm.

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Analyses of tumor response and duration of response based on a blinded radiologic review committee (excludes assessment by the independent oncologist) and on a different tumor response criteria (irRC) were supportive of the primary ORR analysis. The BICR-assessed median PFS per RECIST v. 1.1 was 5.5 months (95% CI: 3.0, 9.0) in the 2 mg/kg arm and 3.5 months (95% CI: 3.0, 6.0) in the 10 mg/kg arm [HR was 0.84 (95% CI: 0.57, 1.23, p-value=0.36)]. The median OS was 13 months (95% CI: 10.3, not reached) in the 2 mg/kg arm and not reached (NR) in the 10 mg/kg arm (95% CI: NR, NR) [HR 1.04, (95% CI: 0.6, 1.82), p=0.88].

The treatment effect of MK-3475 in Part B2 appeared consistent across all subgroups in the exploratory subgroup analyses of ORR based on demographics and baseline disease characteristics. In addition, objective responses were reported in patients with and without BRAF V600 mutations. Similar ORRs were observed and objective responses remained durable in other cohorts of P001 with a longer duration of follow-up (exceeding one year)—cohorts consisting of an ipilimumab-naïve and prior ipilimumab treated population of patients with unresectable and metastatic melanoma who received MK-3475 at three dosage regimens (2mg/kg q3w, 10 mg/kg q3w, and 10 mg/kg q2w). The percentage of patients with an ongoing response in Parts B1 and D are similar to that observed in Part B2.

### 6.1 Indication

The Applicant proposes the following indication for the MK-3475 label:

“KEYTRUDA® is indicated for the treatment of patients with (b) (4) melanoma with progressive (b) (4) metastatic disease.”

#### 6.1.1 Methods

The Applicant submitted data from Trial P001, a multicenter, open-label, randomized (1:1), dose-comparative, activity-estimating trial in patients with advanced solid tumors with expansion cohorts in patients with non-small cell lung cancer and melanoma to estimate the anti-tumor activity of MK-3475, as described in detail in Section 5.3. The primary population for the efficacy data is based on Part B2 of trial P001, a randomized, dose comparative, activity-estimating cohort in patients with ipilimumab-refractory, unresectable or metastatic melanoma.

The efficacy analysis set consisted of all patients-as-treated (APaT) population, defined by the Applicant as all subjects who received at least one dose of MK-3475 in Part B2. Categorization of patients in the treatment arms was based on the dose of MK-3475

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administered to the patient (2 mg/kg or 10 mg/kg). There were 173 patients in the APaT population, with 89 patients in the 2 mg/kg arm and 84 patients in the 10 mg/kg arm. Tumor response, using imaging modalities and clinical data, was assessed every 12 weeks until disease progression.

A retrospective BICR, which consisted of a combined independent radiology (with adjudication for radiology) and oncology review using RECIST v. 1.1 to evaluate tumor response, was implemented in Amendment 8 of the protocol to support Part B2 as a potential registration trial.

### *REVIEWER COMMENT:*

*According to Applicant's response to FDA information request received on March 21, 2014, the independent radiology review required adjudication in 91 (53%) patients, 46 (51%) patients in the 2 mg/kg arm, and 45 (54%) patients in the 10 mg/kg arm.*

### 6.1.2 Demographics

Patients could enroll in Part B2 of the Trial P001, provided that they had ipilimumab-refractory disease, defined by the Applicant as:

- Received at least two doses of ipilimumab (minimum dose of 3 mg/kg).
- Progressive disease after ipilimumab according to irRC. The initial evidence of PD confirmed by a second assessment, no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression (this evaluation based on investigator assessment; Applicant collection of imaging scans for retrospective analysis). Initial date of PD documentation considered as the date of disease progression.
- Documented disease progression within 24 weeks of the last dose of ipilimumab. Patients re-treated with ipilimumab and patients on maintenance ipilimumab allowed to enter the trial as long as there is documented PD within 24 weeks of the last treatment date (with ipilimumab).
- Resolution of ipilimumab-related AEs (including irAEs) to Grade 0-1 and requirement of  $\leq 10$  mg/day prednisone or equivalent dose for irAEs for at least two weeks prior to first dose of study drug.
- No history of severe irAEs from ipilimumab CTCAE Grade 4 requiring steroid treatment.
- No history of CTCAE Grade 3 irAEs from ipilimumab requiring steroid treatment ( $>10$  mg/day prednisone or equivalent dose)  $>12$  weeks.
- Minimum of 4 weeks (wash out period) from the last dose of ipilimumab.
- Patients with BRAF V600 mutant melanoma must have had a prior treatment regimen that includes vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitors.

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- Patient must have progressive disease after the most recent treatment regimen. Subsequent to the initial BLA submission, the Applicant provided updated data on May 13 and 30, 2014, and June 4 and 12, 2014, in response to FDA information requests to clarify missing and/or incorrect information to define ipilimumab-refractory disease for 20% of patients in Part B2, including prior ipilimumab dose, number of doses, and missing dates of last dose and dates of progression. An analysis of the proportion of patients meeting each criterion in the definition of ipilimumab-refractory disease based on the corrected information is displayed in **Table 4** below.

**Table 4: Patients Meeting the Applicant’s Criteria to Define Ipilimumab-Refractory Melanoma, APaT Population, Part B2**

Requirement	2 mg/kg Q3W n (%)	10 mg/kg Q3W n (%)	Comment
<b>All Patients</b>	<b>N=89</b>	<b>N=84</b>	
Received at least two doses of ipilimumab (minimum dose of 3 mg/kg).	89 (100)	84 (100)	None
Progressive disease after ipilimumab will be defined according to irRC. The initial evidence of PD is to be confirmed by a second assessment, no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression (this evaluation is based on investigator assessment; Sponsor will collect imaging scans for retrospective analysis). Once PD is confirmed, initial date of PD documentation will be considered as the date of disease progression.	86 (97)	81 (96)	<p>All (100%) patients, in the absence of rapid clinical progression, had 2nd assessments confirming initial evidence of disease progression.</p> <p>Of 173 patients, the interval between 1st and 2nd assessment was a few days shorter than 4 weeks in 6 patients, the Applicant did not consider this difference clinically meaningful; therefore, did not query the site to see if the scans were performed due to rapid clinical progression.</p> <p>While the Applicant considered the difference in the interval clinically insignificant for these patients, they are included in the columns to the left</p> <p>The patients with scans of &lt; 28 days were:  <u>2 mg/kg arm</u>            0010000254, 27 days</p>

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Requirement	2 mg/kg Q3W n (%)	10 mg/kg Q3W n (%)	Comment
			<p>0021000292, 25 days 0021000324, 25 days</p> <p><u>10 mg/kg arm</u> 0019000351, 24 days 0021000288, 23 days 0018000409, 21 days</p> <p>In addition, six patients had rapid clinical progression; therefore, no imaging was performed to confirm progression prior to enrollment:</p> <p><u>2 mg/kg arm</u> 0016000313 0021000287 0001000284 0015000331</p> <p><u>10 mg/kg arm</u> 0015000360 0019000278</p> <p>The Applicant considered these patients to have met the criterion based on documented rapid clinical progression.</p>
<p>Documented disease progression within 24 weeks of the last dose of ipilimumab. Patients who were re-treated with ipilimumab and patients who were on maintenance ipilimumab will be allowed to enter the trial as long as there is documented PD within 24 weeks of the last treatment date (with ipilimumab).</p>	88 (99)	83 (99)	<p>All patients except 2 experienced disease progression within 24 weeks of the last dose of ipilimumab (Patients 0015000336* on the 2mg/kg arm and 0020000293* on the 10 mg/kg arm).</p> <p>The sponsor previously reported 0020000293 in the protocol deviation response submitted May 13th as a follow-up BLA FDA request of March 26, 2014 submission response of April 10th.</p>

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Requirement	2 mg/kg Q3W n (%)	10 mg/kg Q3W n (%)	Comment
			0015000336 was reported in the May 30 <sup>th</sup> response to the May 8th FDA request Note that Patient 0021000378 had progressive disease exactly 168 days after last dose and therefore is considered meeting eligibility criteria.
Resolution of ipilimumab related AEs (including irAEs) back to Grade 0-1 and ≤10 mg/day prednisone or equivalent dose for irAEs for at least two weeks prior to first dose of study drug.	89 (100)	84 (100)	Confirmation that all patients on steroids at the time of study entry were receiving ≤10 mg/day prednisone or equivalent dose.
No history of severe irAEs from ipilimumab CTCAE Grade 4 requiring steroid treatment.	89 (100)	84 (100)	
No history of CTCAE Grade 3 irAEs from ipilimumab requiring steroid treatment (>10 mg/day prednisone or equivalent dose) >12 weeks.	89 (100)	84 (100)	
Minimum of four weeks (wash out period) from the last dose of ipilimumab.	89 (100)	84 (100)	
Patient must have progressive disease after the most recent treatment regimen.	89 (100)	84 (100)	The reviewer identified 12 patients with either missing or unclear information; the Applicant updated the information for these patients after querying study sites and all patients had documented disease progression after the most recent treatment regimen. These patients were <u>2 mg/kg arm</u> 0016000362 0019000407 0020000322 0021000352

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Requirement	2 mg/kg Q3W n (%)	10 mg/kg Q3W n (%)	Comment
			10 mg/kg arm 0012000423 0015000271 0016000368 0018000300 0019000350 0019000367 0020000372 0021000312
<b>BRAF V600 Mutation Positive Subgroup</b>	<b>N=12</b>	<b>N=18</b>	
Patients with BRAF V600mutant melanoma must have had a prior treatment regimen that includes vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitors.	12 (100)	18 (100)	The BRAF mutation status of patient 0013000275 (10 mg/kg arm) was entered incorrectly. The database has been updated with the correct status, i.e., BRAF wild-type melanoma.

Source: Response to FDA information request received June 12, 2014. Comment=Applicant's response.

\* Patient numbers.

**REVIEWER COMMENT:**

*The Applicant's explanations to FDA's information request, with regard to the criteria for ipilimumab-refractory disease appear to clarify the discrepancies. Although some patients did not meet the <28 day-window for second assessments confirming initial evidence of disease progression, the explanations appear reasonable.*

A total of 173 ipilimumab-refractory patients were treated with MK-3475, with 89 patients in the 2 mg/kg arm and 83 patients in the 10 mg/kg arm in Part B2 of the trial. Overall, the demographics for the efficacy analysis population were well-balanced between the two treatment arms as shown in **Table 5**, except a greater proportion of males were enrolled in the 10 mg/kg arm (67%), compared to the 2 mg/kg arm (54%). The majority of the patients were younger than 65 years of age (67% and 61%), predominantly White (>96% in both arms), and enrolled in the United States (79% and 85%). At the time of enrollment, the majority of patients had an ECOG PS of 0 (66% in the 2 mg/kg, 69% in the 10 mg/kg), M1c disease (74% and 67%), no prior history of brain metastases (91% and 89%), and normal LDH (55% and 65%). Thirteen percent of patients in the 2 mg/kg arm and 22% in the 10 mg/kg arm had a BRAF V600 mutation. All patients received treatment with ipilimumab prior enrolling into the trial, and five patients received ipilimumab as adjuvant therapy, one in the 2 mg/kg arm and four in the 10 mg/kg arm. All patients, except for one, who had a BRAF V600 mutation were

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treated with a BRAF inhibitor with or without a MEK inhibitor—two patients in the 2 mg/kg arm and three patients in the 10 mg/kg arm were treated with the combination of a BRAF inhibitor and MEK inhibitor. Four patients (001000394 and 0001000401 in the 2 mg/kg arm and 0012000385, and 0018000300 in the 10 mg/kg arm) who were BRAF V600-wild-type/normal were treated with a single-agent MEK inhibitor.

**Table 5** summarizes the demographics and baseline disease characteristics of patients randomized to Part B2 of the Trial P001.

**Table 5: Demographics and Baseline Characteristics, Part B2**

	MK-3475 2 mg/kg Q3W N=89 n (%)	MK-3475 10 mg/kg Q3W N=84 n (%)	All N=173 n (%)
<b>Gender</b>			
Female	41 ( 46)	27 ( 32)	68 ( 39)
Male	48 ( 54)	57 ( 65)	105 ( 61)
<b>Age</b>			
Median, years	59	63	61
Range, years	18-88	27-86	18-88
<65	59 ( 66)	51 ( 62)	110 ( 64)
>=65	30 ( 23)	32 ( 38)	62 ( 36)
<75	82 ( 92)	73 ( 87)	155 ( 90)
>=75	7 ( 8)	11 ( 13)	18 ( 10)
<b>Countries</b>			
Australia	6 ( 7)	4 ( 5)	10 ( 6)
Canada	5 ( 6)	9 ( 11)	15 ( 9)
France	8 ( 9)	9 ( 11)	17 ( 10)
United States	70 ( 79)	62 ( 74)	132 ( 76)
<b>Race</b>			
White	87 ( 98)	81 ( 96)	168 ( 97)
Asian	1 ( 1)	2 ( 2)	3 ( 2)
Multiracial	0	1 ( 1)	1 ( 1)
Black or African American	1 ( 1)	0	1 ( 1)
<b>ECOG PS</b>			
0	59 ( 66)	57 ( 69)	116 ( 67)
1	30 ( 34)	27 ( 32)	57 ( 33)
<b>BRAF mutation subtype<sup>S</sup></b>			
Mutant	12 ( 13)	19 ( 23)	31 ( 18)
Wild-type	77 ( 87)	66 ( 79)	143 ( 83)
<b>LDH<sup>T</sup></b>			
Elevated	39 ( 44)	29 ( 35)	68 ( 42)
Normal	49 ( 55)	54 ( 65)	104 ( 56)
Unknown	1 ( 1)	0	1 ( 1)
<b>Disease stage<sup>T</sup></b>			

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	MK-3475 2 mg/kg Q3W N=89 n (%)	MK-3475 10 mg/kg Q3W N=84 n (%)	All N=173 n (%)
M1a	7 ( 8)	11 ( 13)	18 ( 10)
M1b	16 ( 18)	15 ( 18)	31 ( 18)
M1c	66 ( 74)	56 ( 67)	122 ( 71)
Mx	1 ( 1)	1 ( 1)	2 ( 1)
Unknown	0	1 ( 1)	1 ( <1)
<b>Brain metastases</b>			
Yes	7 ( 8)	8 ( 10)	15 ( 9)
No	81 ( 91)	75 ( 89)	156 ( 90)
Unknown	1 ( 1)	1 ( 1)	2 ( 1)
<b>Measureable disease by IRC*</b>			
With measureable disease	81 ( 91)	76 ( 90)	157 ( 91)
Without measureable disease	8 ( 9)	8 ( 10)	16 ( 9)
<b>Prior regimens for advanced or metastatic disease</b>			
1	29 ( 32)	19 ( 23)	48 ( 28)
2	31 ( 35)	34 ( 40)	65 ( 38)
3 or more	29 ( 33)	31 ( 37)	60 ( 35)
<b>Prior ipilimumab</b>			
Yes	89 (100)	84 (100)	173 (100)
Adjuvant	1 (1)	4 ( 5)	5 ( 3)
Retreatment <sup>a</sup>	7 ( 8)	11 ( 3)	18 ( 10)
<b>Prior chemotherapy regimens</b>			
Yes	39 ( 44)	41 ( 49)	80 ( 46)
No	50 ( 56)	43 ( 51)	93 ( 54)
Adjuvant		4 ( 5)	5 ( 3)
<b>Prior BRAF/MEK inhibitor*</b>			
Yes <sup>b</sup>	12 ( 16)	18 ( 24)	34 ( 20)
BRAF inhibitor only	11 ( 12)	18 ( 24)	29 ( 35)
BRAF inhibitor and MEK inhibitor	2 ( 2)	3 ( 4)	5 ( 3)
MEK inhibitor only	2 ( 2) <sup>c</sup>	2 ( 2) <sup>c</sup>	4 ( 2)
No	75 ( 84)	64 ( 76)	139 ( 80)
<b>Prior immunotherapy<sup>d</sup></b>			
Yes	27 ( 30)	26 ( 31)	53 ( 31)
No	62 ( 70)	58 ( 69)	120 ( 69)

<sup>a</sup> Required at screening for patients without documented BRAF status.

<sup>†</sup> LDH=lactate dehydrogenase

<sup>‡</sup> Based on response to FDA information request received on June 4, 2014.

\* IRC=independent review committee consists of radiology assessment only, no oncology assessment; retrospective analysis.

<sup>a</sup> Patients in both arms were retreated twice with ipilimumab, except for two patients, one in each arm, were retreated three times with ipilimumab.

<sup>b</sup> Patients may have been counted more than once for type of treatment.

<sup>c</sup> Patients had BRAF V600 wild-type.

<sup>d</sup> Does not include prior ipilimumab treatment.

Source: ADSL.xpt and DM.xpt

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### REVIEWER COMMENTS:

1. *In terms of satisfying the eligibility criteria of locally advanced or metastatic disease at time of enrollment, initial review of the data revealed that 24 patients were classified as having M0 disease, and the status of metastatic disease was unknown in four patients. FDA requested clarification of these patients and in a response received on June 4, 2014, the Applicant stated that although the patients were classified as M0, all had metastatic disease due to sites incorrectly entering staging at the time of diagnosis rather than enrollment, as shown in Table 5. The Applicant used the investigator's baseline imaging assessments as evidence of metastatic disease at time of study enrollment. Overall, slightly more than two-thirds of the patients had M1c disease in both arms, with more patients with M1c disease allocated to the 2 mg/kg arm.*
2. *One patient who was positive for the BRAF V600 mutation did not receive prior treatment with a BRAF- or MEK-inhibitor. This constitutes a protocol violation, per eligibility criteria.*
3. *Four patients, two patients in each arm, with BRAF wild-type normal subtype were received prior treatment with trametinib.*
4. *Retrospective evaluation of PD-L1 expression in the patient's tumor tissue was determined in Part B2 cohort and was not included in the BLA submission.*

**Table 6** summarizes the prior anti-cancer therapy received by patients randomized in Part B2. Per inclusion criteria, all patients were previously treated with ipilimumab. All patients in both treatment arms had received prior anti-cancer therapy. One patient, 0019000252, in the 10 mg/kg arm, received an investigational anti-CTLA-4 monoclonal antibody, tremelimumab, in addition to ipilimumab, prior to study entry. The treatment with tremelimumab preceded ipilimumab treatment.

**Table 6: Prior Anti-cancer Therapy**

Therapy	MK-3475 2 mg/kg N=89 (%)	MK-3475 10 mg/kg N=84 (%)	Total N=173 (%)
ipilimumab	89 (100)	84 (100)	173 (100)
interferon alfa	22 (25)	18 (21)	40 (23)
temozolomide	20 (22)	16 (19)	36 (21)
aldesleukin	14 (16)	12 (14)	26 (15)
dacarbazine	11 (12)	14 (17)	25 (14)
paclitaxel	11 (12)	17 (20)	28 (26)
vemurafenib	9 (10)	18 (22)	27 (16)
antineoplastic (unspecified)	7 (8)	8 (10)	15 (9)
carboplatin	8 (9)	16 (19)	24 (14)
bevacizumab	5 (6)	3 (4)	8 (5)
cisplatin	5 (6)	5 (6)	10 (6)
dabrafenib	4 (4)	1 (1)	5 (3)

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Therapy	MK-3475 2 mg/kg N=89 (%)	MK-3475 10 mg/kg N=84 (%)	Total N=173 (%)
trametinib	4 (4)	3 (4)	7 (4)
vinblastine sulfate	3 (3)	5 (6)	8 (5)
afuresertib	2 (2)	0	2 (1)
fotemustine	2 (2)	5 (6)	7 (4)
granulocyte-macrophage colony stimulating factor (unspecified)	2 (2)	5 (6)	7 (4)
L-001948211	2 (2)	0	2 (1)
anti-CD248 monoclonal antibody (unspecified)	1 (1)	0	1 (<1)
anti-TWEAK monoclonal antibody (unspecified)	1 (1)	1 (1)	2 (1)
axitinib	1 (1)	0	1 (<1)
buparlisib hydrochloride (+) mitogen-activated protein kinase kinase inhibitor (unspecified)	1 (1)	0	1 (<1)
cancer ganglioside GD2 GM2 conj vaccine (keyhole limpet hemocyanin)	1 (1)	0	1 (<1)
cancer gp100 peptide vaccine	1 (1)	0	1 (<1)
cyclophosphamide	1 (1)	3 (4)	4 (2)
denenicokin	1 (1)	1 (1)	2 (1)
fludarabine phosphate	1 (1)	1 (1)	2 (1)
fluorouracil	1 (1)	0	1 (<1)
gamma-secretase inhibitor (unspecified)	1 (1)	0	1 (<1)
gemcitabine	1 (1)	1 (1)	2 (1)
hydroxychloroquine sulfate	1 (1)	0	1 (<1)
imatinib mesylate	1 (1)	1 (1)	2 (1)
imiquimod	1 (1)	0	1 (<1)
mitogen-activated protein kinase kinase inhibitor (unspecified)	1 (1)	0	1 (<1)
ontuxizumab	1 (1)	2 (2)	3 (2)
panobinostat	1 (1)	0	1 (<1)
PI3 kinase inhibitor (unspecified)	1 (1)	2 (2)	3 (2)
pimasertib	1 (1)	0	1 (<1)
raf kinase B inhibitor (unspecified)	1 (1)	0	1 (<1)
sargramostim	1 (1)	3 (4)	4 (2)
selumetinib	1 (1)	0	1 (<1)
talimogene laherparepvec	1 (1)	0	1 (<1)
temsirolimus	1 (1)	0	1 (<1)
tumor infiltrating lymphocytes [composition unspecified]	0	1 (1)	1 (<1)
BCG vaccine	0	1 (1)	1 (<1)
bortezomib	0	1 (1)	1 (<1)
cancer DD-CD/SMR vaccinia vaccine	0	1 (1)	1 (<1)
carmustine (+) cisplatin (+) dacarbazine (+) tamoxifen citrate	0	1 (1)	1 (<1)
celecoxib	0	1 (1)	1 (<1)
cobimetinib	0	2 (2)	2 (1)
cyclin dependent kinase inhibitor (unspecified)	0	1 (1)	1 (<1)
dendritic cell vaccine (unspecified)	0	2 (2)	2 (1)
doxorubicin	0	1 (1)	1 (<1)

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Therapy	MK-3475 2 mg/kg N=89 (%)	MK-3475 10 mg/kg N=84 (%)	Total N=173 (%)
immunotherapy (unspecified)	0	1 (1)	1 (<1)
leflunomide	0	1 (1)	1 (<1)
lenvatinib	0	2 (2)	2 (1)
leuprolide acetate	0	1 (1)	1 (<1)
naltrexone	0	1 (1)	1 (<1)
nilotinib	0	1 (1)	1 (<1)
pemetrexed disodium	0	1 (1)	1 (<1)
platinum	0	1 (1)	1 (<1)
poly(ADP-ribose) polymerase inhibitor (unspecified)	0	1 (1)	1 (<1)
sorafenib	0	1 (1)	1 (<1)
tamoxifen citrate	0	1 (1)	1 (<1)
tesetaxel	0	1 (1)	1 (<1)
tremelimumab	0	1 (1)	1 (<1)
vascular endothelial growth factor trap (unspecified)	0	1 (1)	1 (<1)
verubulin hydrochloride	0	1 (1)	1 (<1)

Source: DM.xpt, CM.xpt, SUPPDM.xpt

*REVIEWER COMMENT: As stated above, patient 001900252, received an investigational anti-CTLA-4 monoclonal antibody, tremelimumab, which is a protocol violation as the eligibility criteria excluded patients who have received prior treatment targeting anti-CTLA-4, with the exception of ipilimumab in Part B. A number of patients were treated with investigational agents, possibly indicative of the treatment refractoriness of this patient population.*

### 6.1.3 Subject Disposition

A total of 173 patients were enrolled at 15 centers in four countries, 1 center each in Australia, Canada, and France, and 12 centers in the United States. The first patient received the first dose of study drug in Part B2 on August 12, 2012, and the last patient received the first dose of study drug on April 5, 2013.

One patient (0008000421) was randomized to the 2 mg/kg q3w but received MK-3475 at the 10 mg/kg q3w dose instead. This patient is included in the 10 mg/kg q3w arm within the APaT population for efficacy analysis.

A total of 609 patients were screened and 130 (21%) patients were screen failures. Per response to an FDA information request received on May 22, 2014, the allocation of screen failures to the specific cohorts was not captured as Part B2 and D were enrolling at the same time. Additionally, the Applicant clarified that these screen failures also included patients that were allocated/randomized, but not treated. One hundred

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eighteen patients did not meet eligibility criteria, as summarized in **Table 7**. The most common ( $\geq 10\%$ ) reasons for screen failure were brain metastases (17%), incorrect diagnosis of melanoma or carcinoma (13%), depending on disease cohort, and age  $< 18$  years (10%). Note that a patient could have more than one reason as a screen failure and therefore, be counted more than once, as summarized in **Table 7**. The remaining 12 of 130 patients were allocated, but not treated for the following reasons: six patients had adverse events, two were lost-to-follow-up, and four patients were not treated as they did not meet the eligibility criteria after allocation. For three patients (0020S00200, 0020S00203, and 0015S00132), the screen failure information was not recorded until after the database lock.

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**Table 7: Reasons for Screen Failures by Inclusion and Exclusion Criteria**

Reason	N=118 (%)
<b>Inclusion criteria</b>	
Patients must have a histological or cytological diagnosis of MEL or any type of carcinoma, progressive metastatic disease, or progressive locally advanced disease not amenable to local therapy. In Part A of the study, patients with MEL or any type of carcinoma are eligible for participation. i. Please note: tumor types of primary interest in this study are malignant MEL, RCC, hepatocellular carcinoma, non-small cell lung cancer, gastric carcinoma, ovarian carcinoma and colo-rectal carcinoma. These are the tumor types where clinical PD-1 inhibition has achieved objective tumor responses, or where high expression of PD-L1 or PD-L2 has been associated with poor prognosis. In Part B of the study, only patients with a histological diagnosis of malignant MEL or RCC are eligible for participation.	18 ( 13)
Patient is male or female and >=18 years of age on day of signing informed consent.	14 ( 10)
Patient must have a performance status of <=2 on the ECOG Performance Scale.	9 ( 6)
Patients must have failed established standard medical anti-cancer therapies for a given tumor type or have been intolerant to such therapy, or in the opinion of the Investigator have been considered	9 ( 6)
Patient must have adequate organ function as indicated by the following laboratory values. Please refer to table in protocol.	7 ( 5)
Measurable disease: In Part A of the study, patients may have non-measurable disease. In Part B of the study, patients must have measurable disease as defined per RECIST version 1.1.	3 ( 2)
Not specified	2 ( 1)
<b>Exclusion criteria</b>	
Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable	29 ( 17)
Patient has a known history of a hematologic malignancy, primary brain tumor or sarcoma, unless the patient has undergone potentially curative therapy with no evidence of that disease for 5 years.	10 ( 6)
Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full dur(sic).	8 ( 5)
Patient has any active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy.	5 ( 3)
Patient is on chronic anti-coagulation treatment with warfarin (Low molecular weight heparin or low dose aspirin are permitted).	4 ( 2)
Patient who has had chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study therapy, or who has not recovered to CTCAE grade 1 or better from the advers(sic)	4 ( 2)
Patients with symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.	4 ( 2)
Patient had prior therapy with an anti-PD-1 or anti-CTLA-4 antibody (or any other antibody targeting T cell co-stimulatory pathways).	2 ( 1)
Patient is expected to require any other form of antineoplastic therapy while on study. Exempted are patients with prostate cancer who are on luteinizing hormone-releasing hormone (LHRH) agonists and and continue on the same dose and type of LHRH agonists.	2 ( 1)
Patient is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B or	2 ( 1)

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Reason	N=118 (%)
<b>Inclusion criteria</b>	
Hepatitis C virus.	
Patient is on chronic systemic steroid therapy at doses >10 mg/day, or on any other form of immunosuppressive medication.	2 ( 1)
Not specified	1 ( <1)
Patient had previously a severe hypersensitivity reaction to another mAb.	1 ( <1)
Patient has an active infection requiring therapy.	1 ( <1)
Patient has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.	1 ( <1)
Patient is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of administration of MK-3475.	1 ( <1)

Source: IE.xpt

### REVIEWER COMMENTS:

1. *Due to the nature of this expansion cohort study, the attribution of screen failures to the appropriate cohort is difficult to determine, as several melanoma cohorts were simultaneously enrolling patients.*
2. *These screen failures are not expected to impact the interpretation of the efficacy or safety analyses of trial P001.*

At time of data cutoff, the proportion of patients with ongoing treatment was slightly higher in the 10 mg/kg arm than the 2 mg/kg arm, 45% versus 39%, respectively. Progressive disease was the most common reason for treatment discontinuation in the two treatment arms [34/92 (37%) in the 2 mg/kg arm, 25/86 (29%) in the 10 mg/kg arm]. Adverse events leading to treatment discontinuation occurred at a greater incidence in the 10 mg/kg arm compared to the 2 mg/kg arm, 20% versus 13%, respectively. Four patients, two in each arm, withdrew from the study by withdrawing consent. **Table 8** summarizes the treatment status and reasons for treatment discontinuations for patients in Part B2, and **Table 9** summarizes the reasons for study discontinuation.

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**Table 8: Summary of Subject Disposition by Treatment Discontinuation, Part B2**

	MK-3475 2 mg/kg N=89 n (%)	MK-3475 10 mg/kg N=84 n (%)	All N=173 n (%)
Ongoing*	35 (39)	38 (45)	73 (42)
End of treatment (discontinued study medication) <sup>1</sup>	<b>54 (60)</b>	<b>46 (55)</b>	<b>100 (58)</b>
Progressive disease	34 (38)	25 (30)	59 (34)
Adverse event	12 (13)	17 (20)	29 (17)
Physician decision	3 (3)	1 (1)	4 (2)
Withdrawal by subject	2 (2)	2 (2)	4 (2)
Protocol violation	2 (2)	0	2 (1)
Lost to follow-up	1 (1)	1 (1)	2 (1)

Source: DS.xpt and ADSL.xpt

<sup>1</sup> Patients had only one primary reason for treatment discontinuation.

\* Per Applicant, patients that are still on study at time of database cut-off.

**Table 9: Summary of Subject Disposition by Study Discontinuation, Part B2**

	MK-3475 2 mg/kg N=89 n (%)	MK-3475 10 mg/kg N=84 n (%)	All N=173 n (%)
Ongoing	54 (61)	53 (63)	107 (62)
End of study	35 (39)	31 (37)	66 (38)
Progressive disease	21 (24)	12 (14)	33 (19)
Adverse event	8 (9)	11 (13)	19 (11)
Lost to follow-up	3 (3)	2 (2)	5 (3)
Withdrawal by subject	3 (3)	6 (7)	9 (5)

Source: DS.xpt and ADSL.xpt

<sup>1</sup> Patients had only one primary reason for treatment discontinuation.

\* Per Applicant, patients that are still on study at time of database cut-off.

**REVIEWER COMMENTS:**

1. According to Table 8, a slightly higher percentage of patients discontinued treatment in the 2 mg/kg arm (60%) compared to 10 mg/kg arm (55%). The primary reason for discontinuation of treatment was progressive disease for both arms. A higher percentage of patients discontinued treatment due to adverse events in the 10 mg/kg arm (20%) compared to the 2 mg/kg arm (13%).
2. According to Table 9, the percentage of patients who discontinued from the study are similar in the two arms. A greater percentage (24%) of patients discontinued due to progressive disease in the 2 mg/kg arm, compared to the 10 mg/kg arm (14%).

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### 6.1.4 Analysis of Primary Endpoint(s)

*Please refer to the FDA Statistical BLA Review conducted by Emmanuel Sampene, Ph.D., Statistical Reviewer, Division of Biometrics V, Office of Biostatistics, for this application.*

#### **Overall Response Rate and Duration of Response**

The primary endpoint was BICR-assessed ORR (confirmed complete and partial responses) per RECIST v. 1.1. The BICR was implemented in Amendment 8, received on August 1, 2013, whereby the Applicant submitted a protocol amendment to change the primary measure of tumor response to RECIST 1.1 as assessed by BICR from immune-related response criteria (irRC) as assessed by the investigator. ORR as assessed by investigator per irRC became a secondary measure of tumor response. In addition, use of irRC continued at the site investigator level to guide decisions on MK-3475 discontinuation for progression of disease. The BICR review was a retrospective review as provided in the independent review charter by (b) (4) version 3, dated September 18, 2013 (see Section 5.3).

The duration of response was a secondary endpoint and an additional outcome measure of efficacy to support the ORR. It was defined as the time from the first documented evidence of a CR or PR until the first documented disease progression or death due to any cause.

The BICR-assessed ORR per RECIST v. 1.1 was 23.6% (95% CI: 15.2, 33.8) in the 2 mg/kg arm and was 23.8% (95% CI: 15.2, 34.3) in the 10 mg/kg arm based on the APaT population (all patients randomized in Part B2 who received at least one dose of MK-3475). The Miettinen-Nurminen's method to compare the risk difference between the two treatment arms was not statistically significant (CI: -41.5, 38.8,  $p=0.9737$ ), suggesting that the treatment arms were not different from each other.

The median duration of response was not reached in either arm. Twenty-one patients in the 2 mg/kg arm had an objective response. Of these, three had progression of disease, two after response durations of 2.8 and 2.9 months and one after a response duration of 8.3 months. The duration of responses among the remaining 18 patients ranges from 1.4+ to 8.5+ months, which includes eight patients with ongoing responses of 6 months or longer. Similar results were observed in the 10 mg/kg arm. **Table 10** summarizes the results for ORR and duration of response, based on BICR assessment. Table 11 shows the duration of response for each of the 21 patients who achieved a objective response in the 2 mg/kg arm.

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**Table 10: Response Rate and Duration of Response Based on BICR per RECIST v. 1.1, Part B2**

	MK-3475 2 mg/kg, N=89 n (%)	MK-3475 10 mg/kg, N=84 n (%)	All, N=173 n (%)
Overall Response Rate (%)	21 (23.6)	20 (23.8)	41 (23.6)
95% CI	(15.2, 33.8)	(15.2, 34.3)	(15.2, 34.3)
Complete Response	1 (1)	1 (1)	2 (1)
Partial Response	20 (22)	19 (23)	39 (23)
Duration of Response			
Median, months	NR	NR	NR
(range)	(1.4+, 8.5+)	(2+, 9+)	(1.5+, 9+)
Ongoing Response (%)	86	90	88

Source: FDA Statistical Review  
NR=not reached

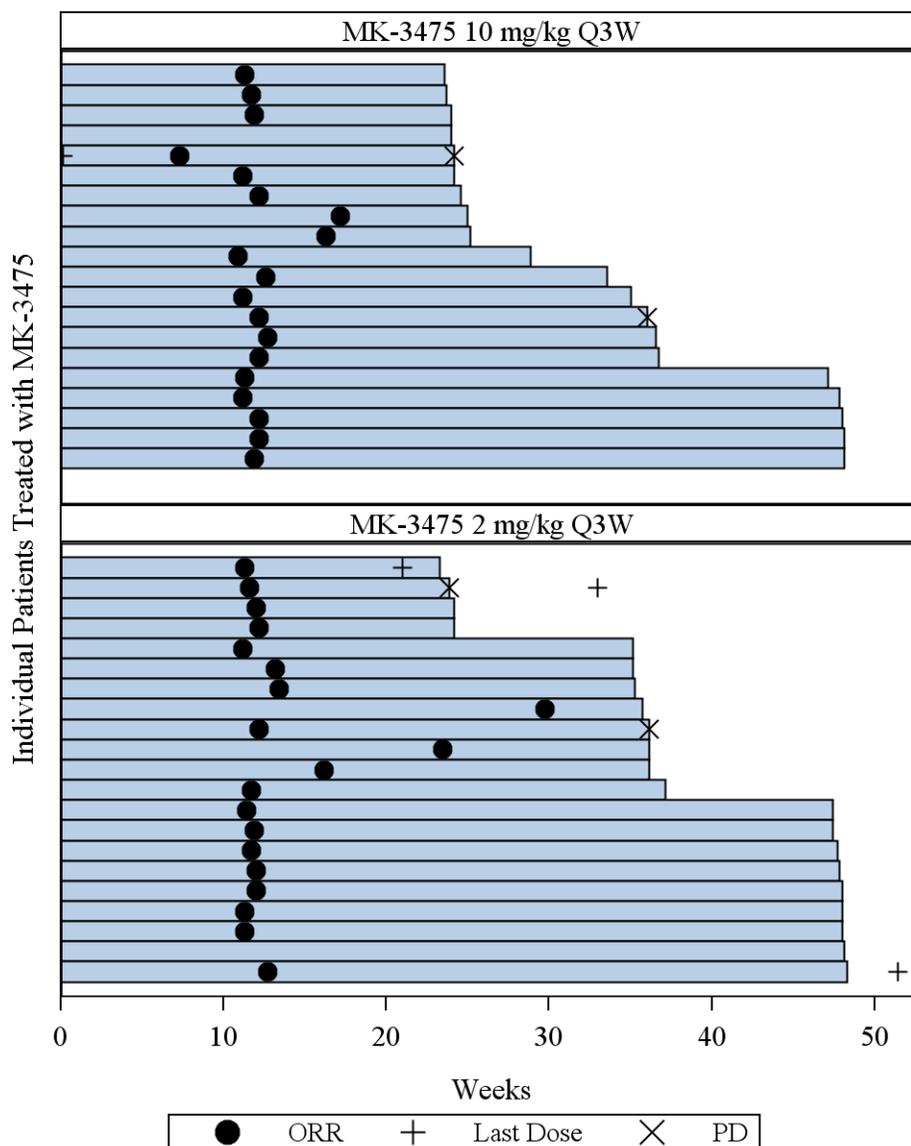
**Table 11: Response Duration by BICR per RECIST v. 1.1 in MK-3475 2 mg/kg q3w Arm, Part B2**

Patient ID	MK-3475 2 mg/kg Q3W Response duration (months)
0011000315	1.4
0019000279	2.8*
0021000369	2.8
0001000284	2.8
0019000380	2.8
0010000253	2.9*
0019000338	3.0
0021000324	4.7
0020000318	5.1
0020000322	5.1
0016000346	5.6
0010000341	5.6
0011000307	5.9
0010000274	8.3*
0020000290	8.3
0016000306	8.3
0010000255	8.4
0015000294	8.4
0021000287	8.4
0023000269	8.5
0023000280	8.5

Source: FDA Statistical Review  
\* Patient with progression of disease

**Figure 1** plots the duration of response and time to response for each responder by treatment arm.

**Figure 1: Plot of Time to Response and Duration of Response, Part B2**



Database Cutoff Date: 18OCT013

Data Source: [16.4]

Source: FDA statistical review

Comparison of the response assessments between the independent radiology review and independent oncology review revealed discordance in 25 cases. In three of the 25 cases, the independent oncologist recorded progressive disease when no response

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was recorded by the radiologist as imaging was incomplete. In one case, the oncologist recorded the response assessment as progressive disease and the radiologist recorded it as not evaluable. For the other 21 cases, the oncologist recorded not evaluable when no response was recorded for the radiologist. This occurred at a higher percentage in the 2 mg/kg arm (14%) compared to the 10 mg/kg arm (10%).

### REVIEWER COMMENTS:

- 1. The ORR may not reliably predict a treatment effect that translates to clinical benefit; however, the positive effect on ORR appears to provide some meaningful advantage over available therapy. In the 24% of patients that had a response in the 2 mg/kg arm, 86% of these patients have ongoing responses, although the duration of response has not been reached. The ongoing duration of response may be to predict clinical benefit in a refractory patient population with a minimum of 28 weeks follow-up.*
- 2. Informative bias may be introduced by retrospective analysis of efficacy endpoints based on independent review by central imaging vendor assessment of tumor response endpoints when tumor response is based on investigator-assessment. Sensitivity analyses were performed to assess the robustness of the primary endpoint as discussed in Section 6.1.5.*
- 3. The overall response rates are similar between the lower dose (2 mg/kg) arm (23.6%) and higher dose (10 mg/kg) arm (23.8%); use of ORRs in this application as an effect that is reasonably likely to predict clinical benefit is supported by the relatively long duration of response observed in the 2 mg/kg arm and 10 mg/kg arm and in other cohorts within trial P001. Although the median duration of response has not been reached in Part B2, ongoing responses in over 80% in both arms potentially indicates the effect of MK-3475 is durable in patients with metastatic melanoma. The durability of response observed in Part B2 is further supported by the high proportion of ongoing responses of 89-100% in the other cohorts, Parts B1 and D, as discussed in Section 6.1.7. These cohorts, as previously described were treated at multiple dose levels and consisted of a heterogeneous melanoma population.*
- 4. The swimmer's plot illustrates that most patients responded by the first imaging assessment; however, several patients had a delayed response. The data are also summarized in Table 11. Ten patients have a follow-up time of  $\geq 24$  weeks in the 2 mg/kg q3w arm. Three of the responding patients progressed, two patients after 2.8 and 2.9 months and one patient after 8.3 months. The duration of ongoing responses among the 18 patients range from 1.4+ to 8.5+ months.*
- 5. The BICR assessment is generally considered the primary method of ORR analysis in an open-label study to support a regulatory action.*
- 6. No discordance between radiologist and oncologist was observed in responders.*
- 7. The biomarker PD-1 analyses to assess the impact on tumor activity was not included in the BLA submission.*

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### 6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints for Part B2 of P001 study were to evaluate PFS and OS of patients who were treated with MK-3475. Response rates in patients with unresectable or metastatic melanoma refractory or naïve to ipilimumab were additional secondary endpoints.

#### **Response Rates and Duration of Response by BICR, IRC, and Investigator**

The response rates and durations of response by independent review committee (IRC) per RECIST, BICR per RECIST and irRC, and Investigator per irRC are summarized in **Table 12**. The IRC is radiology assessment only--no oncology assessment.

Furthermore, the investigators did not use RECIST to assess tumor responses, only irRC; therefore, no direct comparisons can be made. As shown in **Table 12**, the number of patients in the IRC differ than that of the BICR using the RECIST v. 1.1 as patients did not have measurable disease at baseline, and/or discontinued study medication due to adverse event (15 patients), lost to follow-up (2), protocol violation (1), and withdrawal by subject (3).

Objective response rates per RECIST v. 1.1 as assessed by the BICR were nominally lower than IRC-assessed ORRs, 24% in the 2 mg/kg arm and 24% in the 10 mg/kg arm, compared with 28% in the 2 mg/kg arm and 27% in the 10 mg/kg arm, respectively. This may be attributable to the additional clinical data provided to the BICR in order to assess response. When comparing ORRs by irRC, the ORRs were similar between arms, but higher in both arms for the investigator compared to the BICR. Within each of the methodologies for response assessment (RECIST or irRC), the ORRs were similar between the 2 mg/kg arm and 10 mg/kg, further supporting that the 2 mg/kg dose is appropriate for the treatment of patients with metastatic melanoma.

**Table 12: Response Rate and Duration of Response Based on BICR and Investigator’s Assessment per RECIST v. 1.1 and irRC, Part B2**

	MK-3475 2 mg/kg,	MK-3475 10 mg/kg,
	n (%)	n (%)
<b>BICR per RECIST</b>	N=89	N=84
Overall response rate, %	21 (24)	20 (24)
CR	1	1
PR	20	19
95% CI	(15, 34)	(15, 34)
Duration of Response		
Median, months	Not reached	Not reached
(95% CI)	(1.4+, 9+)	(2+, 9+)
<b>BICR per irRC<sup>†</sup></b>	<b>N=89</b>	<b>N=84</b>
Overall Response Rate (%)	17 (19)	20 (24)
CR	0	1
PR	17	19
95% CI	(12, 29)	(15, 34)
Duration of Response		
Median, months	Not reached	Not reached
(95% CI)	(1.5+, 9+)	(1.5+, 9+)
<b>IRC per RECIST*</b>	N=74	N=75
Overall response rate, %	21 (28)	20 (27)
CR	1	1
PR	20	19
95% CI	(19, 40)	(17, 38)
Duration of response		
Median, months	Not reached	Not reached
(95% CI)	(1.5+, 9+)	(2+, 9+)
<b>INV per irRC<sup>‡</sup></b>	N=79	N=73
Overall Response Rate (%)	24 (30)	27 (37)
CR	3	0
PR	21	27
95% CI	(21, 42)	(26, 49)
Duration of Response		
Median, months	Not reached	Not reached
(95% CI)	(3+, 10.5+)	(2+, 9+)

Source: ADINVBOR.xpt and FDA Statistical Review

\* Patients were not evaluable by radiologists in IRC per RECIST if a patient had incomplete imaging

† IRC=independent radiology committee; irRC=immune-related Response Criteria; INV=investigator

‡ No assessment of response in 21 patients was made, 10 in 2 mg/kg arm and 11 in 10 mg/kg arm, due to adverse event (15), lost to follow-up (2), protocol violation (1), and withdrawal by subject (3)

**REVIEWER COMMENTS:**

1. *The sensitivity analyses demonstrates the concordance using the different response criteria, RECIST v. 1.1 and irRC, and different reviewers, BICR, IRC, and investigator. These analyses demonstrate that the method of assessing the primary endpoint, BICR per RECIST v. 1.1, is robust.*

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2. *The BICR used RECIST v. 1.1 criteria to assess response, while the investigators used irRC. As the irRC criteria vary from RECIST, no comparison of response assessments between BICR and investigator can be made.*
3. *Immune-related response criteria were used by investigator throughout the study, as it was also used to assess disease progression prior to enrollment in the P001 study. Please refer to Section 6.1.9 of the review for an analysis of BICR-assessed ORRs per RECIST or per irRC for Parts B1, B2, and D of the trial.*

### Progression-free Survival

Progression-free survival in Part B2 was defined as the interval between the start of treatment to documentation of definitive disease progression or death due to any cause, whichever occurred first. The PFS results by BICR per RECIST v. 1.1 are presented in **Table 13**. There were 54 events in each arm, and the median PFS was 5.5 months in the 2 mg/kg arm, and 3.5 months in the 10 mg/kg arm. The stratified HR was 0.84 (95% CI: 0.57, 1.23; p-value=0.36).

**Table 13: Analysis of Progression-free Survival by BICR per RECIST v. 1.1, Part B2**

	MK-3475 2 mg/kg, N=89 n (%)	MK-3475 10 mg/kg, N=84 n (%)
Number of Events (%)	54 (61)	54 (64)
Progression	38 (43)	46 (55)
Death	16 (18)	8 (10)
Median PFS, months (95% CI)	5.5 (3.0, 9.0)	3.5 (3.0, 6.0)
HR (95% CI) by Cox		0.84 (0.57, 1.23)
p-value		0.36

Source: ADPFS.xpt and FDA statistical review

#### REVIEWER COMMENTS:

1. *A higher percentage of deaths were observed in the 2 mg/kg arm. Attributable factors may be due to worse prognostic factors in the 2 mg/kg arm, compared to the 10 mg/kg arm. Table 5 shows that a greater percentage of patients in the 2 mg/kg arm had elevated LDH and M1c disease. Note that PFS results are uninterpretable in single arm studies.*
2. *Informative bias based on investigator-assessment of tumor response may exist when the efficacy analyses are based on blinded central imaging vendor.*

### Overall Survival

Overall survival was defined as the interval of time between date of randomization and date of death due to any cause. The OS results are summarized in **Table 14** below. A

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total of 54 patients died at the time of analysis; 32 (36%) deaths occurred in the 2 mg/kg arm and 22 (26%) deaths occurred in the 10 mg/kg arm. The median overall survival was 13 months (95% CI: 10.1, NR) in the 2 mg/kg arm and not reached in the 10 mg/kg arm, with a stratified HR of 1.1 (95%CI: 0.6, 1.8; p-value= 0.83).

**Table 14: Analysis of Overall Survival, Part B2**

	<b>MK-3475 2 mg/kg, N=89 n (%)</b>	<b>MK-3475 10 mg/kg, N=84 n (%)</b>
Deaths (%)	32 (36)	22 (26)
Median OS, months (95% CI)	13 (10.1, NR*)	Not reached (NR, NR)
Hazard Ratio (95% CI)		1.1 (0.6, 1.8)
p-value		0.83

Source: ADOS.xpt and FDA Statistical Review

\* NR=not reached

*REVIEWER COMMENT: The OS is uninterpretable in a single-arm study.*

### 6.1.6 Subpopulations

Exploratory subgroup analyses of response rate were evaluated by Dr. Sampene, FDA Statistical Reviewer. The subgroups that were analyzed, as summarized in **Table 15**, include demographic and baseline disease characteristics such as age, gender, ECOG status, geographic region, presence of brain metastases, elevated LDH, and BRAF V600 mutation. Race was not evaluated as 97% of the patients were White. A forest plot of the ORRs in these subgroups is illustrated in **Figure 2**. Overall, the results of the subgroup analyses were consistent with those of the primary analysis for Part B2.

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**Table 15: Subgroup Analyses of ORR by Baseline Demographics by BICR per RECIST v. 1.1**

	<b>2 mg/kg q3w N=89</b>	<b>10 mg/kg q3w N=83</b>
<b>Age</b>		
<65 years	n=59	n=52
CR+PR (%)	16 (27)	12 (23)
CR	0	1
PR	16	11
(95% CI)	(16, 40)	(13, 39)
≥ 65 years	n=30	n=32
CR+PR (%)	5 (17)	8 (25)
CR	1	0
PR	4	8
95% CI	(6, 35)	(11, 43)
<b>Gender</b>		
Female	n=41	n=27
CR+PR (%)	10 (24)	7 (26)
CR	0	1
PR	10	6
(95% CI)	(12, 40)	(11, 46)
Male	n=48	n=57
CR+PR (%)	11 (23)	13 (23)
CR	1	0
PR	10	13
(95% CI)	(12, 37)	(13, 36)
<b>ECOG PS</b>		
ECOG PS 0	n=59	n=57
CR+PR (%)	15 (32)	11 (21)
CR	0	1
PR	15	11
(95% CI)	(15, 38)	(11, 34)
ECOG PS 1	n=30	n=27
CR+PR (%)	6 (20)	8 (30)
CR	1	0
PR	5	8
95% CI	(8, 39)	(14, 50)
<b>Geographic region</b>		
USA	n=70	n=62
CR+PR (%)	13 (19)	16 (26)
CR	1	0
PR	12	16
95% CI	(10, 30)	(16, 39)
Canada	n=5	n=9
CR+PR (%)	3 (60)	2 (22)
CR	0	0
PR	3	2
95% CI	(15, 95)	(3, 60)
France	n=8	n=9
CR+PR (%)	3 (38)	0

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	2 mg/kg q3w N=89	10 mg/kg q3w N=83
CR	0	0
PR	3	0
95% CI	(9, 76)	NA0
Australia	n=6	n=4
CR+PR (%)	2 (33)	2 (50)
CR	0	1
PR	2	1
95% CI	(4, 78)	(7, 93)
<b>Brain metastases*</b>		
Yes	n=7	n=8
CR+PR (%)	2 (29)	2 (25)
CR	0	0
PR	2	2
(95% CI)	(4, 71)	(3, 65)
No	n=81	n=75
CR+PR (%)	19 (23)	18 (24)
CR	1	1
PR	18	17
(95% CI)	(15, 34)	(15, 35)
<b>BRAF V600 mutation</b>		
Mutant	n=12	n=19
CR+PR (%)	2 (17)	3 (16)
CR	0	0
PR	2	3
95% CI	(2, 48)	(4, 41)
Wild type	n=77	n=65
CR+PR (%)	19 (25)	17 (26)
CR	1	1
PR	18	16
95% CI	(16, 36)	(16, 3)
<b>Lactate Dehydrogenase†</b>		
Elevated	n=39	n=29
CR+PR (%)	12 (31)	4 (14)
CR	1	0
PR	11	4
95% CI	(17, 48)	(4, 32)
Normal	n=49	n=55
CR+PR (%)	9 (18)	16 (29)
CR	0	1
PR	9	15
95% CI	(9, 32)	(18, 43)

Source: FDA Statistical Review

\* Brain metastases unknown in two patients, one in each arm.

† LDH level was unknown in one patient in the 2 mg/kg arm.

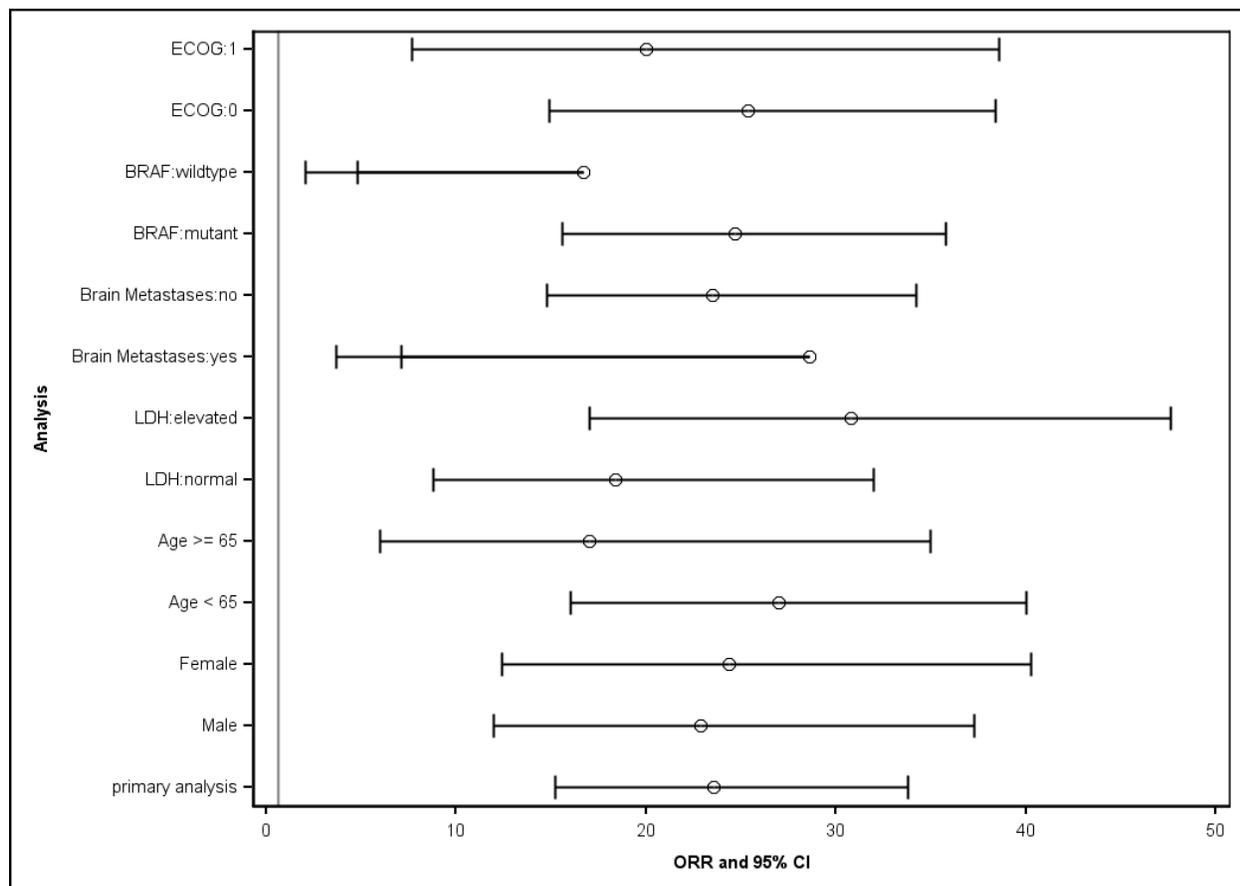
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**Figure 2: Forest Plot of ORR by Baseline Demographics and Characteristics by BICR per RECIST v. 1.1**



Source: FDA Statistical Review

### REVIEWER COMMENTS:

1. *The multiple subgroup analyses based on brain metastases, baseline elevated LDH, and BRAF V600 mutation, provide confirmation of the robustness of the primary response rate results; however, the number of patients in each arm are too small to make definitive conclusions, so interpretation of these results must be taken with caution.*
2. *No prognostic factor or demographic characteristic were identified in the subgroup analyses; the ORRs were similar across all these subgroups.*

### 6.1.7 Other Findings to Support Efficacy

Data from nonrandomized cohorts of trial P001, Parts B1 and D, were supportive of the results observed in Part B2. Part B1 was initiated in Amendment 2, received by FDA on September 12, 2011. It was then amended twice to increase the sample size and

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include more ipilimumab-treated patients and open the 2 mg/kg q3w arm in Amendments 3 and 4, received on March 2, 2012, and April 5, 2012, respectively. Part B1 had the longest duration of follow-up in trial P001, with more than one year for all patients. Part B1 consisted of a more heterogeneous patient population compared to Part B2, as patients in Part B1 were ipilimumab-naïve and ipilimumab-treated. Additionally, the dosing regimen comprised of three groups: 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks (q2w), or 10 mg/kg every 3 weeks. Patients who were previously treated with ipilimumab were enrolled in the 10 mg/kg q2w or q3w arm. Patients who were ipilimumab-naïve were accrued to all arms.

The protocol defined ipilimumab-treated patients for Part B1 as:

- Unequivocal PD during or after treatment with ipilimumab (Amendment 2) or within 6 months of the last dose of ipilimumab (Amendment 3 and 4)
- Full resolution of all AEs from prior ipilimumab and at least 12 weeks since the first dose and 6 weeks since the last dose of ipilimumab
- Not more than two prior systemic therapies for melanoma (Amendment 2) or up to 2 prior systemic therapies for melanoma for ipilimumab-naïve patients and up to 3 prior systemic therapies for melanoma for ipilimumab-treated patients (Amendment 3 and 4)
- Patients with autoimmune diseases or who required corticosteroids or other immunosuppressive treatments were excluded
- Brain metastases, if present, must be treated and stable for at least 8 weeks

**Table 16** summarizes the distribution of patients in Part B1 according to history of prior treatment with ipilimumab. Only patients who were ipilimumab-naïve were enrolled in the 2 mg/kg q3w arm.

**Table 16: Ipilimumab Status of Part B1 Patients**

	2 mg/kg q3w N=22	10 mg/kg q3w N=56	10 mg/kg q2w N=57	Total N=135
Ipilimumab-naïve	22 (100)	24 (43)	41 (72)	87 (64)
Ipilimumab-treated	0	32 (57)	16 (28)	48 (29)

Source: ADSL.xpt

Ipilimumab-treated patients in Part B1 are presented in **Table 17**. The overall response rate by BICR per RECIST v. 1.1 was 22% (95% CI: 10, 41) in 10 mg/kg q3w subgroup and 56% (95% CI: 30, 80) in the 10 mg/kg q2w subgroup. The median duration of response was not reached in both subgroups; however, all (100%) responders in the 10 mg/kg q3w subgroup and 89% of responders in the 10 mg/kg q2w subgroup had an ongoing response at the time of data cut-off.

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**Table 17: ORR and Duration of Response based on BICR per RECIST v. 1.1, Part B1 (Ipilimumab-treated only)**

	Ipi-treated	
	10 mg/kg q3w N=32	10 mg/kg q2w N=16
CR+PR (%)	7 (22)	9 (56)
CR	0	3
PR	7	6
(95% CI)	(10, 41)	(30, 80)
Response duration median, weeks (range)	Not reached (34+, 72+)	Not reached (72+, 76+)
Ongoing responses (%)	100	89

Source: ADIOBOR.xpt and FDA Statistical Review

**Table 18** summarizes the ORR and median duration of response inclusive of all patients, ipilimumab naïve and prior ipilimumab treated, for the three subgroups. The overall response rate was 41% (95% CI: 21, 64) in the 2 mg/kg q3w subgroup, 29% (95% CI: 17, 42) in 10 mg/kg q3w subgroup, and 49% (95% CI: 36, 63) in the 10 mg/kg q2w subgroup. The median response duration was not reached in the three subgroups; however, all (100%) responders in the 2 mg/kg q3w arm, 88% of responders in the 10 mg/kg q3w, and 89% of responders in the 10 mg/kg q2w subgroup had an ongoing response at the time of data cut-off. **Figure 3** is a graphical display of the time to response and duration of response for responders in Part B1.

**Table 18: ORR and Duration of Response based on BICR per RECIST v. 1.1, Part B1**

	2 mg/kg q3w N=22	10 mg/kg q3w N=56	10 mg/kg q2w N=57
CR+PR (%)	9 (41)	16 (29)	28 (49)
CR	2	3	11
PR	7	16	17
(95% CI)	(21, 64)	(17, 42)	(36, 63)
Response duration median, weeks (range)	Not reached (9+, 60+)	Not reached (11+, 72+)	Not reached (8+, 76+)
Ongoing responses (%)	100	88	89

Source: Applicant's Summary of Clinical Efficacy

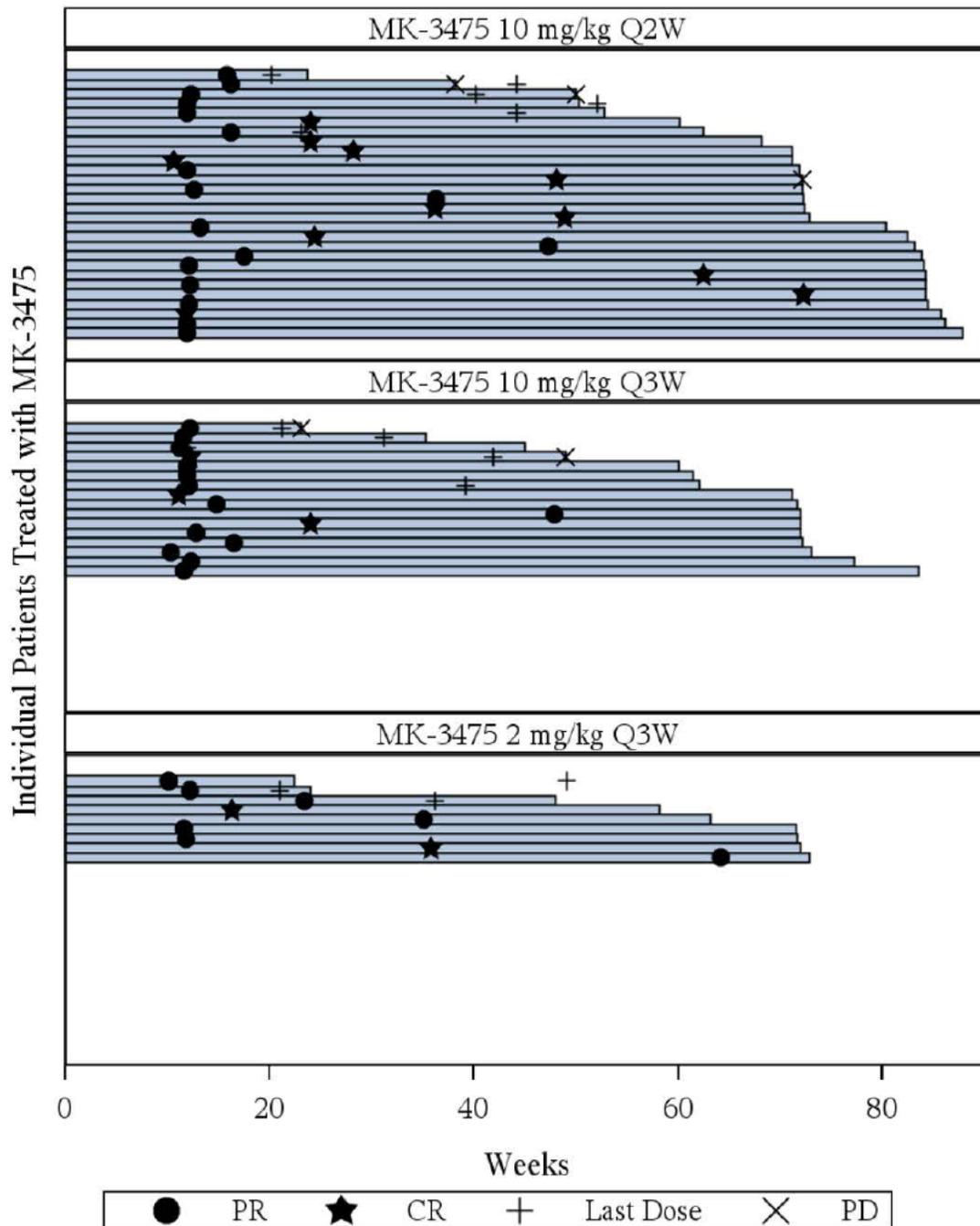
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**Figure 3: Plot of Time to Response and Duration of Response by IRO per RECIST v. 1.1, Part B1**



Source: Applicant's Clinical Study Report

Part D consisted of patients who were ipilimumab-naïve, defined as no prior treatment with ipilimumab, and who had received not more than two prior systemic treatment

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regimens for melanoma. The overall response rate by BICR per RECIST v. 1.1 was 33% (95% CI: 21, 48) in the 2 mg/kg arm and 37% (95% CI: 24, 51) in the 10 mg/kg arm and the median duration was not reached in either arm. All (100%) responders in the 2 mg/kg arm and 89% of responders in the 10 mg/kg had an ongoing response at the time of data cut-off.

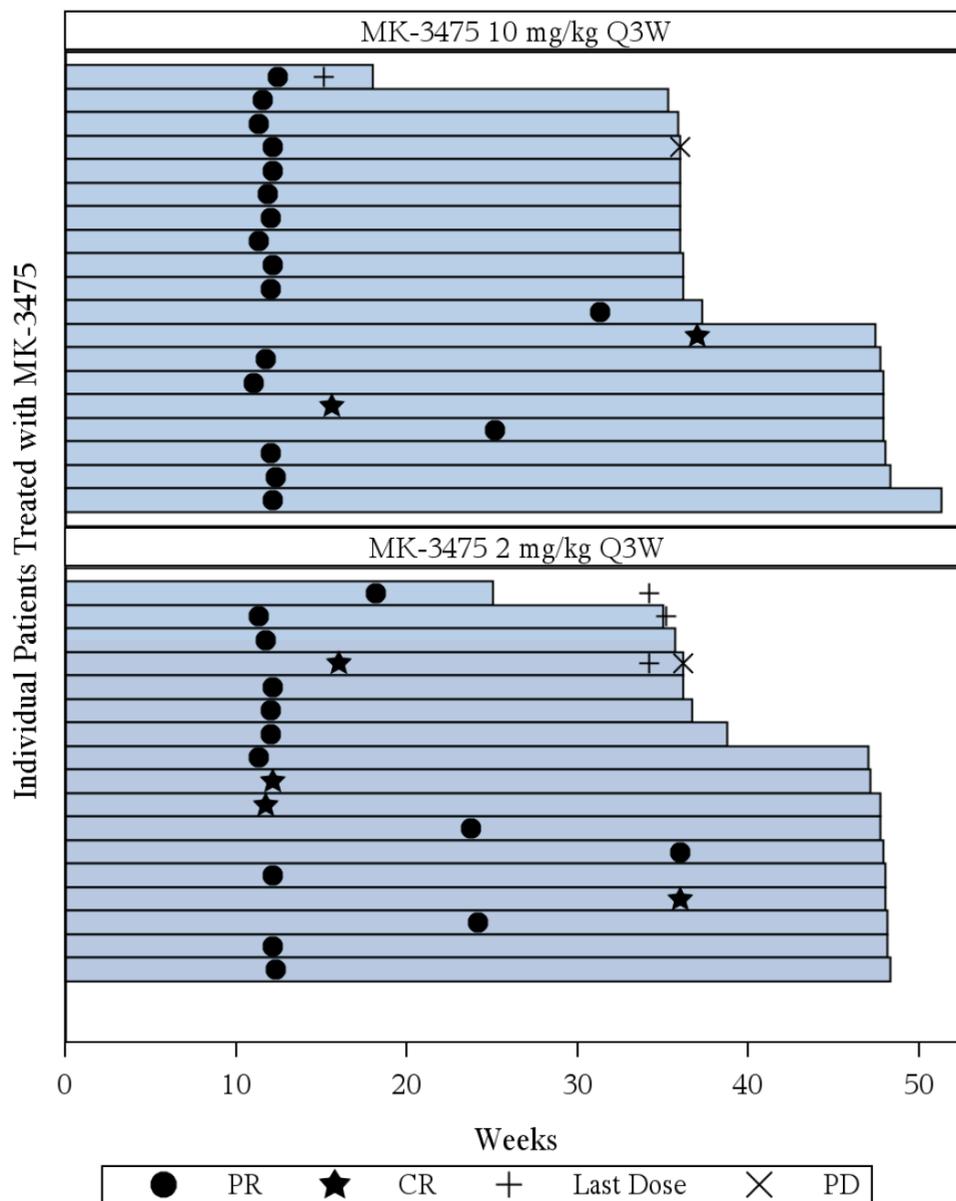
The results from Parts D are summarized below. **Figure 4** displays the times to response and durations of response for the patients in Part D.

**Table 19: Part D ORR and Duration of Response based on BICR per RECIST v. 1.1**

	2 mg/kg q3w N=51	10 mg/kg q3w N=52
CR+PR (%)	17 (33)	19 (37)
CR	4	2
PR	13	17
(95% CI)	(21, 48)	(24, 51)
Response Duration Median in weeks (range)	Not reached (7+, 36+)	Not reached (6+, 39+)
Ongoing responses (%)	100	89

Source: ADIOBOR.xpt and FDA Statistical Review

**Figure 4: Plot of Time to Response and Duration of Response by IRO per RECIST v. 1.1, Part D**



Source: Applicant's Clinical Study Report

**REVIEWER COMMENTS:**

1. The definitions of ipilimumab-treated in Part B1 and ipilimumab-refractory in Part B2 differ in that the requirements were less restrictive for ipilimumab-treated. Additionally, enrollment into Part B1 did not require patients who were positive for the BRAF V600 mutation to have received treatment with a BRAF or MEK

*inhibitor. Additionally, there were no requirements of a minimum number of ipilimumab doses or confirmation of disease progression.*

- 2. Of the 30 patients who were BRAF V600 mutation-positive, 18 patients (4 in 2 mg/kg q3w, 4 in 10 mg/kg Q3W, and 10 in 10 mg/kg q2w) were not treated with a BRAF and/or MEK inhibitor prior to enrolling into the trial.*
- 3. In Part D, there was also no requirement for prior BRAF and/or MEK inhibitor treatment in patients with BRAF V600 mutation-positive melanoma. Of the 36 patients who were BRAF V600 mutation-positive, 10 patients in the 2 mg/kg arm and 7 patients in the 10 mg/kg arm who were BRAF V600 mutation-positive did not receive prior treatment with a BRAF and/or MEK inhibitor.*
- 4. No direct comparisons in ORRs among the dose levels in Part B1 can be made based on the design of this part of the trial, including the heterogeneity of the ipilimumab status across the three dosage levels.*
- 5. Overall, the response rates in Parts B1 and D are supportive of those observed in Part B2. Higher response rates were observed in Parts B1 and D, compared to Part B2. Possible reasons for the higher response rates include the differences in frequency of administration, every 2 weeks vs. every 3 weeks, and patients might not have been as heavily pretreated; however, caution should be taken in interpreting the results as the number of patients were small.*

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Analyses of dose- and exposure-response relationships were performed in trial P001. Per clinical pharmacology review by Hongshan Li, Ph.D., FDA Pharmacology Reviewer, a flat relationship exists between steady-state AUC, AUC<sub>T</sub>, and overall response rate (ORR) for patients in study Part B2 who were on 2 mg/kg or 10 mg/kg MK-3475 (N=173). As shown in **Figure 5**, this flat exposure-response relationship supports that the 2 mg/kg Q3W regimen is the appropriate dose for the proposed indication.

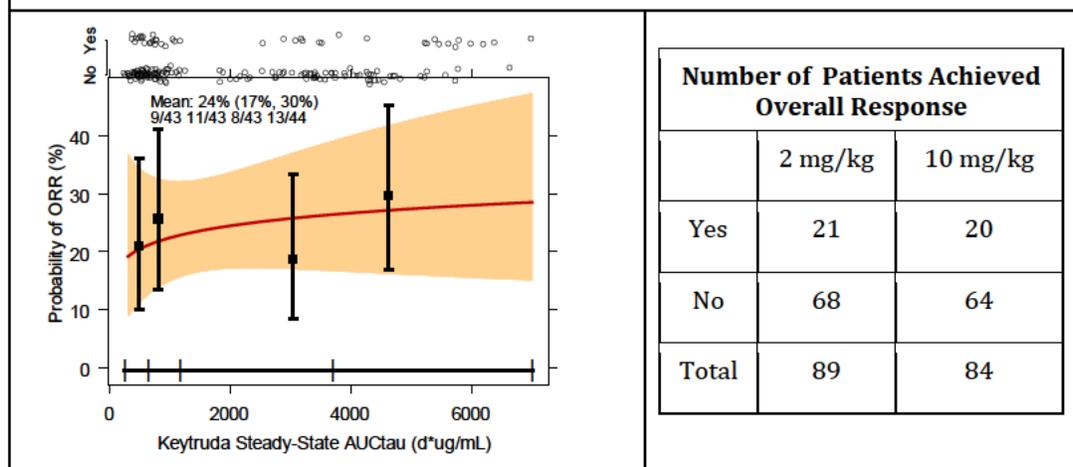
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**Figure 5: Relationship between Steady-State AUC<sub>τ</sub> and Overall Response Rate (ORR) of Part B2 Patients**



Source: FDA clinical pharmacology review. Analysis based on dataset p001pkeffae.xpt from the sponsor.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The irRC and RECIST criteria are both used to assess tumor response, but differ in terms of how response is determined. The irRC is an alternate tumor response criteria in use by some investigators to measure anti-tumor responses in the evaluation of immunotherapeutic agents, as the pattern of response may differ from cytotoxic agents. It accounts for transient tumor flare or tumor progression that may manifest initially with immunotherapy, followed by disease response. Additionally, it requires confirmation of progression at a subsequent time point after first detection and takes into consideration new lesions into measurements of the overall tumor burden. **Table 20** summarizes the ORR in a side-by-side comparison of cohorts consisting of Parts B1, B2, and D by BICR per RECIST and by BICR per irRC.

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**Table 20: Overall Response Rate in Parts B1, B2, and D by BICR per RECIST v. 1.1 and irRC, Parts B1, B2, and D**

Response Criteria:	MK-3475 2 mg/kg q3w n (%)		MK-3475 10 mg/kg q3w n (%)		MK-3475 10 mg/kg Q2w n (%)	
	RECIST	irRC	RECIST	irRC	RECIST	irRC
<b>Part B1</b>	<b>N=22</b>	<b>N=22</b>	<b>N=56</b>	<b>N=56</b>	<b>N=57</b>	<b>N=57</b>
Overall response rate, %	9 (41)	8 (36)	16 (29)	18 (32)	28 (49)	30 (53)
CR	2	2	3	3	11	12
PR	7	6	13	15	17	18
95% CI	(21, 64)	(17, 59)	(17, 42)	(20, 46)	(36, 63)	(39, 66)
Median time to response, weeks	16 (10, 64)	-	12 (10, 48)	-	16 (11,72)	-
Median duration of response						
Median, weeks (range)	NR (9+, 60+)	-	NR (11+, 72+)	-	NR (8+, 76+)	-
Ongoing response, %	100	-	88	-	89	-
<b>Part B2</b>	<b>N=89</b>	<b>N=89</b>	<b>N=84</b>	<b>N=84</b>	<b>NA</b>	<b>NA</b>
Overall Response Rate (%)	21 (24)	17 (19)	20 (24)	20 (24)		
CR	1	0	1	1		
PR	20	17	19	19		
95% CI	(15, 34)	(12, 29)	(15, 34)	(15, 34)		
Median time to response, weeks	12 (11, 36)	-	12 (7, 17)	-		
Duration of Response						
Median, weeks (range)	NR (6+, 37+)	-	NR (6+, 37+)	-		
Ongoing response, %	86	-	90	-		
<b>Part D</b>	<b>N=51</b>	<b>N=51</b>	<b>N=52</b>	<b>N=52</b>	<b>NA</b>	<b>NA</b>
Overall response rate, %	17 (33)	18 (35)	19 (37)	19 (37)		
CR	4	4	2	2		
PR	13	14	17	17		
95% CI	(21, 48)	(22, 50)	(24, 51)	(24, 51)		
Median time to response, weeks	12 (11, 36)	-	12 (11, 37)	-		
Duration of response						
Median, weeks (range)	NR (7+, 37+)	-	NR (6+, 39+)	-		
Ongoing response, %	100	100	89	89		

Source: Applicant's Summary of Clinical Efficacy and FDA Statistical Review\* Median time to response and duration of response was not provided by Applicant.

Abbreviations in Table: CR, complete response; CI, confidence interval; irRC, immune-related response criteria; NA, not applicable; NR, not reached; PR, partial response; RECIST, RECIST version 1.1;

Note: information not available for cells containing a hyphen.

**REVIEWER COMMENTS:**

1. *The treatment effect of MK-3475 appears similar across all cohorts and among the dose levels, as observed with time to response, duration of response, and ORRs per RECIST and irRC. This further supports the appropriateness of the 2 mg/kg dose for the proposed indication.*

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- 2. Although the median duration of response has not been reached as follow-up has not been extensive, between 80-90% of patients across all cohorts per RECIST have ongoing responses. As Part B1 has the longest follow-up of the cohorts, the duration of response exceeds 1 year for some patients.*
- 3. The highest ORR (49%) per RECIST was observed in the 10 mg/kg Q2W arm in Part B1; however, caution must be taken as this was a nonrandomized cohort.*
- 4. Part D has the highest ORRs by BICR per RECIST and irRC, potentially attributable to the difference in baseline characteristics of the patients, lack of ipilimumab exposure, and fewer prior treatments.*

### 6.1.10 Additional Efficacy Issues/Analyses

The efficacy data that forms the basis of the proposed indication consists of Part B2, an expansion cohort in unresectable or metastatic melanoma in a single, multicenter, open-label, randomized (1:1), dose-comparative, activity-estimating trial, has several issues that remain unresolved. Due to the trial design, a concern pertaining to efficacy that was observed exists as the trial was not blinded and the patient population was heterogeneous. Additionally, the trial had multiple protocol amendments to increase the sample size, study additional tumor types, and the primary endpoint was revised. Despite the concerns, the durability of responses in Part B2 and additional efficacy data in the supplemental cohorts, Parts B1 and D, provide supportive evidence of efficacy.

As MK-3475 is a monoclonal antibody that targets PD-1, one issue is whether anti-tumor activity is modulated by PD-1 expression in patients. The patients in this trial had a retrospective evaluation of PD-L1 expression and the data were not included at the time of the BLA submission.

Additionally, the question of clinical benefit with the endpoint of ORR as a surrogate for survival remains. Confirmatory studies are ongoing for MK-3475 in patients with melanoma, as discussed in Section 1.4.

## 7 Review of Safety

### **Safety Summary**

The safety of MK-3475 was primarily evaluated in patients from Part B2 of trial P001 who were randomized to receive MK-3475 at a dose of 2mg/kg every 3 weeks (Part B2-2q3, N=89). Patients in Part B2 had documented disease progression following treatment with ipilimumab, and a BRAF or MEK inhibitor if indicated. Patients were excluded if they had severe immune-related toxicity related to ipilimumab defined as any Grade 4 toxicity requiring treatment with steroids or Grade 3 toxicity requiring

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steroid treatment (>10mg/day prednisone or equivalent dose) for >12 weeks, had a medical condition that required systemic steroids or other immune suppressive medication, had a history of pneumonitis or interstitial lung disease, or had any active infection requiring therapy, including HIV or hepatitis B or C. In Part B2, 34% of patients were ≥65 years of age (range 18-88), 54% were male, and all but two patients were white. The average treatment duration of MK-3475 was 203 days (range 1-465 days); 45 patients were treated for greater than 6 months and 19 for greater than one year.

The safety of MK-3475 was also evaluated in all patients with unresectable or metastatic melanoma treated on Parts B1, B2, and D of trial P001 (Melanoma ISS, N=411). These patients received MK-3475 at a dose of either 2mg/kg every 3 weeks (N=162), 10mg/kg every 3 weeks (N=192), or 10mg/kg every 2 weeks (N=57). Patients in the Melanoma ISS were either treatment naïve or refractory to previous therapy.

The most common adverse events in trial P001, Part B2-2q3 were fatigue (47%), cough (30%), pruritus (30%), rash (29%), nausea (28%), and decreased appetite (25%). Most were Grade 1-2. The safety profile of common adverse events was similar for the Melanoma ISS. No patients had treatment-emergent Grade 5 events within 30 days of MK-3475 on Part B2 2q3.

Thirty percent of patients in Part B2-2q3 and 35% in Melanoma ISS experienced an SAE. The most common SAEs in ≥ 2% of patients in the Melanoma ISS were renal failure/acute renal failure (2.9%), dyspnea (2.4%), pneumonia (2.2%) and cellulitis (2.2%).

Grade 3-5 AEs occurred in 38.2% of patients in Part B2-2q3 and 38.9% of patients in the Melanoma ISS. Seven percent of patients in Part B2-2q3 and 10% of patients in the Melanoma ISS discontinued MK-3475 for AEs. Pneumonitis was the most common reason for discontinuation in 0.7% of the patients. Sixteen percent of patients in Part B2-2q3 and 18% of patients in the Melanoma ISS had treatment delays due to AEs.

Sixteen percent of patients had events that were considered immune-related as assessed by the investigator (irAEs) in Part B2-2q3. Only one of these events was greater than or equal to Grade 3. Twenty-three percent of patients in the Melanoma ISS experienced an immune-related adverse event as assessed by the investigator up to 90 days after their last dose of MK-3475. The most common immune-related adverse events in more than 1% of patients in the Melanoma ISS were rash (4%), hypothyroidism (4%), vitiligo (4%), pruritus (3%), arthralgia (2%), diarrhea (2%), pneumonitis (1.7%), myalgia (1.5%), cough (1.5%), and pyrexia (1.2%). Five percent were Grade 3 or 4 (colitis N=3, rash N=3, renal failure/renal failure acute N=2, and ALT increased, AST increased, autoimmune hepatitis, creatinine phosphokinase increased, diarrhea, hemolytic anemia, hyperthyroidism, hypothyroidism, pancreatitis, pancytopenia, and pleural effusion all N=1.)

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The safety profile of MK-3475 is acceptable in patients with melanoma that is refractory to treatment with ipilimumab, and a BRAF or MEK inhibitor if indicated, as this is a severe and life-threatening disease. This reviewer does not recommend a risk evaluation and mitigation strategy (REMS) given the current safety profile of MK-3475 and the experience of the medical community in managing immune-related adverse reactions based on use of other FDA-approved immune-modulating agents such as ipilimumab. The side-effect profile of MK-3475 regarding immune-mediated adverse events is similar to ipilimumab; however, available safety data suggests that these events are less severe. Recommendations for safe and effective use of MK-3475, including monitoring for immune-mediated adverse events, will be made in labeling, including a patient medication guide.

### 7.1 Methods

Analyses in the safety review used a cut-off date of October 18, 2013, unless otherwise specified. The safety update submitted by the Applicant had a cut-off date of December 31, 2013. The primary population used for the safety analyses of MK-3475 are the 89 patients from Part B2 of trial P001 who received 2mg/kg of MK-3475 every 3 weeks (Part B2-2q3). These patients with unresectable or metastatic melanoma refractory to ipilimumab are the population on which the indication is based. A total of 173 patients were treated in Part B2 of trial P001 and were randomized to MK-3475 at a dose of either 2mg/kg (n=89) or 10mg/kg (n=84) every 3 weeks. Data from the patients in Part B2 treated at 10mg/kg are used to explore any dose-related toxicities. Data from the Melanoma ISS population, which is defined in this review as the 411 patients with advanced melanoma treated in Parts B1, B2, and D of P001, was also reviewed for additional safety information of MK-3475 in patients with advanced melanoma. These patients received three dosage regimens of MK-3475 [2mg/kg q3w (n=162), 10mg/kg q3w (n=192), and 10mg/kg q2w (n=57)] and include both pre-treated and treatment-naïve patients.

In addition, the safety evaluation was supplemented with a review of data analyses and adverse event data from non-melanoma patients in Parts A and C of trial P001. Serious adverse event (SAE) line-listings for non-melanoma patients enrolled prior to the October 18, 2013 data cut-off in Part B3 and Cohort F of trial P001 and for patients enrolled on studies P002, P006, P010, and P012, which included approximately 983 additional patients, were included in the submission and were also reviewed in the safety analysis of MK-3475.

#### **REVIEWER COMMENT:**

*The Applicant did not use a treatment-emergent flag for their analyses. The Applicant stated that they used the EPOCH variable which consisted of “screening”, “cycle X”, “safety follow-up”, “extended safety follow-up”, and “post-study” terms. The start date of*

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*“extended safety follow-up” is 30 days after the last dose and the start date of “post-study” is 90 days after the last dose of MK-3475. The Applicant stated that their analyses of AEs excluded those in “screening”, “extended safety follow-up”, and “post-study”, and thus included AEs up to 30 days after the last dose of MK-3475. Analyses of SAEs excluded “screening” and “post-study” and thus included SAEs up to 90 days after the last dose of MK-3475. The same EPOCH variables were used by this reviewer for the safety analyses. For purposes of this review, the term treatment-emergent AE refers to AEs up to 30 days after the last dose of MK-3475. Some analyses done by this reviewer include data up to 90 days after the last dose of MK-3475 given the long half-life of the drug; however, since the protocol only mandated AE reporting up to 30 days, these analyses are considered exploratory as the data may be incomplete.*

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The majority of the data for this BLA submission is from 479 patients treated with MK-3475 on Protocol 001, Parts A, A1, A2, B1, B2, C, and D (see Table 2). The first and last patients who are included in the data provided in the study report were assigned to treatment on April 27, 2011, and April 5, 2013, respectively. The first patient in Part B2 received the first dose of study drug on August 12, 2012. The initial cut-off date for this application is October 18, 2013, and the safety update has a data cut-off date of December 31, 2013.

### 7.1.2 Categorization of Adverse Events

The Applicant coded verbatim adverse event (AE) terms for trial P001 using MedDRA version 16.1 and graded the severity of AE toxicities using CTCAE version 4 except for laboratory analyses which were coded using CTCAE version 3. Treatment-emergent adverse events are defined as all AEs occurring up to 30 days after the last dose of MK-3475. SAEs are reported up to 90 days after the last dose of MK-3475. The Applicant defined “extended safety follow-up” as the time period from 30 to 90 days after the last dose of MK-3475.

#### Immune-related adverse events:

The Applicant defined immune-related AEs (irAEs), as AEs that appear to be associated with an immune-mediated mechanism of action of MK-3475. Investigators were encouraged to rule out neoplastic, infectious, metabolic, toxic or other etiologies before characterizing an AE as an irAE, but the final determination of irAE was made by the investigator and recorded on the case report forms (CRFs). The Applicant further defined adverse events of special interest (AEOSI) which consisted of MedDRA preferred terms (PT) based on prior knowledge of immune-related AEs for other cancer immunotherapies and ongoing monitoring of trial P001 that suggested a potential immune etiology. If these AEs met prespecified CTCAE Grade criteria [as defined in an excerpt from the document “MK-3475 Event of Clinical Interest and Immune-Related

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Adverse Event Guidance Document” provided to investigators (see Appendix 9.6 MK-3475 Event of Clinical Interest Guidance Document)], they were reported regardless of investigator-determined causality and additional information was required for collection in the trial database. The first version of the guidance document was given to the investigators in August 2012 with a revised version in June 2013 that included the designation of AEOSI terms as shown in Appendix 9. The Applicant stated that investigators were encouraged to apply the criteria retrospectively, but the data may not be complete for patients who experienced these events prior to that time period; the Applicant performed its analyses of AEOSI events using an algorithm of MedDRA preferred terms (PT) and CTCAE Grades.

### *REVIEWER COMMENT:*

*The reviewer assessed the adequacy of the Applicant’s mapping of AE verbatim terms to MedDRA PTs for 100% of the P001 AE dataset. Of the 6,523 AE line listings in the AE.xpt dataset, the reviewer used matching of identical verbatim and MedDRA PTs (n=2,398 line listings) as well as manual evaluation of the remaining verbatim terms (n=4,125 line listings) to assess the acceptability of the Applicant’s mapping of verbatim term to MedDRA PT. The MedDRA PTs listed in the dataset adequately represented the verbatim term from the CRF in all but a few instances that did not affect the overall interpretation of the safety data.*

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Melanoma integrated summary of safety (ISS) is defined by this reviewer as data from the 411 patients with advanced melanoma treated in Parts B1, B2, and D of trial P001.

Table 21 lists the most common ( $\geq 10\%$ ) treatment-emergent adverse events for patients receiving 2mg/kg every 3 weeks in Part B2 and in the Melanoma ISS.

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**Table 21: Incidence of Treatment-Emergent Adverse Events (≥10%) by Toxicity Grade, B2-2q3 compared with Melanoma ISS**

Adverse Event	Part B2-2q3 N=89		Melanoma ISS N=411	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Fatigue	42 (47)	6 (7)	187 (46)	10 ( 2)
Cough	27 (30)	1 (1)	118 (29)	1 (0.2)
Pruritus	27 (30)	0	113 (28)	1 (0.2)
Nausea	25 (28)	0	121 (29)	8 ( 2)
Decreased appetite	22 (25)	0	76 (18)	3 (0.7)
Rash	19 (21)	0	98 (24)	3 (0.7)
Diarrhea	17 (19)	0	115 (28)	5 ( 1)
Arthralgia	17 (19)	0	101 (25)	1 (0.2)
Constipation	15 (17)	0	83 (20)	3 (0.7)
Pain in extremity	15 (17)	1 (1)	48 (12)	3 (0.7)
Dyspnea	15 (17)	2 (2)	75 (18)	10 ( 2)
Edema peripheral	14 (16)	1 (1)	53 (13)	2 (0.5)
Headache	14 (16)	0	74 (18)	4 ( 1)
Vomiting	13 (15)	0	65 (16)	9 ( 2)
Chills	12 (13)	0	44 (11)	0
Anemia	11 (12)	3 (3)	68 (17)	14 ( 3)
Back pain	11 (12)	1 (1)	55 (13)	4 ( 1)
Myalgia	11 (12)	1 (1)	52 (13)	1 (0.2)
Abdominal pain	10 (11)	0	50 (12)	6 ( 2)
Pyrexia	10 (11)	0	54 (13)	0
Upper respiratory tract infection	10 (11)	1 (1)	32 (8)	1 (0.2)
Dizziness	10 (11)	0	38 (9)	1 (0.2)
Vitiligo	10 (11)	0	47 (11)	0
Insomnia	9 (10)	0	36 ( 9)	0
Asthenia	8 ( 9)	(0)	55 (13)	1 (0.2)

(Source: AE.xpt)

*REVIEWER COMMENT: There were minor differences in AE counts from the Applicant's analysis and this reviewer's analysis of the AE.xpt dataset which are not expected to significantly impact the safety analysis of MK-3475.*

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## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In trial P001, 89 patients were treated with MK-3475 in Part B2 at a dose of 2mg/kg every 3 weeks and form the basis for the main efficacy and safety evaluation (see Section 6.1.2 Demographics). These patients received a median of nine doses of MK-3475 and were on trial for a median of 188 days with a range of 1 to 402 days. Table 22 summarizes the exposure to MK-3475 for patients in Part B2.

**Table 22: Summary of Exposure to MK-3475 for Part B2**

	MK-3475 2mg/kg q3w N=89	MK-3475 10mg/kg q3w N=84
Study days on therapy		
Mean	176	164
Median	188	186
SD	121	105
Range	1 to 402	1 to 378
Number of doses		
Mean	9	8
Median	9	10
SD	6	5
Range	1 to 20	1 to 19

(Source: CSR, Table 12-1)

Abbreviations in table: SD, standard deviation

There were 411 patients with advanced melanoma on trial P001 treated in Parts B1, B2, and D who provide additional relevant safety information (see Table 45 in Appendix 9.7). These patients received a median of 10 doses of MK-3475 and were on trial for a median of 188 days with a range of 1 to 680 days. Table 23 summarizes the exposure to MK-3475 for all melanoma patients.

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**Table 23: Summary of Exposure of MK-3475 for Melanoma ISS**

	MK-3475 2mg/kg q3w N=162	MK-3475 10mg/kg q3w N=192	MK-3475 10mg/kg q2w N=57	Total N=411
Study days on therapy				
Mean	196	197	314	213
Median	190	170	296	188
SD	139	152	250	169
Range	1 to 526	1 to 589	1 to 680	1 to 680
Number of doses				
Mean	10	10	21	12
Median	10	9	19	10
SD	6	7	16	10
Range	1 to 26	1 to 28	1 to 47	1 to 47

(Source: CSR, Table 12-3)

### 7.2.2 Explorations for Dose Response

As per the FDA Pharmacometric review there is a flat relationship between steady-state exposure of MK-3475 and overall response rate for patients in Part B2 who were treated with either 2 mg/kg or 10 mg/kg MK-3475 every 3 weeks. This provides supportive data for the proposed dose.

See the FDA Pharmacometric Review for details.

### 7.2.3 Special Animal and/or In Vitro Testing

See the summary of the FDA Pharmacology/Toxicology Review in section 4.3.

### 7.2.4 Routine Clinical Testing

See Section 5.3.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of the FDA Clinical Pharmacology Review in section 4.4.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Immune-related adverse events including colitis, dermatitis, autoimmune hepatitis, thyroiditis, uveitis, interstitial nephritis and hypophysitis are unique toxicities associated with this and other immune-modulating cancer therapies. The safety monitoring and treatment of these immune-related adverse events in trial P001 was similar to that done for the ipilimumab clinical program, in which similar immune-related toxicities are seen.

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### 7.3 Major Safety Results

#### 7.3.1 Deaths

A total of 32 patients (36%) from Part B2 receiving 2mg/kg q3w of MK-3475 had died at the time of data cutoff; 17 patients (19%) died within 90 days of their last dose of MK-3475. Disease progression was the most commonly reported cause of death (31/32, 97%). The patient death in Part B2-2q3 that was not related to disease progression was related to a Grade 5 AE (septic shock) which occurred within 90 days of her last dose of MK-3475. Review of the patient narrative and CRF follows:

- Patient 3475-001\_0008000422, a 49-year-old female with BRAF wild type melanoma diagnosed in (b) (6) previously treated with surgery, radiation therapy and ipilimumab, received her first and only dose of MK-3475 on (b) (6). On study day (D) 10 she was hospitalized with abdominal pain and jaundice and was found to have a common bile duct obstruction from a tumor mass at the head of the pancreas and other evidence of progressive disease. She underwent an ERCP with sphincterotomy and a common bile duct stent was placed. She was discharged on D12 with improving hepatic labs, but was readmitted on D39 with septic shock reportedly due to cholangitis and died 3 days later.

#### *REVIEWER COMMENT:*

*This reviewer's assessment of this patient death was that it was more likely related to her progressive disease and cholangitis and unlikely related to MK-3475.*

A total of 117 patients (28%) in the Melanoma ISS had died at the time of data cutoff; 68 deaths (16%) occurred within 90 days of the last dose of MK-3475. Disease progression was the most commonly reported cause of death (110/117, 94%).

Five deaths (1%) from AEs up to 90 days after the last dose of MK-3475 were reported in the Melanoma ISS. Two deaths were reported in the ce.xpt that occurred more than 90 days after the last dose of MK-3475: Patient 3475-001\_0010000030 (acute myocardial infarction) and Patient 3475-001\_0015000159 (septic shock).

Table 24 lists the reported causes of death for patients in the Melanoma ISS. The investigators reported that all Grade 5 AEs in Table 24 were unrelated to MK-3475.

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**Table 24: All Grade 5 Adverse Events in Melanoma ISS**

Subject ID	Age/Sex	MK-3475 Dose (Study Part)	Grade 5 Adverse Event	Last dose (study day)	Onset AE (study day)	Death (study day)	Investigator reported primary cause of death
3475-001_0008000422/	49/F	2mg/kg q3w (B2)	Septic shock	1	39	42	Septic shock
3475-001_0010000032/	69/M	10mg/kg q2w (B1)	Cellulitis	43	50	81	Cellulitis
3475-001_0010000052/	77/F	10mg/kg q2w (B1)	Pulmonary embolism	15	39	39	Pulmonary emboli
3475-001_0010000051/	94/M	10mg/kg q2w (B1)	Acute myocardial infarction	72	99	100	Cardiac failure
3475-001_0020000424	78/F	10mg/kg q3w (B2)	Increased LDH	20	87	87	Increased LDH

(Source: AE.xpt, ce.xpt, CRFs)

Abbreviations in table: F=female, M=male, q<sub>x</sub>w=every x weeks

### REVIEWER COMMENTS:

- The raw dataset (ce.xpt) and corresponding CRFs for patients in Table 24 were reviewed and no significant discrepancies were found.
- Patient (3475-001\_0020000424) had increased LDH listed as cause of death in ce.xpt. Review of the CRF revealed that the investigator had originally noted the immediate cause of death to be melanoma which was later changed to malignant neoplasm progression and then to increased LDH after multiple data queries.
- There were no additional deaths from AEs in patients in the Melanoma ISS reported in the safety update with a data cut-off of December 31, 2013.
- Deaths reported as related to AEs in the Melanoma ISS are typical for an advanced melanoma patient population and do not in nature of event or number of events suggest a causative effect of MK-3475.

### 7.3.2 Nonfatal Serious Adverse Events

Non-fatal serious adverse events up to 90 days after the last dose of MK-3475 occurred in 30% of patients in Part B2-2q3. Pneumonia (4.5%) and dyspnea (3.4%) were the most common SAEs reported. None of the cases of pneumonia and only one of the cases of dyspnea were considered drug-related by the investigators. SAEs with a potential autoimmune etiology included hyphophysitis (2.2%), pneumonitis (1.1%), hyperthyroidism (1.1%), intestinal obstruction (1.1%), and autoimmune hepatitis (1.1%). The investigators considered all cases of autoimmune SAEs drug-related with the

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exception of intestinal obstruction which resolved with bowel rest and did not recur with subsequent MK-3475 doses. Table 25 summarizes all non-fatal SAEs in Part B2-2q3.

**Table 25: Incidence of All Non-Fatal SAEs, Part B2-2q3**

Adverse Event		Part B2-2q3 N=89 n (%)
Patients with at least one non-fatal SAE		27 (30.3)
Infections and infestations		9 (10.1)
	Pneumonia	4 (4.5)
	Lung infection	1 (1.1)
	Sepsis	1 (1.1)
	Upper respiratory tract infection	1 (1.1)
	Urinary tract infection	1 (1.1)
	Wound infection	1 (1.1)
Neoplasms benign, malignant and unspecified		7 (7.9)
	Malignant melanoma	2 (2.2)
	Tumor pain	2 (2.2)
	Metastases to central nervous system	1 (1.1)
	Metastatic pain	1 (1.1)
	Squamous cell carcinoma	1 (1.1)
Respiratory, thoracic and mediastinal disorders		7 (7.9)
	Dyspnea	3 (3.4)
	Pleural effusion	2 (2.2)
	Hypoxia	1 (1.1)
	<sup>**</sup> Pneumonitis	1 (1.1)
Metabolism and nutrition disorders		5 (5.6)
	Dehydration	2 (2.2)
	Diabetes mellitus (steroid-induced)	1 (1.1)
	Failure to thrive	1 (1.1)
	Hyponatremia	1 (1.1)
Nervous system disorders		4 (4.5)
	Encephalopathy	1 (1.1)
	Hemorrhage intracranial	1 (1.1)
	Partial seizures	1 (1.1)
	Spinal cord compression	1 (1.1)
Endocrine disorders		3 (3.4)
	<sup>**</sup> Hypophysitis	2 (2.2)
	<sup>**</sup> Hyperthyroidism	1 (1.1)
Gastrointestinal disorders		3 (3.4)
	Ascites	1 (1.1)
	Constipation	1 (1.1)
	<sup>^</sup> Small intestinal obstruction	1 (1.1)
Cardiac disorders		2 (2.2)

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Adverse Event		Part B2-2q3 N=89 n (%)
	Atrial fibrillation	1 ( 1.1)
	Atrial flutter	1 ( 1.1)
General disorders and administration site conditions		2 ( 2.2)
	Generalized edema	1 ( 1.1)
	Non-cardiac chest pain	1 ( 1.1)
Musculoskeletal and connective tissue disorders		2 ( 2.2)
	Musculoskeletal pain	1 ( 1.1)
	Pain in extremity	1 ( 1.1)
Hepatobiliary disorders		1 ( 1.1)
	*Autoimmune hepatitis	1 ( 1.1)
Psychiatric disorders		1 ( 1.1)
	Confusional state	1 ( 1.1)
Skin and subcutaneous tissue disorders		1 ( 1.1)
	Hemorrhage subcutaneous	1 ( 1.1)

(Source: AE.xpt)

\* Designated irAE by investigator

^ Designated AEOSI by investigator

Note: PT term "malignant neoplasm progression" excluded from analysis

### **Immune-related SAEs**

Narratives for patients with SAEs considered to be an immune-related event (irAE) or an adverse event of special interest (AEOSI) related to MK-3475 in Part B2-2q3 including hyphophysitis (n=2), pneumonitis (n=1), and hyperthyroidism (n=1) are below:

Patient 3475-001\_0011000291, a 74-year-old male with BRAF wild type melanoma with disease involving the skin at study entry and a relevant history of diabetes and hyphophysitis who had previously received IPI developed an SAE of **hyphophysitis** (irAE and AEOSI). On study day 52 after 3 doses of MK-3475, the patient presented with weakness, mental status change, fever, hyponatremia and pituitary abnormality on CT scan and was diagnosed with Grade 4 hyphophysitis. MK-3475 was held as a result of this event and he did not receive further doses. The patient was treated with hydrocortisone, levothyroxine and supportive care and discharged on study day 58. After initial improvement, the patient was readmitted to the hospital on study day 83 for 3 days with adrenal insufficiency, hypothyroidism and urinary tract infection following a taper of prednisone. The patient was again admitted on day 90 for 8 days for weakness, hyponatremia, and hyperglycemia. Grade 2 hyphophysitis was reported as ongoing and the patient reportedly died of progressive disease in hospice care on study day 155.

Patient 3475-001\_0012000389, a 69-year-old female with BRAF wild type melanoma and disease involving lymph nodes and lungs at study entry and no relevant medical history except for previous treatment with IPI experienced an SAE of **hyphophysitis**

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(irAE and AEOSI). On study day 34 after 2 doses of MK-3475, she presented with severe fatigue, weakness and visual changes. Her free and total T3, free T4 and thyroid antithyroglobulin antibodies were elevated, TSH was decreased and she was diagnosed with Grade 3 immune-related **hyperthyroidism** (irAE and AEOSI). She was also hyponatremic and diagnosed with Grade 3 adrenal insufficiency considered unrelated to MK-3475 by the investigator. Brain MRI showed slight enlargement of the infundibulum with no enlargement of the pituitary gland. She was treated with hydrocortisone with improvement of symptoms. Hypophysitis was recorded as resolved on Study day 140, hyperthyroidism and adrenal insufficiency was listed as still ongoing. MK-3475 was discontinued as result of these events.

Patient 3475-001\_0010000265, a 61-year-old female with BRAF mutant melanoma with disease in the lower back and lymph nodes at the time of study entry and no relevant medical history developed an SAE of Grade 3 **pneumonitis** (irAE, AEOSI) on study day 170. MK-3475 was held as a result of the pneumonitis. She was treated with prednisone starting on study day 182 after infectious etiologies were eliminated. The patient was reportedly fully recovered and resumed study treatment. Following her ninth dose of MK-3475 on study day 211 she presented with **recurrent pneumonitis** (irAE, AEOSI, Grade 2). She was treated with prednisone, and empiric fluconazole and levofloxacin. The patient was reported as fully recovered by study day 385 and steroids were ongoing at the time of report. MK-3475 was permanently discontinued as a result of the pneumonitis.

Patient 3475-001\_0015000336, a 58-year-old male with BRAF wild type melanoma with disease involving the skin and no relevant medical history experienced an SAE of Grade 4 **autoimmune hepatitis** (irAE, AEOSI). On study day 29 after one dose of MK-3475, the patient presented with an 8 day history of abdominal pain, nausea and emesis. ALT was 1482 U/L, AST was 819 U/L and bilirubin was 5 mg/dL. Liver tests were within normal limits on study entry. The patient was hospitalized and treated with methylprednisolone followed by prednisone with improvement. No biopsy was performed. As per the LB.xpt dataset, by study day 83, ALT, AST, and bilirubin were normal. MK-3475 was discontinued as a result of the event.

Patient 3475-001\_0016000313, a 62-year-old male with BRAF V600 wild type melanoma with disease involving the lungs was reported to have Grade 2 **dyspnea** and Grade 3 **hypoxia**. No results of chest imaging were provided. The patient was treated with dexamethasone and supplemental oxygen and symptoms were reported to improve. MK-3475 was discontinued as a result of these events.

*REVIEWER COMMENT: FDA requested additional information from the Applicant regarding this event as there was concern that this patient may represent an additional SAE of pneumonitis. A CT scan was obtained and showed "innumerable pulmonary nodules throughout both lungs" consistent with metastatic melanoma, and "scattered*

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*ground glass opacities in the right lower lobe". The patient had a bronchiolaveolar lavage (BAL) which showed *Enterobacter aerogenes*, *Candida dubliensis*, and *M* abscessus. He was treated with antibacterial and antifungal therapy along with steroids and experienced resolution of symptoms. The treating physician's assessment was that this was an infectious process given the focal CT finding. This reviewer's assessment of this case is that determining exact etiology of the respiratory symptoms in this case is challenging and may have been multifactorial including both infectious and immune-related causes.*

Other selected SAE narratives:

Patient 0259 a 66-year-old male with BRAF wild type melanoma with disease involving the soft tissue, lymph nodes, lungs and liver and a relevant history of hypertension and diabetes experienced an SAE of **partial seizures**. He received a total of 10 doses of MK-3475. On study day 162, the patient had occasional tremors of the left arm. On study day 190, the tremors increased and an MRI showed diffuse bilateral T2/flair hyperintensity involving the caudate and temporal lobes with enhancement also noted in the left cortical/subcortical and occipital regions and right frontal cortex. An EEG showed right central region epileptiform transients consistent with encephalitis. The patient was treated first with dexamethasone and levetiracetam followed by oxacarbazepine and lorazepam for persistent seizures. On study day 225, the patient underwent a right frontal brain biopsy and pathology showed non-specific findings of "focal perivascular lymphocytic infiltrate and reactive vascular proliferation" consistent with an unidentified infectious or inflammatory cause. The patient discontinued drug as a result of this event and his seizures were reported as improving at the time of report.

Patient 0326 a 73-year-old female with BRAF V600 wild type melanoma with disease involving skin and lung and relevant medical history of resolved renal cell carcinoma, experienced an SAE of Grade 3 **encephalopathy** on study day 23. She complained of bilateral lower extremity weakness, unsteady gait, and slurred speech. She had a head CT that was nondiagnostic and was admitted to the hospital. Restaging of her disease was done at the same time and showed disease progression and MK-3475 was discontinued. No additional neurologic evaluations were reported and the patient resolved without any intervention and was discharged 3 days later.

### REVIEWER COMMENT:

*FDA requested additional information regarding this case and the Applicant stated that the site reported that the patient's symptoms were transient (lasting 15 minutes) and fully resolved without intervention prior to medical evaluation. No MRI was performed. Concomitant medications at the time were oxycontin, glipizide and metformin. No additional information was provided. This reviewer's assessment of this case is that the etiology of this event is unclear, and there is no pattern of similar events to attribute the patient's symptoms to MK-3475.*

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Patient 0114 an 88-year-old male with BRAF wild type melanoma with disease involving skin and lung and a relevant medical history of stable lower extremity peripheral neuritis and gait imbalance, hypothyroidism and history of polio experienced an SAE of **confusional state** along with generalized weakness and dysarthria. On study day 231, the patient experienced asthenia (Grade 2), confusional state (Grade 1) and dysarthria (Grade 1) leading to hospitalization for evaluation. A diagnostic evaluation (CT of brain, ECG, and chest X-ray) did not reveal any abnormality to reveal an etiology of his symptoms. The patient was started on prednisone 40 mg once daily and his symptoms reportedly improved significantly. The patient had previously been on steroids for arthralgias. On study day 233, the patient recovered from the confusional state and dysarthria. The patient recovered from generalized weakness on study day 243. MK-3475 was interrupted due to asthenia, confusional state, and dysarthria and was not restarted. The investigator considered asthenia, confusional state, and dysarthria to be possibly related to study treatment. Confusional state and dysarthria were reported by to be immune related.

Non-fatal SAEs were reported in 35% of patients in the Melanoma ISS. Non-fatal SAEs were more common in the 10mg/kg q2w subgroup (45.6%) than in the 10mg/kg q3w (33.9%) and 2mg/kg q3w (32.1%) subgroups. The most common SAEs reported in  $\geq$  2% of patients were renal failure/acute renal failure (2.9%), dyspnea (2.4%), pneumonia (2.2%), and cellulitis (2.2%). Table 26 lists the non-fatal SAEs reported in two or more patients in the Melanoma ISS.

**Table 26: Incidence of Non-Fatal SAEs in Two or More Patients, Melanoma ISS**

Severe Adverse Event	Melanoma ISS N=411 n (%)
Patients with at least 1 SAE	143 ( 35)
Renal failure/Renal failure acute	12 (2.9)
Dyspnea	10 (2.4)
Pneumonia	9 (2.2)
Cellulitis	9 (2.2)
Abdominal pain	7 (1.7)
Dehydration	7 (1.7)
Pleural effusion	7 (1.7)
Anemia	6 (1.5)
Vomiting	6 (1.5)
Pyrexia	6 (1.5)
Squamous cell carcinoma	6 (1.5)
Nausea	5 (1.2)
Urinary tract infection	5 (1.2)
Colitis	4 (1 )

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Severe Adverse Event	Melanoma ISS N=411 n (%)
Sepsis	4 (1 )
Spinal cord compression	4 (1 )
Pulmonary embolism	4 (1 )
Cardiac failure congestive	3 (0.7)
Pericardial effusion	3 (0.7)
Constipation	3 (0.7)
Small intestinal obstruction	3 (0.7)
Diarrhea	3 (0.7)
Pain	3 (0.7)
Asthenia	3 (0.7)
Confusional state	3 (0.7)
Tumor pain	3 (0.7)
Tumor hemorrhage	3 (0.7)
Dizziness	3 (0.7)
Pneumonitis	3 (0.7)
Atrial fibrillation	2 (0.5)
Hypophysitis	2 (0.5)
Hyperthyroidism	2 (0.5)
Ascites	2 (0.5)
Intestinal obstruction	2 (0.5)
Intestinal perforation	2 (0.5)
Esophagitis	2 (0.5)
Fatigue	2 (0.5)
Bile duct stone	2 (0.5)
Lung infection	2 (0.5)
Diabetes mellitus	2 (0.5)
Failure to thrive	2 (0.5)
Hyponatremia	2 (0.5)
Hyperglycemia	2 (0.5)
Hypoglycemia	2 (0.5)
Musculoskeletal pain	2 (0.5)
Pain in extremity	2 (0.5)
Muscular weakness	2 (0.5)
Malignant melanoma	2 (0.5)
Basal cell carcinoma	2 (0.5)
Hemorrhage intracranial	2 (0.5)
Convulsion	2 (0.5)
Embolism	2 (0.5)

(Source: AE.xpt)

Note: term "malignant neoplasm progression" excluded

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### REVIEWER COMMENTS:

- *Renal failure was more commonly reported as an SAE in patients receiving MK-3475 at a dose of 10mg/kg either q3w or q2w. Twelve cases (12/249, 4.5%) were reported overall, seven (3.6%) in the 10mg/kg q3w arm and five (8.8%) in the 10mg/kg q2w arm. No cases of renal failure as an SAE were reported in patients receiving 2mg/kg q3w of MK-3475. The limitations of determining causality in this analysis include that this is a single arm trial and some of the cases have plausible alternative explanations; however, renal impairment is a potential safety concern with MK-3475, particularly as there may be a dose-response relationship.*
- *The clinical review of safety included a review of the SAE line-listings and tables from melanoma patients in Parts B3 and F of trial P001; non-melanoma patients in Parts A and C of trial P001; and melanoma and non-melanoma patients in trials 002, 006, and 012. This review showed a toxicity profile of MK-3475 that is generally consistent with the toxicity profile demonstrated in Part B2-2q3 and the Melanoma ISS. Notable SAEs identified in this review were:*
  - *Patient 100006 with Stevens Johnson Syndrome*
  - *Patient 100042 with myasthenic syndrome with isolated bilateral eye ptosis occurring 3 months after treatment that did not respond to plasmapheresis or steroids (Acetylcholine receptor antibody test, muscle-specific tyrosine kinase antibody and anti-titin antibody were negative.)*
  - *Patient 0063 with Grade 3 hemolytic anemia*
  - *Patient 0068 with Grade 3 rhabdomyolysis*
  - *Patient 101820 with melanoma and liver metastases with fatal liver failure approximately 20 days after the first dose of MK-3475 (reported as not related to MK-3475, related to disease progression of hepatic metastases)*

### 7.3.3 Dropouts and/or Discontinuations

Sixty-one percent (54/89) of patients in Part B2-2q3 discontinued MK-3475 at the time of data cut-off. The most common reason for discontinuation was progressive disease in 38% of patients. The reasons for discontinuation are summarized in Table 27.

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**Table 27: Summary of Treatment Discontinuations, Part B2-2q3**

	Part B2-2q3 N=89 n (%)
Total Discontinued	54 (61)
Disease Progression	34 (38)
Adverse Event	12 (13)
Subject Withdrew Consent	2 ( 2)
Protocol Violation	2 ( 2)
Physician Decision	3 ( 3)
Lost to follow up	1 ( 1)

(Source: DS.xpt)

**REVIEWER COMMENT:**

The discontinuation due to AEs category presented in Table 27 included five patients who discontinued MK-3475 due to clinical disease progression. Patients must have had imaging for the investigator to list "Disease Progression" as a reason for study medication discontinuation on the CRF.

Seven percent (8/89) of patients discontinued MK-3475 due to adverse events at the time of initial data cutoff. All events except hemiparesis, considered related to disease progression in a patient with brain metastases, were assessed as related to MK-3475. Table 28 lists the adverse events that led to discontinuation.

**Table 28: AEs Leading to Treatment Discontinuation, Part B2-2q3**

Patient ID	Age/ Sex	Adverse Event	Onset (D)	Duration (D)	Outcome
3475-001_0015000336	58/M	Autoimmune Hepatitis	22	32	R
3475-001_0001000284	65/M	Fatigue	148	34	R <sup>^</sup>
3475-001_0023000276	52/F	Hemiparesis	69	-	O <sup>^</sup>
3475-001_0012000389	68/F	Hyperthyroidism	40	184	R
		Hyphophysitis	40	100	R
3475-001_0012000259	65/M	Partial seizures	197	-	O
3475-001_0010000265	61/F	Pneumonitis	229	156	R
3475-001_0008000422	49/F	Septic shock	39	3	F
3475-001_0016000313	62/M	Hypoxia	129	5	R
		Dyspnea	129	5	R

(Source: AE.xpt, DS.xpt, CRFs)

Abbreviations: F, female; M, male; O, ongoing; R, resolved; F, fatal at time of death

<sup>^</sup> Site updated CRF after data cut-off to MK-3475 interrupted, not discontinued

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**REVIEWER COMMENT:**

*According to review of CRFs for treatment discontinuations in patients in Part B2-2q3, AEs were listed as resolved at the time of death in the AE.xpt even if ongoing prior. This reviewer modified the outcome for patient 3475-001\_0023000276 in the table above as ongoing as a value for duration of the AE is unreliable in this situation and can alter certain time-dependent analyses of AEs.*

Forty-two patients (10%) discontinued MK-3475 due to an AE at the time of data cut-off in the Melanoma ISS. Pneumonitis was the most common reason for treatment discontinuation due to AE (0.7%). (Source: AE.xpt; DS.xpt)

Table 29 summarizes the incidence of AEs leading to treatment discontinuation in the Melanoma ISS and Table 30 lists the AEs leading to treatment discontinuation by patient in the Melanoma ISS.

**Table 29: Incidence of AEs leading to Discontinuation, Melanoma ISS**

<b>Adverse Event</b>	<b>Melanoma ISS N=411 n (%)</b>
Respiratory, thoracic and mediastinal disorders	10 (2.4)
Pneumonitis	3 (0.7)
Dyspnea	1 (0.2)
Hypoxia	1 (0.2)
Interstitial lung disease	1 (0.2)
Pleural effusion	1 (0.2)
Pneumothorax	1 (0.2)
Respiratory distress	1 (0.2)
Respiratory failure	1 (0.2)
Musculoskeletal and connective tissue disorders	5 (1.2)
Arthralgia	1 (0.2)
Myopathy	1 (0.2)
Myositis	1 (0.2)
Pain in extremity	1 (0.2)
Rhabdomyolysis	1 (0.2)
Nervous system disorders	4 (1 )
Cerebrovascular accident	1 (0.2)
Hemiparesis	1 (0.2)
Partial seizures	1 (0.2)
Peripheral sensory neuropathy	1 (0.2)
General disorders and administration site conditions	4 (1 )

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Adverse Event	Melanoma ISS N=411 n (%)
Fatigue	2 (0.4)
Pain	2 (0.4)
Gastrointestinal disorders	3 (0.7)
Gastrointestinal hemorrhage	1 (0.2)
Hematochezia	1 (0.2)
Pancreatitis	1 (0.2)
Hepatobiliary disorders	3 (0.7)
Autoimmune hepatitis	1 (0.2)
Bile duct obstruction	1 (0.2)
Hyperbilirubinemia	1 (0.2)
Infections and infestations	3 (0.7)
Cellulitis	1 (0.2)
Sepsis	1 (0.2)
Septic shock	1 (0.2)
Neoplasms benign, malignant and unspecified	3 (0.7)
Cancer pain	1 (0.2)
Metastases to central nervous system	1 (0.2)
Metastases to meninges	1 (0.2)
Cardiac disorders	3 (0.7)
Acute myocardial infarction	2 (0.5)
Cardiac failure	1 (0.2)
Renal and urinary disorders	3 (0.7)
Renal failure	2 (0.5)
Renal failure acute	1 (0.2)
Blood and lymphatic system disorders	2 (0.5)
Hemolytic anemia	1 (0.2)
Thrombocytopenia	1 (0.2)
Endocrine disorders	2 (0.5)
Hyperthyroidism	1 (0.2)
Hypophysitis	1 (0.2)
Injury, poisoning and procedural complications	2 (0.5)
Wound decomposition	1 (0.2)
Wound hemorrhage	1 (0.2)
Investigations	2 (0.5)
ALT increased	1 (0.2)
Blood LDH increased	1 (0.2)
Metabolism and nutrition disorders	2 (0.5)
Decreased appetite	1 (0.2)

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Adverse Event	Melanoma ISS N=411 n (%)
Hypoglycemia	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.2)
Skin lesion	1 (0.2)

(Source: AE.xpt; DS.xpt)

**Table 30: Listing of AEs Leading to Treatment Discontinuation, Melanoma ISS**

System Organ Class		Onset (D)	Duration (days)	Outcome
Patient ID	Adverse Event			
<b>Blood and lymphatic disorders</b>				
3475-001_0021000063	Hemolytic anemia	323	21	R
3475-001_0011000520	Thrombocytopenia	69	-	O
<b>Cardiac disorders</b>				
3475-001_0010000051	Acute myocardial infarction	99	1	F
	Cardiac failure	100	-	F
<b>Endocrine disorders</b>				
3475-001_0012000389	Hyperthyroidism	40	184	R
	Hyphophysitis	40	100	R
<b>Gastrointestinal disorders</b>				
3475-001_0015000177	Hematochezia	283	1	R
3475-001_0002000395	Pancreatitis	76	-	O
3475-001_0002000053	Gastrointestinal hemorrhage	7	5	R
<b>General disorders and administration site conditions</b>				
3475-001_0023000174	Pain	21	14	R
3475-001_0015000355	Pain	37	4	R
3475-001_0001000284	Fatigue	148	34	R <sup>^</sup>
3475-001_0001000079	Fatigue	155	27	R
<b>Hepatobiliary disorders</b>				
3475-001_0021000064	Hyperbilirubinemia	15	-	O
3475-001_0020000501	Bile duct obstruction	37	10 <sup>^</sup>	O <sup>^</sup>
3475-001_0015000336	Autoimmune hepatitis	22	32	R
<b>Infections and infestations</b>				
3475-001_0015000406	Sepsis	155	7	R <sup>^</sup>
3475-001_0010000032	Cellulitis	50	31	F
3475-001_0008000422	Septic shock	39	3	F
<b>Injury, poisoning and procedural complications</b>				
3475-001_0023000094	Wound decomposition	60	140	R
3475-001_0019000131	Wound hemorrhage	15	22	R
<b>Investigations</b>				
3475-001_0023000090	Alanine aminotransferase increased	20	7	R

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System Organ Class		Onset (D)	Duration (days)	Outcome
Patient ID	Adverse Event			
3475-001_0020000424	Blood lactate dehydrogenase increased	40	-	O
<b>Metabolism and nutrition disorders</b>				
3475-001_0015000360	Hypoglycemia	7	8*	O*
3475-001_0001000079	Decreased appetite	141	42	R
<b>Musculoskeletal and connective tissue disorders</b>				
3475-001_0024000110	Myositis	54	150	R
3475-001_0019000351	Pain in extremity	84	-	O
3475-001_0019000116	Arthralgia	71	16	R
3475-001_0015000039	Myopathy	365	-	O*
3475-001_0011000068	Rhabdomyolysis	101	-	O
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>				
3475-001_0021000378	Metastases to central nervous system	33	-	O
3475-001_0021000149	Cancer pain	167	-	O
3475-001_0012000386	Metastases to meninges	10	-	O
<b>Nervous system disorders</b>				
3475-001_0023000276	Hemiparesis	69	100	O*
3475-001_0015000039	Peripheral sensory neuropathy	365	-	O
3475-001_0012000259	Partial seizures	197	-	O
3475-001_0011000520	Cerebrovascular accident	58	12	R
<b>Renal and urinary disorders</b>				
3475-001_0015000048	Renal failure acute	388	33	R
3475-001_0010000051	Renal failure	100	1*	O*
3475-001_0001000061	Renal failure	351	17	R
<b>Respiratory, thoracic and mediastinal disorders</b>				
3475-001_0021000534	Respiratory distress	64	-	O
3475-001_0021000076	Interstitial lung disease	2	71	R
3475-001_0016000313	Dyspnea	129	5	R
	Hypoxia	129	5	R
3475-001_0012000088	Pneumonitis	295	139	R
3475-001_0010000265	Pneumonitis	229	156	R
3475-001_0003000066	Pneumonitis	141	267	R
3475-001_0010000051	Pleural effusion	86	14*	O*
	Pneumothorax	97	3*	O*
	Respiratory failure	96	4*	O*
<b>Skin and subcutaneous tissue disorders</b>				
3475-001_0020000393	Skin lesion	66	15	R

(Source: AE.xpt; DS.xpt, CRFs)

Abbreviations: D, Study day; R, recovered; O, ongoing; F, fatal at time of death

\* Site updated CRF after data cut-off to MK-3475 interrupted, not discontinued

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### *REVIEWER COMMENT:*

*The Applicant used a cut-off date of 30 days after the last dose of MK-3475 in the analyses of AEs leading to treatment discontinuation, which identified 36 patients. Given the delayed nature of some adverse events related to MK-3475, this reviewer evaluated all data up to the data cut-off, irrespective of time of onset in relation to time of the last MK-3475 dose, and identified an additional six patients who discontinued MK-3475 due to AE. Review of the additional AEs did not alter the interpretation of the safety analysis.*

## 7.3.4 Significant Adverse Events

### **Treatment Delays**

#### *REVIEWER COMMENT:*

*The P001 protocol specified that MK-3475 could not be dose reduced for subsequent administrations in patients experiencing toxicity; however, the protocol permitted dose delays up to 12 weeks.*

Fourteen out of 89 (16%) patients in Part B2-2q3 had MK-3475 interrupted for AEs. Only fatigue caused treatment delay in more than one patient. Table 31 summarizes the AEs leading to treatment delays in Part B2-2q3.

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**Table 31: Incidence of AEs Leading to Treatment Delays, Part B2-2q3**

Adverse Event	Part B2-2q3 N=89 n (%)
Any Patients with delay	14 (15.7)
Fatigue	2 ( 2.2)
Rash	1 ( 1.1)
Alanine aminotransferase increased	1 ( 1.1)
Aspartate aminotransferase increased	1 ( 1.1)
Anemia	1 ( 1.1)
Diarrhea	1 ( 1.1)
Blood bilirubin increased	1 ( 1.1)
Hyponatremia	1 ( 1.1)
Abdominal pain	1 ( 1.1)
Arthralgia	1 ( 1.1)
Bronchiectasis	1 ( 1.1)
Chills	1 ( 1.1)
Cognitive disorder	1 ( 1.1)
Hepatomegaly	1 ( 1.1)
Hypophysitis	1 ( 1.1)
Menorrhagia	1 ( 1.1)
Metastases to central nervous system	1 ( 1.1)
Mucosal inflammation	1 ( 1.1)
Myalgia	1 ( 1.1)
Neutrophilic dermatosis	1 ( 1.1)
Pyrexia	1 ( 1.1)
Skin infection	1 ( 1.1)

(Source: AE.xpt)

Seventy-two out of 411 (18%) of patients in the Melanoma ISS had delays in administration of MK-3475 due to AEs. Table 32 summarizes the AEs leading to treatment delays reported in two or more patients in the Melanoma ISS.

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**Table 32: Incidence of AEs Leading to Treatment Delays in Two or More Patients, Melanoma ISS**

Adverse Event	Melanoma ISS N=89 n (%)
Patients with delay	72 ( 18)
Rash	7 (1.7)
Alanine aminotransferase increased	6 (1.4)
Aspartate aminotransferase increased	6 (1.4)
Pneumonitis	5 (1.2)
Anemia	4 (1.0)
Diarrhea	4 (1.0)
Hypothyroidism	4 (1.0)
Blood bilirubin increased	3 (0.7)
Dehydration	3 (0.7)
Fatigue	3 (0.7)
Hyponatremia	3 (0.7)
Upper respiratory tract infection	3 (0.7)
Abdominal pain	2 (0.5)
Arthralgia	2 (0.5)
Cellulitis	2 (0.5)
Colitis	2 (0.5)
Cough	2 (0.5)
Decreased appetite	2 (0.5)
Nausea	2 (0.5)
Pruritus	2 (0.5)
Rash maculo-papular	2 (0.5)
Urinary tract infection	2 (0.5)

(Source: AE.xpt)

One patient in Part D of trial P001 had a treatment delay due to tuberculosis (TB). This case is of note given the preclinical data regarding TB in mice (See Section 4.3 and FDA Pharmacology/Toxicology review); however, the clinical significance of a single case is uncertain.

Patient 0537, a 50-year-old male with BRAF wild type melanoma with disease involving skin, lung, and adrenal glands who had not previously received ipilimumab, was diagnosed with tuberculosis (TB) on study day 85. The patient had received four doses of MK-3475 at a dose of 10mg/kg q3w prior to the development of TB. On study day 152, the patient was hospitalized for thoracoscopy and talc pleurodesis. On day 153,

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the pathology was reported to show epithelial granuloma and giant cell with a final diagnosis of TB. The patient was treated with rifater and dexambutol. The outcome of TB was reported as recovered on day 153 and was discharged from the hospital 5 days later. MK-3475 was interrupted due to this event and resumed on day 106. The patient reportedly had contact with a patient with TB in the past.

### Treatment-Emergent Grade 3-5 Events

Treatment emergent Grade 3-5 AEs occurred in 38.2% of patients in Part B2-2q3. There were two Grade 4 events (autoimmune hepatitis and hypophysitis) but no Grade 5 events. Table 33 lists Grade 3-4 AEs reported in two or more patients in Part B2-2q3.

**Table 33: Treatment-emergent Grade 3-4 AEs in Two or More Patients, Part B2-2q3**

Adverse Event	Part B2-2q3 N=89 n (%)
Any Grade 3-4 event	34 (38.2)
Fatigue	6 ( 6.7)
Pneumonia	4 ( 4.5)
Anemia	3 ( 3.4)
Dehydration	3 ( 3.4)
Dyspnea	2 ( 2.2)
Muscular weakness	2 ( 2.2)
Hyponatremia	2 ( 2.2)
Tumor pain	2 ( 2.2)

(Source: AE.xpt)

Treatment-emergent Grade 3-5 AEs occurred in 38.9% of patients in the Melanoma ISS. There was no significant difference in Grade 3-5 events for patients receiving 2mg/kg of MK-3475 every 3 weeks who had previously been treated with ipilimumab (38.2%) compared to those who were naïve to ipilimumab (31.4%); however no formal randomized comparison was performed. Table 34 lists the Grade 3-5 AEs that occurred in greater than or equal to 1% of patients in the Melanoma ISS.

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**Table 34: Incidence of Treatment-emergent Grade 3-5 AEs in ≥1% of Patients, Melanoma ISS**

Adverse Event	Melanoma ISS N=411			
	Grade 3-5 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Anemia	14 (3.4)	14 (3.4)	0	0
Fatigue	10 (2.4)	10 (2.4)	0	0
Dyspnea	10 (2.4)	9 (2.2)	1 (0.2)	0
Vomiting	9 (2.2)	9 (2.2)	0	0
Cellulitis	9 (2.2)	8 (1.9)	0	1 (0.2)
Nausea	8 (1.9)	8 (1.9)	0	0
Dehydration	8 (1.9)	8 (1.9)	0	0
Pneumonia	8 (1.9)	8 (1.9)	0	0
AST increased	7 (1.7)	6 (1.5)	1 (0.2)	0
Renal failure/Acute renal failure	7 (1.7)	5 (1.2)	2 (0.5)	0
Hyponatremia	7 (1.7)	6 (1.5)	1 (0.2)	0
Abdominal Pain	6 (1.5)	6 (1.5)	0	0
Pleural effusion	6 (1.5)	6 (1.5)	0	0
Diarrhea	5 (1.2)	5 (1.2)	0	0
ALT increased	5 (1.2)	5 (1.2)	0	0
Hypertension	5 (1.2)	5 (1.2)	0	0
Pulmonary embolism	5 (1.2)	3 (0.7)	1 (0.2)	1 (0.2)
Blood bilirubin increased	5 (1.2)	5 (1.2)	0	0
Headache	4 ( 1)	4 ( 1)	0	0
Back pain	4 ( 1)	4 ( 1)	0	0
Gamma-glutamyltransferase increased	4 ( 1)	4 ( 1)	0	0
Squamous cell carcinoma	4 ( 1)	3 (0.7)	1 (0.2)	0
Sepsis	4 ( 1)	2 (0.5)	2 (0.5)	0

(Source: AE.xpt)

PT malignant neoplasm progression excluded

*REVIEWER COMMENT: Although there was no major differences between Grade 3-5 AEs experienced by patients treated with 2mg/kg of MK-2375 every 3 weeks who had previously been treated with ipilimumab and those who had not, the protocol excluded patients who had significant side effects to ipilimumab (Grade 4 requiring steroid treatment or Grade 3 requiring steroid treatment with >10 mg/day prednisone or equivalent dose for >12 weeks), so there is no toxicity data for patients who experience significant side effects with ipilimumab.*

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### 7.3.5 Submission Specific Primary Safety Concerns

This review further discusses the following adverse events which are likely immune-mediated given the mechanism of action of MK-3475 and similar events seen with other immune-modulating agents:

- Pneumonitis
- Colitis
- Hepatitis
- Hypophysitis
- Thyroid disorders
- Nephritis

The review also discusses acute renal failure/renal failure as a potential safety signal with MK-3475.

The data below is from the Applicant analysis of immune-related adverse events and steroid use as requested by FDA and from FDA analyses of the safety dataset (AE.xpt), CSR, and Applicant safety update. Given the small numbers of patients overall who experienced these events, the analyses and data reported below are for the Melanoma ISS.

#### Pneumonitis

There were 12 cases of pneumonitis (2.9%) and 2 cases of interstitial lung disease in the Melanoma ISS as of the safety update. Grade 3 pneumonitis occurred in 0.2%; there were no Grade 4 or 5 cases of pneumonitis.

The median time to development of pneumonitis was 21.8 weeks (range 0.3 - 43.1). The median duration of pneumonitis was 21.1 weeks (range 1 - 62.4). Discontinuation of MK-3475 due to pneumonitis was reported in 0.5% of patients.

Five of eight patients with Grade 2 and the single patient with Grade 3 pneumonitis were treated initially with high-dose oral or intravenous corticosteroids ( $\geq 40$  mg prednisone equivalent per day), with a median initial dose of 63.4 mg/day of prednisone or equivalent. The median duration of initial treatment was 3 days (range 1 - 34), followed by a corticosteroid taper. One of eight patients with Grade 2 pneumonitis was treated with low-dose systemic corticosteroids, 30 mg prednisone equivalent per day, for 33 days followed by a corticosteroid taper. Two patients with Grade 2 pneumonitis were treated only with inhaled corticosteroids.

The patient with Grade 3 pneumonitis experienced complete resolution of the event. Among the eight patients with Grade 2 pneumonitis, six experienced complete

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resolution, one improved to Grade 1, and one did not improve and died of myocardial infarction with pneumonitis still ongoing.

### Colitis

There were four cases of colitis or microscopic colitis in the Melanoma ISS (1%) as of the safety update. Grade 3 colitis was reported in 0.5% of patients. There were no cases of Grade 4 or 5 colitis. Discontinuation of MK-3475 due to colitis was reported in 0.2% of patients.

The median time to onset of colitis was 28.1 weeks (range 10 – 42.3). The median duration was 11.3 weeks (range 0.6 – 15.7).

The two patients with Grade 3 and one patient with Grade 2 colitis were treated with high dose corticosteroids ( $\geq 40$  mg prednisone equivalent per day), with a median initial dose of 70 mg/day of prednisone or equivalent; the median duration of initial treatment was 7 days (range 4 – 41), followed by a corticosteroid taper.

All patients with colitis experienced complete resolution of the event.

### Hepatitis

Hepatitis (including autoimmune hepatitis) occurred in 0.5% patients in the Melanoma ISS as of the safety update, one Grade 1, the other Grade 4 (0.2%). Discontinuation of MK-3475 due to hepatitis was reported in 0.2% of patients.

The time to onset was 3.1 and 9 weeks, respectively, for the Grade 4 and Grade 1 hepatitis. The duration of hepatitis was 4.7 and 1.1 weeks for the Grade 4 and Grade 1 hepatitis, respectively.

The patient with Grade 4 hepatitis was treated with high-dose systemic corticosteroid for 12 days (80 mg daily methylprednisolone IV for 6 days and 80 mg daily prednisone orally for 6 days), followed by a corticosteroid taper.

All patients with hepatitis experienced complete resolution of the event.

### Hypophysitis

Hypophysitis occurred in 0.5% of patients in the Melanoma ISS as of the safety update; one case was Grade 2, the other was Grade 4 (0.2%).

Both cases occurred in patients who had received ipilimumab 10-12 weeks before starting MK-3475. The time to onset was 7.4 and 5.7 weeks for the Grade 4 and Grade 2 hypophysitis, respectively. The Grade 4 hypophysitis lasted 6 days and then improved to Grade 2.

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The patient with Grade 4 hypophysitis was treated with an initial dose of 300 mg per day of hydrocortisone I.V. (75 mg/day prednisone equivalent) for one day. The patient was then treated with 60 mg /day prednisone for 12 days followed by a prednisone taper. The patient continued 5 mg/day prednisone orally until he expired due to disease progression. The patient with Grade 2 hypophysitis was initially treated with 300 mg hydrocortisone I.V. (75 mg/day prednisone equivalent) for two days followed by oral hydrocortisone taper. Due to adrenal insufficiency following hypophysitis, this patient remained on a low dose hydrocortisone replacement therapy (25 mg daily).

## Thyroid Disorders

### **Hyperthyroidism**

Hyperthyroidism occurred in 1% of patients in the Melanoma ISS as of the safety update. Grade 3 hyperthyroidism was reported in 0.2% of patients; there were no Grade 4 or 5 events. Discontinuation of MK-3475 due to hyperthyroidism was reported in 0.2% of patients.

The median time to onset was 6.5 weeks (range 2.1-9.1). The median duration was 12.0 weeks (range 4.1 to 26.4). The one patient with Grade 3 hyperthyroidism and one of the two patients with Grade 2 hyperthyroidism were treated with 75 mg/day of prednisone equivalent for 8 days and 2 days, respectively, followed by a corticosteroid taper. One patient with Grade 2 hyperthyroidism was not treated with systemic corticosteroids. All hyperthyroidism events resolved.

### **Hypothyroidism**

Hypothyroidism occurred in 8.8% of patients in the Melanoma ISS as of the safety update. Grade 3 hypothyroidism was reported in 0.2% of patients and no patients discontinued due to hypothyroidism. The median time to onset of hypothyroidism was 15.1 weeks (range 0.7-82.3). All but two of the patients with hypothyroidism were treated with long-term thyroid hormone replacement therapy. The other two patients only required short-term thyroid hormone replacement therapy. No patient received corticosteroids for treatment of hypothyroidism

## Nephritis

Three cases of renal disorders were considered potentially immune-related according to the Applicant.

One case of Grade 2 autoimmune nephritis was reported in the Melanoma ISS (0.2%). The event occurred 50.4 weeks after first dose of MK-3475 (5 months after the last dose) and lasted 14.1 weeks. This patient did not have a biopsy, but was treated with 80mg per day of prednisone for 15 days followed by a taper. The patient fully recovered from the event.

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Two additional patients had renal failure (one Grade 3 and 1 Grade 4) and both had renal biopsies that showed acute interstitial nephritis.

The patient with Grade 4 renal failure had an onset 55.4 weeks after starting MK-3475 and had a previous episode of Grade 2 renal impairment. The total duration of renal events was 6 weeks; the duration of the Grade 4 event was 4.9 weeks. The renal failure occurred 1 day after cardiac catheterization and myocardial infarction. Kidney biopsy showed acute interstitial nephritis. The patient was treated with 80 mg per day of prednisone for 19 days for the Grade 4 nephritis followed by a steroid taper. MK-3475 was held for the Grade 2 renal event and withdrawn after progression to Grade 4. The patient fully recovered from the event.

The patient with Grade 3 renal failure had an onset 1.7 weeks after starting MK-3475. The duration of the event was 2.1 weeks. A kidney biopsy showed acute interstitial nephritis. The patient also received ciprofloxacin prior to the event. MK-3475 was withdrawn. The patient was treated with 60mg per day of prednisone for 48 days followed by a taper. The patient fully recovered from the event.

### Renal failure/Acute renal failure

Sixteen cases (3.9%) of renal failure/acute renal failure were reported in the Melanoma ISS as of the safety update. One additional case of Grade 2 renal impairment was reported. Two of the cases of renal failure/acute renal failure were Grade 4, five were Grade 3, two were Grade 2, and seven were Grade 1. There were no Grade 5 cases. Twelve cases (2.9%) were considered SAEs. Nine of the cases occurred in patients receiving 10mg/kg of MK-3475 every 3 weeks (4.7%), four of the cases occurred in patients receiving 10mg/kg every 2 weeks (7%) and three cases occurred in patients receiving 2mg/kg every 3 weeks (1.8%).

*REVIEWER COMMENT: Review of the narratives and line listings for the patients with renal failure SAEs reveals that many of the patients had alternative etiologies for the renal failure, including hydronephrosis due to tumor obstruction, other nephrotoxic medications, and dehydration. The contribution of MK-3475 to the development of these renal failure cases is unclear, but renal disorders is a potential safety signal especially given that there seems to be a dose-response and should be included in the label. Four of the 12 cases of renal failure/acute renal failure SAEs were considered drug-related by the investigator; however, in the context of a single-arm study this is difficult to interpret. The safety results from the ongoing randomized controlled studies with MK-3475 in the melanoma population should help to clarify the contribution of MK-3475 to renal-related adverse events. The Applicant contends that the longer duration of follow up for the patients receiving 10mg/kg could also explain the increased incidence in this group.*

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### Steroid use for treatment of immune-related adverse events

FDA requested that the Applicant provide an additional analysis of steroid use for AEs in patients with melanoma. The Applicant's analysis revealed that 106/411 (26%) patients in the Melanoma ISS were treated with corticosteroids (systemic or topical) during study therapy. The Applicant stated that their clinical database does not specifically link the start of medication with an adverse event; the Applicant used the patient narratives to associate the use of a corticosteroid for management of an AE and where unclear, reviewed the AEs reported within 30 days of the start of the corticosteroid. The Applicant's analysis showed that 55 (13%) patients received systemic corticosteroids for an AE; 34 (8%) patients received systemic corticosteroids for AEs that were considered related to MK-3475 by the investigator. Twenty (5%) patients received topical corticosteroids for an AE; 13 (3%) patients received topical corticosteroids for AEs that were considered related to MK-3475 by the investigator. An additional 31 (8%) patients received corticosteroids (systemic or topical) for unclear reasons.

See Appendix 9.8 for a further discussion on adverse events classified as irAEs by the investigator and AEOSIs by the Applicant.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The most frequently affected ( $\geq 10\%$ ) MedDRA System Organ Classes (SOCs) in patients in Part B2-2q3 vs. the Melanoma ISS are as below.

- General disorders and administration site conditions (72% vs. 72%)
- Gastrointestinal disorders (61% vs 66%)
- Musculoskeletal and connective tissue disorders (53% vs. 55%)
- Skin and subcutaneous tissue disorders (53% vs. 59%)
- Respiratory, thoracic and mediastinal disorders (49% vs. 52%)
- Nervous system disorders (45% vs. 42%)
- Infections and infestations (44% vs. 43%)
- Metabolism and nutrition disorders (35% vs. 35%)
- Investigations (29% vs. 36%)
- Neoplasms benign, malignant and unspecified (incl cysts and polyps) (19% vs. 17%)
- Psychiatric disorders (18% vs. 18%)

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- Blood and lymphatic system disorders (15% vs. 23%)
- Eye disorders (13% vs. 15%)
- Injury, poisoning and procedural complications (11% vs. 14%)
- Vascular disorders (9% vs. 16%)
- Renal and urinary disorders (8% vs. 11%)
- Endocrine disorders (8% vs. 10%)

Treatment emergent adverse events occurred in almost all patients in trial P001 (>98% all doses) **Table 35** shows the treatment emergent AEs reported in greater than or equal to 10% of patients in Part B2-2q3.

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**Table 35: Incidence of Treatment-emergent AEs in  $\geq 10\%$  of Patients, Part B2-2q3**

Adverse Event	Part B2-2q3 N=89 n (%)
Fatigue	42 (47)
Cough	27 (30)
Pruritus	27 (30)
Rash*	26 (29)
Nausea	25 (28)
Decreased appetite	22 (25)
Diarrhea	17 (19)
Arthralgia	17 (19)
Constipation	15 (17)
Pain in extremity	15 (17)
Dyspnea	15 (17)
Edema peripheral	14 (16)
Headache	14 (16)
Vomiting	13 (15)
Chills	12 (13)
Anemia	11 (12)
Back pain	11 (12)
Myalgia	11 (12)
Abdominal pain	10 (11)
Pyrexia	10 (11)
Upper respiratory tract infection	10 (11)
Dizziness	10 (11)
Vitiligo	10 (11)
Insomnia	9 (10)

(Source: AE.xpt)

\*Includes PT terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, drug eruption, exfoliative rash, and dermatitis exfoliative

Treatment-emergent adverse events in the Melanoma ISS were similar to those in Part B2-2q3. Table 36 summarizes the treatment-emergent adverse events reported in greater than or equal to 10% of the Melanoma ISS.

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**Table 36: Incidence of Treatment-emergent AEs in  $\geq 10\%$  of Patients, Melanoma ISS**

Adverse Event	Melanoma ISS N=411 n (%)
Fatigue	187 (45)
Rash*	126 (31)
Nausea	121 (29)
Cough	118 (29)
Diarrhea	115 (28)
Pruritus	113 (27)
Arthralgia	101 (25)
Constipation	83 (20)
Decreased appetite	77 (19)
Dyspnea	76 (18)
Headache	74 (18)
Anemia	68 (17)
Vomiting	65 (16)
Asthenia	55 (13)
Back pain	55 (13)
Pyrexia	54 (13)
Edema peripheral	53 (13)
Myalgia	52 (13)
Abdominal pain	50 (12)
Pain in extremity	48 (12)
Vitiligo	47 (11)
Chills	44 (11)

(Source: AE.xpt)

\*Includes PT terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, drug eruption, exfoliative rash, and dermatitis exfoliative

*REVIEWER COMMENT: Minor differences were noted in AE counts between the Applicant's analysis and this reviewer's analysis of the AE.xpt. These differences are not alter the interpretation of the safety profile of MK-3475.*

The clinical review of safety also evaluated potential toxicities through an analyses of AEs based on hierarchical composites of MedDRA preferred terms (high level terms, HLT) and high level terms (high level group terms, HLGT). Table 37 and Table 38 summarize the analyses of adverse events based on HLT and HLGT in the Melanoma ISS.

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**Table 37: Incidence of Treatment Emergent Adverse Events (≥10%) by High Level Term, Melanoma ISS**

HLT	Melanoma ISS N =411 n (%)
Asthenic conditions	234 (57)
Nausea and vomiting symptoms	140 (34)
Coughing and associated symptoms	135 (33)
Musculoskeletal and connective tissue pain and discomfort	127 (31)
Pruritus NEC	123 (30)
Diarrhea (excl infective)	115 (28)
Rashes, eruptions and exanthems NEC	109 (27)
Joint related signs and symptoms	105 (26)
Gastrointestinal atonic and hypomotility disorders NEC	97 (24)
Breathing abnormalities	86 (21)
Appetite disorders	76 (18)
Headaches NEC	76 (18)
Upper respiratory tract infections	74 (18)
Anemias NEC	68 (17)
Gastrointestinal and abdominal pains (excl oral and throat)	70 (17)
Edema NEC	65 (16)
Febrile disorders	54 (13)
Liver function analyses	54 (13)
Muscle pains	52 (13)
Pain and discomfort NEC	55 (13)
Physical examination procedures and organ system status	54 (13)
Hypopigmentation disorders	50 (12)
Feelings and sensations NEC	47 (11)
General signs and symptoms NEC	41 (10)
Neoplasms malignant site unspecified NEC	43 (10)
Neurological signs and symptoms NEC	40 (10)

(Source: AE.xpt)

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**Table 38: Incidence of Treatment Emergent Adverse Events (≥10%) by High Level Group Term, Melanoma ISS**

HLGT	Melanoma ISS N =411 n (%)
General system disorders NEC	286 (70)
Epidermal and dermal conditions	201 (49)
Respiratory disorders NEC	199 (48)
Gastrointestinal signs and symptoms	184 (45)
Gastrointestinal motility and defecation conditions	180 (44)
Infections - pathogen unspecified	147 (36)
Musculoskeletal and connective tissue disorders NEC	135 (33)
Joint disorders	116 (28)
Neurological disorders NEC	100 (24)
Muscle disorders	84 (20)
Appetite and general nutritional disorders	78 (19)
Headaches	77 (19)
Anemias nonhemolytic and marrow depression	71 (17)
Body temperature conditions	56 (14)
Electrolyte and fluid balance conditions	58 (14)
Hepatobiliary investigations	54 (13)
Physical examination and organ system status topics	54 (13)
Pigmentation disorders	53 (13)
Skin appendage conditions	55 (13)
Miscellaneous and site unspecified neoplasms malignant and unspecified	43 (10)
Sleep disorders and disturbances	40 (10)
Upper respiratory tract disorders (excl infections)	42 (10)

(Source: AE.xpt)

The clinical review of safety also included analyses using narrow-based Standardized MedDRA Queries (SMQ). Table 39 summarizes the incidences of narrow based SMQ terms for patients in Part B2-2q3 and the Melanoma ISS.

**Table 39: Analyses of Narrow Standardized MedDRA Queries  $\geq 10\%$ , Part B2-2q3 and Melanoma ISS**

Narrow SMQ	Part B2-2q3 N=89 n (%)	Melanoma ISS N=411 n (%)
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	49 (55)	249 (61)
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	47 (52)	241 (59)
(1) Hypersensitivity	25 (28)	135 (33)
(1) Hemodynamic edema, effusions and fluid overload	20 (22)	97 (24)
(1) Malignancies	17 (19)	63 (15)
(1) Noninfectious diarrhea	17 (19)	115 (28)
(1) Hemorrhages	16 (18)	58 (14)
(2) Hemorrhage terms (excl laboratory terms)	16 (18)	58 (14)
(2) Malignant or unspecified tumors	14 (16)	50 (12)
(3) Malignant tumors	14 (16)	50 (12)
(1) Hepatic disorders	11 (12)	70 (17)
(2) Drug related hepatic disorders - comprehensive search	11 (12)	70 (17)
(2) Gastrointestinal nonspecific dysfunction	10 (11)	28 (7)
(1) Oropharyngeal disorders	9 (10)	57 (14)
(3) Liver related investigations, signs and symptoms	7 (8)	64 (16)
(2) Oropharyngeal conditions (excl neoplasms, infections and allergies) *	5 (6)	45 (11)

(Source: AE.xpt)

#### 7.4.2 Laboratory Findings

Laboratory tests including complete blood count (CBC) with differential, and serum chemistries including electrolytes, glucose, BUN, creatinine, uric acid, total protein, albumin, liver function tests (total and direct bilirubin, alkaline phosphatase, ALT, AST), total cholesterol, and triglycerides were performed at baseline and every 2 weeks during Trial P001. Thyroid function tests including TSH, total T3 and free T4, were performed at baseline and every 4 weeks while patients were on study.

The most common laboratory abnormalities for patients in Part B2-2q3 are listed in Table 40.

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**Table 40: Most Common Laboratory Abnormalities (≥15%) by Highest Grade, Part B2-2q3**

Laboratory Test	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
<b>Chemistry</b>			
Glucose increased	57 (64)	2 (2)	1 (1)
Triglycerides	44 (50)	0	0
Albumin decreased	40 (45)	0	0
Sodium decreased	40 (45)	10 (11)	0
AST increased	30 (34)	1 (1)	1 (1)
Calcium decreased	27 (30)	1 (1)	0
Cholesterol	27 (30)	1 (1)	0
Alkaline phosphatase increased	24 (27)	2 (2)	0
ALT increased	23 (26)	0	1 (1)
Bilirubin increased	14 (16)	2 (2)	1 (1)
Creatinine increased	14 (16)	0	0
Phosphate decreased	13 (15)	6 (7)	0
<b>Hematology</b>			
Hemoglobin decreased	70 (79)	7 (8)	1 (1)
Lymphocytes decreased	32 (36)	12 (14)	0
Leukocytes decreased	18 (20)	0	0

(Source: CSR Section 12.17 updated in response to FDA information request, LB.xpt)

Data cut-off December 31, 2013

Note: Applicant used CTCAE v.3 for toxicity grading.

### REVIEWER COMMENT:

*Laboratory values are post-treatment samples; however, the Applicant did not exclude patients with post-baseline abnormalities that did not represent an increase in toxicity severity grade from baseline. The table likely overestimates an effect of MK-3475 treatment on the incidence of low-grade abnormalities.*

### Hepatic test abnormalities

There were no patients who met Hy's Law criteria (ALT or AST ≥3x upper limit of normal (ULN) and bilirubin ≥2x ULN and alkaline phosphatase <2x ULN) in an analysis of the Melanoma ISS laboratory database.

### Thyroid function tests

In the Melanoma ISS, in patients with normal baseline thyroid function values (N=326), 35.5% of them had at least one abnormal TSH or free T4 level. Most cases were subclinical; however, 9.2% of patients required thyroid replacement therapy for

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hypothyroidism and 0.2% required propylthiouracil for hyperthyroidism. More patients who received MK-3475 10mg/kg q2w required thyroid replacement for hypothyroidism (19.3%), than patients who received 2mg/kg q2w (8.6%), or 10mg/kg q3w (6.8%).

### 7.4.3 Vital Signs

Vital signs (temperature, pulse, respiratory rate, and blood pressure) were collected at baseline and every 2 weeks during the study. The Applicant evaluated mean change in vital signs from baseline over time for patients in Part B2-2q3 and the Melanoma ISS. No clinically meaningful changes from baseline were noted.

### 7.4.4 Electrocardiograms (ECGs)

No dedicated QTc studies were conducted. EKGs were obtained and read locally for patients in Part B2 of Trial P001 at baseline, within 30 minutes of the end of infusion of the first dose of MK-3475, at week 16, and at the follow up visit within 30 days of the last dose of MK-3475.

See the FDA Clinical Pharmacology BLA Review for additional details.

### 7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies/clinical trials conducted with MK-3475.

### 7.4.6 Immunogenicity

The following is an excerpt from the FDA Clinical Pharmacology BLA review:

Immunogenicity data included 2063 samples from 480 patients in study P001 (Parts A, B, C and D) as of the data cut-off date December 31, 2013, among which 449 patients with at least one post-dose sample were defined as evaluable patients. A bridging electrochemiluminescent (ECL) assay was developed for the detection of APA in human serum using a typical 3-tiered assay approach. In the 153 patients treated with dose of 2 mg/kg Q3W, 97 of these patients had a concentration of pembrolizumab in the last post dose sample below the drug tolerance level of the anti-product antibody assay. None of these 97 patients tested positive for treatment emergent anti-pembrolizumab antibodies in an ECL based assay. One patient had a pre-treatment sample tested positive for anti-pembrolizumab antibodies, then the post dose samples were tested negative. Overall, 129 of 449 patients, who treated with doses of 1 to 10 mg/kg, Q2W or Q3W, had a concentration of pembrolizumab in the last post sample below the

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drug tolerance. One patient given 10 mg/kg, Q3W had a post-dose sample that tested positive for treatment emergent anti-pembrolizumab antibodies.

This patient did not develop any clinical hypersensitivity events such as anaphylaxis, urticaria, angioedema or injection site reactions.

See the FDA Clinical Pharmacology BLA review for further details.

### 7.5 Other Safety Explorations

No other safety explorations were conducted.

#### 7.5.1 Dose Dependency for Adverse Events

The frequency of SAEs, Grade 3-5 AEs, irAEs, AEOSIs, treatment discontinuations, and treatment interruptions was higher in the 10mg/kg q2w subgroup compared with the 10mg/kg q3w or 2mg/kg q3w subgroups within the Melanoma ISS; however, no randomized comparison between all three dosage regimens has been conducted. The median exposure to MK-3475 in the 10mg/kg q2w subgroup was longer [median time on therapy 296 days (range 1-680)] compared with the 10mg/kg q3w subgroup [median time on therapy 170 days (range 1 to 589)] and the 2mg/kg q2w subgroup [median time on therapy 190 days (range 1 to 526)]. Table 41 summarizes the incidences of toxicity between the three dosage regimens. AEs and treatment interruptions/discontinuations up to 30 days and SAEs up to 90 days after the last dose of MK-3475 are reported.

**Table 41: MK-3475 Toxicity by Dose, Melanoma ISS**

	10mg/kg q2w N=57 (%)	10mg/kg q3w N=192 (%)	2mg/kg q3w N=162 (%)
SAEs	46	34	32
Grade 5 AEs	5	0	0
Grade 3-5 AEs	46	39	36
irAEs	44	19	19
AEOSI	30	6	7
AEs leading to treatment discontinuations	18	9	6
AEs leading to treatment interruptions	32	15	16

(Source: AE.xpt, DS.xpt, CRFs, ISS)

The safety profile in the randomized B2 cohort was similar between patients who received 2mg/kg and 10mg/kg every three weeks.

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See the FDA Clinical Pharmacology BLA Review.

### 7.5.2 Time Dependency for Adverse Events

Please see Section 7.3.5 and Appendix 9.7 for analyses of time dependency for immune-related adverse events.

### 7.5.3 Drug-Demographic Interactions

No drug-ethnicity analyses were performed as 97% of the population of Part B2-2q3 was white. Analyses based on age and gender are shown below. Serious adverse events and drug discontinuation due to adverse events was more common in patients age 65 and older (see Table 42) and serious adverse events were slightly more common in males (Table 43).

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**Table 42: Adverse Event Summary by Age, Part B2-2q3**

	MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W				Total			
	< 65		≥65		< 65		≥65		< 65		≥65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	59		30		52		32		111		62	
with one or more adverse events	59	(100.0)	29	(96.7)	50	(96.2)	31	(96.9)	109	(98.2)	60	(96.8)
with no adverse event	0	(0.0)	1	(3.3)	2	(3.8)	1	(3.1)	2	(1.8)	2	(3.2)
with drug-related <sup>†</sup> adverse events	48	(81.4)	25	(83.3)	39	(75.0)	30	(93.8)	87	(78.4)	55	(88.7)
with Grade 3- 5 adverse events	21	(35.6)	13	(43.3)	21	(40.4)	15	(46.9)	42	(37.8)	28	(45.2)
with Grade 3- 5 drug-related adverse events	6	(10.2)	7	(23.3)	3	(5.8)	4	(12.5)	9	(8.1)	11	(17.7)
with serious adverse events	13	(22.0)	11	(36.7)	14	(26.9)	10	(31.3)	27	(24.3)	21	(33.9)
with serious drug-related adverse events who died	2	(3.4)	5	(16.7)	0	(0.0)	1	(3.1)	2	(1.8)	6	(9.7)
with drug-related death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued <sup>‡</sup> due to an adverse event	3	(5.1)	3	(10.0)	4	(7.7)	5	(15.6)	7	(6.3)	8	(12.9)
discontinued due to a drug-related adverse event	2	(3.4)	3	(10.0)	0	(0.0)	1	(3.1)	2	(1.8)	4	(6.5)
discontinued due to a serious adverse event	2	(3.4)	2	(6.7)	2	(3.8)	3	(9.4)	4	(3.6)	5	(8.1)
discontinued due to a serious drug-related adverse event	2	(3.4)	2	(6.7)	0	(0.0)	1	(3.1)	2	(1.8)	3	(4.8)

Grades are based on NCI CTCAE version 4.0.  
 MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.  
<sup>†</sup> Determined by the investigator to be related to the drug.  
<sup>‡</sup> Study medication withdrawn.  
 (Database Cutoff Date: 18OCT2013)

(Source: CSR Table 231)

**Table 43: Adverse event summary by gender, Part B2-2q3**

	MK-3475 2 mg/kg Q3W				MK-3475 10 mg/kg Q3W				Total			
	Male		Female		Male		Female		Male		Female	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	48		41		57		27		105		68	
with one or more adverse events	47	(97.9)	41	(100.0)	56	(98.2)	25	(92.6)	103	(98.1)	66	(97.1)
with no adverse event	1	(2.1)	0	(0.0)	1	(1.8)	2	(7.4)	2	(1.9)	2	(2.9)
with drug-related <sup>†</sup> adverse events	39	(81.3)	34	(82.9)	47	(82.5)	22	(81.5)	86	(81.9)	56	(82.4)
with Grade 3- 5 adverse events	20	(41.7)	14	(34.1)	26	(45.6)	10	(37.0)	46	(43.8)	24	(35.3)
with Grade 3- 5 drug-related adverse events	6	(12.5)	7	(17.1)	6	(10.5)	1	(3.7)	12	(11.4)	8	(11.8)
with serious adverse events	15	(31.3)	9	(22.0)	18	(31.6)	6	(22.2)	33	(31.4)	15	(22.1)
with serious drug-related adverse events	3	(6.3)	4	(9.8)	1	(1.8)	0	(0.0)	4	(3.8)	4	(5.9)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued <sup>‡</sup> due to an adverse event	3	(6.3)	3	(7.3)	6	(10.5)	3	(11.1)	9	(8.6)	6	(8.8)
discontinued due to a drug-related adverse event	3	(6.3)	2	(4.9)	1	(1.8)	0	(0.0)	4	(3.8)	2	(2.9)
discontinued due to a serious adverse event	2	(4.2)	2	(4.9)	4	(7.0)	1	(3.7)	6	(5.7)	3	(4.4)
discontinued due to a serious drug-related adverse event	2	(4.2)	2	(4.9)	1	(1.8)	0	(0.0)	3	(2.9)	2	(2.9)

Grades are based on NCI CTCAE version 4.0.  
MedDRA preferred terms 'Progressive Disease' and 'Malignant Neoplasm Progression' not related to the drug are excluded.  
<sup>†</sup> Determined by the investigator to be related to the drug.  
<sup>‡</sup> Study medication withdrawn.  
(Database Cutoff Date: 18OCT2013)

(Source: ISS Table 104)

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### 7.5.4 Drug-Disease Interactions

Refer to the FDA Clinical Pharmacology review of the BLA.

### 7.5.5 Drug-Drug Interactions

No dedicated drug-drug interaction studies have been performed.

Refer to the FDA Clinical Pharmacology review of the BLA for details.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No carcinogenicity studies were conducted.

### 7.6.2 Human Reproduction and Pregnancy Data

No reproductive toxicity studies were conducted due to experimental results in the literature regarding the dependence on the PD-1/PD-L1 pathway in maintaining pregnancy by preserving immune tolerance.

Refer to the FDA Pharmacology/Toxicology review of the BLA for further details.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

MK-3475 has not been studied in the pediatric population. The Applicant has requested a waiver of pediatric studies under PREA as MK-3475 has orphan designation.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No patients received more than 10mg/kg q2w in Trial P001. There is no evidence for drug abuse potential.

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#### 7.7 Additional Submissions / Safety Issues

No additional submissions regarding safety issues were reviewed.

## 8 Postmarket Experience

Not applicable. This is a new molecular entity with no prior approval history.

## 9 Appendices

### 9.1 Literature Review/References

Aldesleukin (Proleukin), Prometheus Laboratories, Inc., USPI 7/30/2012, Drugs@FDA:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/103293s5130lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103293s5130lbl.pdf)

Alexei Shimanovsky, A. J. (2013). Immune alterations in malignant melanoma and current immunotherapy concepts. *Expert Opinion on Biological Therapy*, 1413-1427.

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Dabrafenib (Tafinlar), GlaxoSmithKline, USPI 1/10/2014, Drugs@FDA:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/202806s002lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202806s002lbl.pdf)

Howlander N, N. A. (National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2011/](http://seer.cancer.gov/csr/1975_2011/), based on November 2013 SEER data submission, posted to the SEER web site, April 2014.). *SEER Cancer Statistics Review, 1975-2011*.

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Vemurafenib (Zelboraf), Genentech USA, Inc., USPI 3/19/2014, Drugs@FDA:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/202429s004lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202429s004lbl.pdf)

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### 9.2 Labeling Recommendations

Please refer to the package insert of Keytruda.

### 9.3 Advisory Committee Meeting

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this application as the safety profile is acceptable based on the indicated population; the primary efficacy outcome measures are acceptable and similar to those used for previously approved products granted accelerated approval in patients with unresectable or metastatic melanoma; the application did not raise significant public health questions on the role of MK-3475 in the treatment of in patients with unresectable or metastatic melanoma who have progressed after treatment with ipilimumab, and a BRAF <sup>(b) (4)</sup> inhibitor <sup>(b) (4)</sup>; and outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

### 9.4 Clinical Investigator Financial Disclosure

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>280</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>  Significant payments of other sorts: <u>1</u>  Proprietary interest in the product tested held by investigator: <u>0</u>  Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)

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Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

### 9.5 Protocol P001 Supportive Care Guidelines

Taken from Protocol P001, Amendment 8.

#### Infusion Reactions:

- CTCAE Grade 1 or 2 infusion reaction: Reduce the infusion rate by 50% for the entire remaining duration of that infusion. Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an antihistamine (e.g., diphenhydramine or equivalent), anti-pyretic (e.g., paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen.
  - In the next cycle, the infusion time should be extended to 1 hour. Patients should receive oral premedication with an antihistamine (e.g., diphenhydramine or equivalent) and an anti-pyretic (e.g., paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.
- CTCAE Grade 3 or 4 infusion reaction: Immediately stop the infusion. Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or IV anti-histamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.
  - In the event of a Grade 3 or 4 infusion reaction, patients should be discontinued from further study therapy.

#### Diarrhea:

- Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
- In patients with severe enterocolitis, MK-3475 will be held and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
- In patients with moderate enterocolitis, MK-3475 should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day

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of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

- All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

### Pneumonitis:

- The treatment of symptomatic patients differs from asymptomatic patients. Patients with symptomatic pneumonitis should immediately stop receiving MK-3475 and have an evaluation, which may include bronchoscopy and pulmonary function tests, to rule out other causes such as infection. If the patient is diagnosed with study drug-associated pneumonitis, the following treatment plan is recommended and should be applied.
- Recommended treatment for symptomatic pneumonitis:
  - Dose interruption of MK-3475 and steroid intervention for  $\leq$ Grade 2 with option to return to treatment if improves to Grade  $\leq$ 1.
  - Patients should begin a regimen of steroids and taper, if necessary. MK-3475 may be resumed once clinical improvement is observed.
  - Immediate and permanent discontinuation if  $\geq$ Grade 3.
- After improvement to  $\leq$ Grade 1 of the pneumonitis the following rules should apply:
  - First episode of pneumonitis
    - Improvement occurs in  $\leq$ 2 weeks – dose MK-3475 at usual schedule of Q2W or Q3W.
    - Improvement occurs in  $>$ 2 weeks – add an additional week in between MK-3475 dosing (e.g., Q3W now becomes Q4W).
  - Second episode of pneumonitis
    - Permanently discontinue MK-3475 if upon rechallenge patient develops pneumonitis  $\geq$ Grade 2.

## 9.6 MK-3475 Event of Clinical Interest Guidance Document

The following are recommendations for treatment of immune-mediated events from the MK-3475 Event of Clinical Interest Guidance Document (Version 2, August 2013) provided to investigators for Trial P001. Version 1 was provided in October 2012. The main revisions in version 2 were as follows: inclusion of AEOSI designation, minor revision to the management of hepatic, pneumonitis, and skin events, and addition of renal and “other” immune-related event category for patient management

- **Colitis**

- Grade 1 diarrhea:
  - Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet).
  - Endoscopy is recommended if symptoms persist.
- Grade 2 diarrhea (or persistent Grade 1):
  - Hold MK-3475.
  - GI consultation and endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists >1 week or Grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below).
  - Grade 1 events that persist for >1 week or Grade 2 events should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.
  - Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Grade 3-4 diarrhea (or Grade 2 diarrhea that persist after initial steroid treatment):
  - Hold/Discontinue MK-3475.
  - Rule out bowel perforation. Imaging with plain films or CT can be useful.
  - Consider consultation with Gastroenterologist and confirmation biopsy with endoscopy
  - Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
  - If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis.

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- If symptoms persist despite the above treatment a surgical consult should be obtained.
- **Endocrine**
  - Grade 1-2 events:
    - Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
    - If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
    - Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
  - Symptomatic pan-hypopituitarism and any Grade 3-4 events
    - Hold/discontinue MK-3475.
    - Consider Endocrine consultation.
    - Rule out infection and sepsis with appropriate cultures and imaging.
    - Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and intravenous methylprednisolone should be initiated.
- **Eye**
  - Grade 1-2 events:
    - Evaluation by an ophthalmologist is strongly recommended.
    - Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
    - Discontinue MK-3475 if symptoms persist despite treatment with topical immunosuppressive therapy.
  - Grade 3-4 events:
    - Discontinue MK-3475.
    - Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Hepatic**

- Grade 1 events:
  - Monitor liver function tests more frequently until returned to baseline values.
- Grade 2 events:
  - Monitor liver function tests more frequently until returned to baseline values.
- Grade 3-4 events:
  - Discontinue MK-3475 when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN
  - Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
  - Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
  - If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
  - Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

- **Pneumonitis**

- Grade 1 events: (asymptomatic with radiographic findings only):
  - MK-3475 may be continued with close monitoring.
  - Radiologic findings should be followed on serial imaging studies.
  - Consider pulmonary consultation and/or bronchoscopy if clinically indicated.
- Grade 2 events:
  - Hold MK-3475 as specified in the protocol.
  - Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
  - Consider pulmonary function tests.
  - Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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- Treatment with MK-3475 may be resumed if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg po daily or less.
- Repeat chest imaging monthly as clinically indicated.
- Second episode of pneumonitis – discontinue MK-3475 if upon rechallenge the patient develops a second episode of Grade 2 or higher pneumonitis.
- Grade 3 and 4 events:
  - Permanently Discontinue MK-3475.
  - Consider pulmonary function tests with pulmonary consult.
  - Bronchoscopy with biopsy and/or BAL is recommended.
  - Treat with intravenous steroids (methylprednisolone 125 mg). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
  - If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsening during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.
- **Renal**
  - Grade 1 events:
    - Mild (Grade 1) irAEs – provide symptomatic treatment.
  - Grade 2 events:
    - Moderate (Grade 2) or Grade 1 irAEs that do not improve with symptomatic treatment – consider withholding MK-3475. Systemic corticosteroids may be indicated.
  - Grade 3-4 events:
    - Clinically significant or severe ( $\geq$  Grade 3) irAEs
    - Discontinue MK-3475
    - Renal consultation with consideration of ultrasound and/or biopsy as appropriate
    - Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Skin**

- Grade 1-2 events:
  - Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
  - Treatment with oral steroids is at investigator discretion for Grade 2 events.
- Grade 3 events:
  - Hold MK-3475.
  - Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
  - Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Grade 4 events:
  - Permanently discontinue MK-3475.
  - Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
  - Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Other**

- Mild (Grade 1) irAEs – provide symptomatic treatment.
- Moderate (Grade 2) or Grade 1 irAEs that do not improve with symptomatic treatment – consider withholding MK-3475. Systemic corticosteroids may be indicated. Consider biopsy for confirmation of diagnosis.
- Clinically significant or severe ( $\geq$ Grade 3) irAEs –discontinue MK-3475 and treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. Report as ECI.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - Discontinue MK-3475 if unable to reduce corticosteroid dose for irAEs to  $\leq$ 10 mg.

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**Table 44: Adverse Events of Clinical Interest (AEOSI)**

<b>Colitis (reported as ECI if <math>\geq</math> Grade 2)</b>		
Bowel Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	GI Perforation
Necrotizing Colitis		
<b>Diarrhea (report as ECI if <math>\geq</math> Grade 3 or any grade resulting in dose modification)</b>		
<b>Endocrine (reported as ECI if <math>\geq</math> Grade 3 or any grade resulting in dose modification)</b>		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid Disorder
Thyroiditis		
<b>Eye</b>		
Uveitis (report as ECI if $\geq$ Grade 2 or any grade resulting in dose modification)		
<b>Hepatic (reported as ECI if <math>\geq</math> Grade 2 or any grade requiring dose modification)</b>		
Hepatitis	Hepatitis, Autoimmune	
<b>Pneumonitis (reported as ECI if <math>\geq</math> Grade 2)</b>		
Acute Interstitial Pneumonitis	Interstitial Lung Disease	Pneumonitis
<b>Renal (reported as ECI if <math>\geq</math> Grade 2 or any grade resulting in dose modification)</b>		
Nephritis	Nephritis Autoimmune	Renal Failure
Renal Failure, Acute		
<b>Skin (always reported as ECI regardless of grade)</b>		
Dermatitis Exfoliative	Erythema Multiforme	Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis		
<b>Skin (reported as ECI if <math>\geq</math> Grade 3 or any grade resulting in dose modification)</b>		
Pruritus	Rash	Rash generalized
Rash maculo-papular	Vitiligo	
<b>Other (The following should always be reported as an ECI, regardless of grade)</b>		
Autoimmune Neuropathy	Demyelinating Polyneuropathy	Guillain-Barre
Myasthenia Gravis like syndrome	Non-infectious myocarditis	Non-infectious pericarditis
Pancreatitis	Rapid onset of Grade 3 fatigue in the absence of disease progression	

(Source: P001 MK-3475 Events of Clinical Interest and irAE Guidance Document, Version 2, June 2013)

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9.7 Demographics of Patients in Melanoma ISS

**Table 45: Demographics of Patients in Melanoma ISS**

	<b>MK-3475 2mg/kg q3w N=162  N (%)</b>	<b>MK-3475 10mg/kg q3w N=192  N (%)</b>	<b>MK-3475 10mg/kg q2w N=57  N (%)</b>	<b>Total N=411  N (%)</b>
<b>Gender</b>				
Male	94 (58)	121 (63)	32 (56)	247 (60)
Female	68 (42)	71 (37)	25 (44)	164 (40)
<b>Age</b>				
<65	105 (65)	113 (59)	32 (56)	250 (61)
≥65	57 (35)	79 (41)	25 (44)	161 (39)
Median	60	62	62	61
Range	18 to 88	26 to 87	25 to 94	18 to 94
<b>Race</b>				
Asian	2 ( 1)	6 ( 3)	0	8 ( 2)
Black or African American	1 (0.6)	1 (0.5)	0	2 (0.5)
Multiracial	0	1 (0.5)	0	1 (0.2)
White	129 ( 98)	184 ( 96)	57 (100)	400 ( 97)
<b>ECOG</b>				
0	113 (70)	142 (74)	46 (81)	301 (73)
1	49 (30)	50 (26)	11 (19)	110 (27)
<b>Metastatic Staging*</b>				
MX	3 ( 2)	1 (0.5)	0	4 ( 1)
M0	25 (15)	20 ( 10)	10 (18)	55 (13)
M1a	15 ( 9)	26 ( 14)	5 ( 9)	46 (11)
M1b	23 (14)	33 ( 17)	13 (23)	69 (17)
M1c	93 (57)	110 ( 57)	29 (51)	232 (56)
Null	3 ( 2)	2 ( 1)	0	5 ( 1)
<b>BRAF Mutation</b>				
Mutant	38 (24)	45 (23)	14 (25)	97 (24)
Wild Type	124 (76)	147 (77)	39 (68)	310 (75)
Unknown	0	0	4 ( 7)	4 ( 1)
<b>Brain Metastases</b>				
Yes	10 ( 6)	17 ( 9)	6 (10)	33 ( 8)
No	150 (93)	174 ( 91)	51 (90)	375 (91)
Unknown	2 ( 1)	1 ( 0.5)	0	3 (0.7)

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	<b>MK-3475 2mg/kg q3w N=162  N (%)</b>	<b>MK-3475 10mg/kg q3w N=192  N (%)</b>	<b>MK-3475 10mg/kg q2w N=57  N (%)</b>	<b>Total N=411  N (%)</b>
<b>Number of systemic prior therapies</b>				
0	38 (24)	41 (21)	16 (28)	95 (23)
1	48 (30)	53 (28)	19 (33)	120 (29)
2	44 (27)	56 (29)	15 (26)	115 (28)
3 or more	32 (20)	42 (22)	7 (12)	81 (20)
<b>Baseline LDH</b>				
Normal	97 ( 60)	131 (68)	35 (61)	263 (64)
Elevated	64 ( 40)	58 (30)	21 (37)	143 (35)
Null	1 (0.6)	3 ( 2)	1 ( 2)	5 ( 1)
<b>Prior IPI</b>				
Yes	89 (55)	116 (60)	16 (28)	221 (54)

(Source: ISE Table 94 and 95)

The disease staging of patients in the Melanoma ISS may not be reliable based on Applicant response to FDA information request (See Section 6.1.2)

### 9.8 Immune-mediated Adverse Events as Characterized by Investigator and Applicant

There were 35 adverse events that were considered immune-related as assessed by the investigator (irAEs) in 14 (16%) patients in Part B2-2q3. Only one of these events was greater than or equal to Grade 3. Table 46 lists irAEs for patients in Part B2-2q3.

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Keytruda (pembrolizumab, MK-3475) for the treatment of patients with refractory unresectable or metastatic melanoma

**Table 46: Immune-related Adverse Events as Assessed by Investigator in Part B2-2q3 (N=89)**

Patient ID	Adverse Event	Grade	Onset (D)	Duration (D)	Treatment	Outcome
3475-001_0010000265	pneumonitis	2	229	156	Y	R
3475-001_0010000282	diarrhea	1	231	2		R
	hypothyroidism	2	189		Y	N
3475-001_0011000291	hypophysitis	2	58			N
3475-001_0012000389	hyperthyroidism	2	40	184	Y	R
	hypophysitis	2	40	100	Y	R
3475-001_0015000336	autoimmune hepatitis	4	22		Y	N
3475-001_0019000303	rash	2	183	8		R
	pyrexia	1	183	8		R
	chills	1	183	8		R
	fatigue	2	183	8		R
	arthralgia	2	183	8		R
3475-001_0020000322	night sweats	1	175	2		R
	ALT increased	1	155	7		R
	AST increased	1	155	7		R
	erythema	1	204	3		R
3475-001_0016000306	hypothyroidism	1	107			N
3475-001_0020000318	arthralgia	1	140			N
	vitiligo	1	115			N
	arthralgia	1	60	61		R
	hepatitis	1	63	7		R
	erythema	1	85			N
3475-001_0020000325	rash	1	79			N
	cough	1	2			N
	diarrhea	1	29			N
	pruritus	1	6		Y	N
	neutrophilic dermatosis	2	6	44	Y	R
	erythema	2	36	28		R
	thyroxine free increased	1	34	30		R
3475-001_0013000296	tri-iodothyronine increased	1	22	12		R
	lethargy	2	252	41		R
3475-001_0020000290	chills	1	309	1*		R
	arthritis	2	309	4	Y	R
	arthritis	1	314			N
	vitiligo	1	189			N
	3475-001_0021000324	rash papular	1	23	61	Y

## Clinical Review

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Patient ID	Adverse Event	Grade	Onset (D)	Duration (D)	Treatment	Outcome
3475-001_0023000320	hypothyroidism	2	253		Y	N

Abbreviations: R=recovered; N=not recovered

\*AE listed as resolved same day as occurred

Twenty three percent of patients in the Melanoma ISS experienced an immune-related adverse event as assessed by the investigator up to 90 days after their last dose of MK-3475. The most common immune-related adverse events reported in more than 1% of patients were rash (including PT terms rash, rash erythematous, rash generalized, rash maculo-papular, rash papular, rash pruritic, and dermatitis exfoliative) (6%), hypothyroidism (4%), vitiligo (4%), pruritus (3%), arthralgia (2%), diarrhea (2%), pneumonitis (1.7%), myalgia (1.5%), cough (1.5%), and pyrexia (1.2%). Nineteen (5%) were Grade 3 or 4 [colitis N=3, rash (including PT terms rash, rash erythematous and rash maculo-papular) N=3, renal failure/renal failure acute N=2, and ALT increased, AST increased, autoimmune hepatitis, creatinine phosphokinase increased, diarrhea, hemolytic anemia, hyperthyroidism, hypothyroidism, pancreatitis, pancytopenia, and pleural effusion all N=1.]

Patients receiving 10mg/kg q2w of MK-3475 (N=57) had a higher incidence of irAEs within 30 days of drug (44%) than those receiving either 10mg/kg q3w (19%, N=192), or 2mg/kg q3w (19%, N=162).

### REVIEWER COMMENTS:

- *The Applicant used AEs up to 30 days after the last dose for determination of immune-related events; however, given the long half-life of MK-3475, and the occurrence of late immune-related adverse events in other immune-modulating agents, this reviewer felt that events up to 90 days should be included. Four patients listed below had 7 immune-mediated events that occurred between days 30 and 90 after their last dose of MK-3475. This explains the differences in the incidence of Gr 3-5 irAEs between the Applicant's analysis and this reviewer's analysis. However, since the protocol only mandated collection of AEs for up to 30 days, these results may not be complete. The numbers were unchanged with the inclusion of 30-90 days post-MK-3475 for Part B2-2q3:*
  - *patient 3475-001\_0011000068 Grade 3 hypothyroidism and Grade 3 blood creatine phosphokinase increase*
  - *patient 3475-001\_0011000511 Grade 3 colitis*
  - *patient 3475-001\_0020000205 Grade 2 dyspnea and Grade 1 rash*
  - *patient 3475-001\_0024000110 Grade 2 diabetes mellitus (steroid induced) and Grade 2 myositis*

## Clinical Review

Meredith K. Chuk and Jennie Chang

BLA 125514

Keytruda (pembrolizumab, MK-3475) for the treatment of patients with refractory unresectable or metastatic melanoma

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### Adverse events of special interest (AEOSI)

There were eight (9%) patients in Part B2-2q3 who had events characterized as an AEOSI. Table 47 lists events characterized as AEOSI in patients in Part B2-2q3.

**Table 47: Adverse Events of Special Interest (AEOSI) in Part B2-2q3 (N=89)**

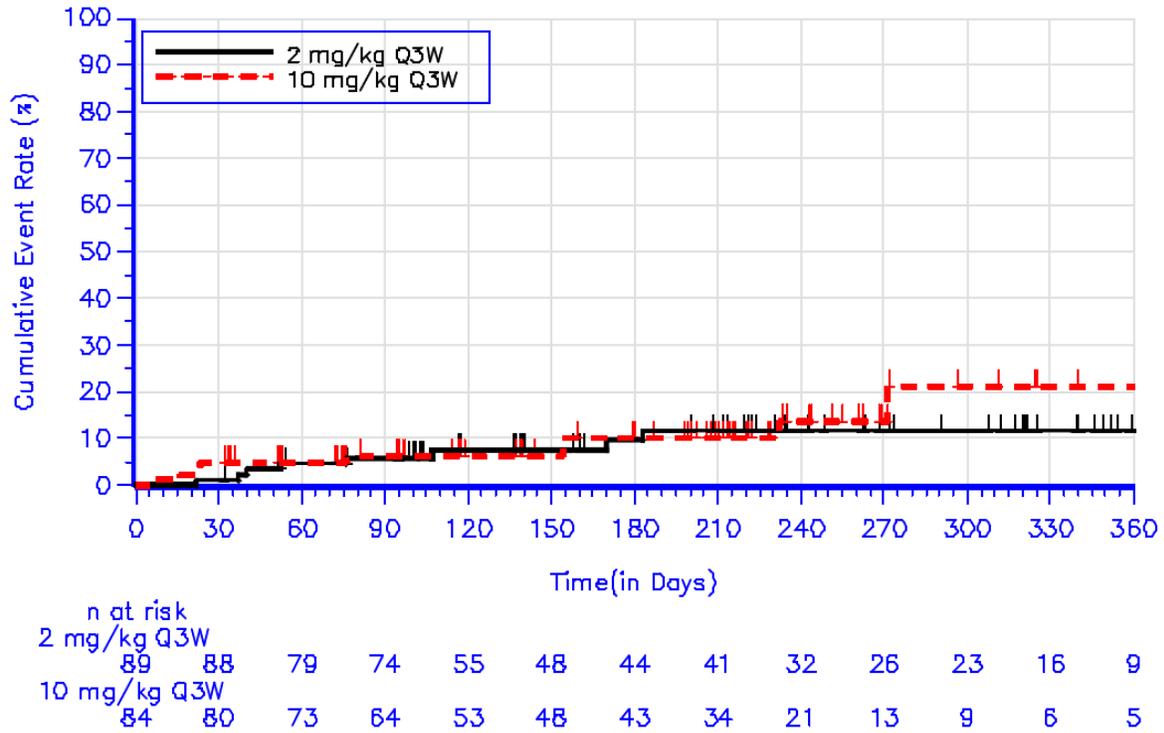
Patient ID	Adverse Event	Grade	Onset (D)	Duration (D)	Treatment	Outcome
3475-001_0010000265	pneumonitis	3	170	12	Y	R
	pneumonitis	2	229	156	Y	R
3475-001_0019000279	uveitis	2	107	10	Y	R
3475-001_0003000286	diarrhea	2	37	27	Y	R
3475-001_0010000295	renal failure	2	76	7		R
3475-001_0011000291	hypophysitis	4	52	5	Y	R
3475-001_0012000389	adrenal insufficiency	3	44	5		R
	hyperthyroidism	2	40	184	Y	R
	hypophysitis	2	40	100	Y	R
3475-001_0015000336	autoimmune hepatitis	4	22		Y	N
3475-001_0019000303	rash	2	183	8		R

(Source: AE.xpt, SUPPAE.xpt, Applicant response to FDA information request)

There were 51 (12%) patients in the Melanoma ISS who experienced an AEOSI up to 90 days after their last dose of MK-3475. The most common AEOSIs reported in 1% or more of patients were rash (includes rash, rash generalized and rash maculo-papular, 2.4%), renal failure/renal failure acute (2.2%), pneumonitis (1.7%), diarrhea (1.7%), and hypothyroidism (1%).

The Applicant presented a Kaplan-Meier curve of a time to first event analysis for AEOSI for patients in Part B2 (Figure 6) and the Melanoma ISS (Figure 7).

**Figure 6: Analysis of time to first event of AEOSI for patients in Part B2**



(Source: ISS Figure 3)

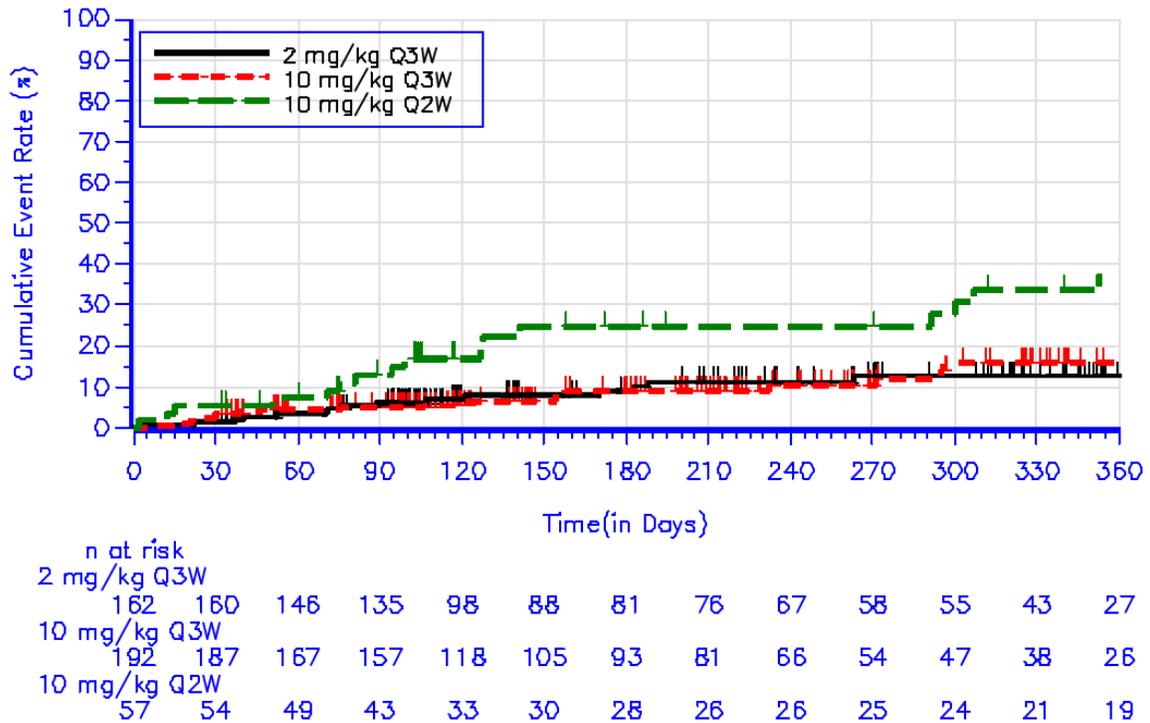
Clinical Review

Meredith K. Chuk and Jennie Chang

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Keytruda (pembrolizumab, MK-3475) for the treatment of patients with refractory unresectable or metastatic melanoma

**Figure 7: Analysis of time to first event of AEOSI for patients in Melanoma ISS**



(Source: ISS Figure 4)

<sup>i</sup> Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

<sup>ii</sup> Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

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/s/  
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MEREDITH K CHUK  
08/02/2014

JENNIE T CHANG  
08/02/2014

MARC R THEORET  
08/02/2014

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**BLA Number: 125514**

**Applicant: Merck**

**Stamp Date: February 28, 2014**

**Drug Name: Keytruda  
(pembrolizumab, MK-3475)**

**NDA/BLA Type: Efficacy  
(Accelerated approval)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			Sponsor submitted revised clinical overview in 2.5 and revised summary of clinical efficacy and safety in 2.7.3 and 2.7.4, respectively, that contain appropriate links to CSR and ISS/ISE
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).			X	BLA – 351 (a)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
<b>DOSE</b>					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X			The attempt is appropriate based on the serious and life-

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>Study Number: PN001</p> <p>Study Title: Phase 1 study of single agent MK-3475 in patients with progressive locally advanced or metastatic carcinoma, melanoma, and non-small cell lung carcinoma</p> <p>Arms: Part B2 randomized patient to 2mg/kg every 3 weeks versus 10 mg/kg every 3 weeks. N=173. Part B3 randomized patients to 10mg/kg every 2 or 3 weeks. N=248.</p>				threatening indication.
<b>EFFICACY</b>					
17.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1: Phase 1 study of single agent MK-3475 in patients with progressive locally advanced or metastatic carcinoma, melanoma, and non-small cell lung carcinoma</p> <ul style="list-style-type: none"> <li>Parts A (including A1 and A2), B (including B1 and B2), and D constitute the efficacy data.</li> </ul> <p>Indication: patients with (b) (4) melanoma with progressive (b) (4) metastatic disease</p> <p>Pivotal Study #2: N/A</p> <p style="text-align: center;">Indication: N/A</p>	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
<b>SAFETY</b>					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			The assessment of the arrhythmogenic potential is adequate based on the serious and life-threatening indication. The IRT-QT Team was consulted to review

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					the QT study report submitted in the BLA.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Granted orphan drug designation for patients with Stage IIB to IV melanoma
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously by the Division?				
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Meredith Chuk (safety) and Jennie Chang (efficacy) April 1, 2014  
 \_\_\_\_\_  
 Reviewing Medical Officer Date

Marc Theoret April 2, 2014  
 \_\_\_\_\_  
 Clinical Team Leader Date

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

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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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MEREDITH K CHUK  
04/21/2014

JENNIE T CHANG  
04/21/2014

MARC R THEORET  
04/21/2014