CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s014

Trade Name:	Keytruda
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp and Dohme, Corp.
Approval Date:	May 23, 2017
Indication:	KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated in: **Melanoma**: • for the treatment of patients with unresectable of metastatic melanoma. **Non-Small Cell Lung Cancer (NSCLC):** • as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. • as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. • in combination with pemetrexed and carboplatin, as first-

line treatment of patients with metastatic nonsquamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Head and Neck Squamous Cell Cancer (HNSCC)

- for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and duration of response.
  Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing

chemotherapy.

Microsatellite Instability-High Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
  - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

CENTER FOR DRUG EVALUATION AND RESEARCH

125514Orig1s014

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	**X**
Microbiology / Virology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-14

ACCELERATED APPROVAL

Merck Sharp and Dohme, Corp.
Attention: Nahid Latif
Executive Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000
UG-2C029
North Wales, PA 19454

Dear Ms. Latif:

Please refer to your supplemental Biologics License Application (sBLA) dated September 8, 2016, and received September 8, 2016 submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) for injection 50 mg and for Keytruda (pembrolizumab) injection 100 mg/4 mL.

We acknowledge receipt of your major amendment dated March 9, 2017, which extended the goal date by three months.

This Prior Approval supplemental biologics application adds a new indication for the treatment of adult and pediatric patients with:

- unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The approval includes the following limitation of use: The safety and effectiveness of KEYTRUDA in pediatric patients with microsatellite instability-high central nervous system cancers has not been established.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the prescribing information and Medication Guide, and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated May 17, 2017. This requirement, along with required completion dates, is listed below.

These postmarketing clinical trials are subject to the reporting requirements of 21 CFR 601.70:

3213-1 Submit the final report, including datasets, from trials conducted to verify and describe the clinical benefit of pembrolizumab 200 mg intravenously every three weeks in patients with microsatellite instability high or mismatch repair deficient

tumors including at least 124 patients with colorectal cancer enrolled in Merck-initiated trials; at least 300 patients with non-colorectal cancer, including a sufficient number of patients with prostate cancer, thyroid cancer, small cell lung cancer; and ovarian cancer; and 25 children. In order to characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

Trial Completion:	September 2022
Final Report Submission:	March 2023

Under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Keytruda was approved on September 4, 2015, we have become aware of the potential risk of cerebral edema in children with microsatellite high or mismatch repair deficient central nervous system tumors who received a programmed death receptor-1 (PD-1)-blocking antibody based on peer-reviewed biomedical literature. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of cerebral edema.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of cerebral edema in children with microsatellite high or mismatch repair deficient central nervous system tumors who are exposed to Keytruda.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3213-2 Conduct a trial that will characterize the safety of pembrolizumab administered intravenously at 2 mg/kg up to a maximum of 200 mg intravenously every three weeks or to determine a reasonably safe dosage regimen in an adequate number of children with primary central nervous system malignancies that are mismatch repair deficient or microsatellite instability high. Submit a final report and datasets for pediatric patients with primary CNS malignancies.

The timetable you submitted on May 17, 2017, states that you will conduct this trial according to the following schedule:

Trial Completion:	September 2022
Final Report Submission:	March 2023

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the postmarketing final report to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3213-3 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry based *in vitro* diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are mismatch repair deficient.

The timetable you submitted on May 18, 2017, states that you will support the submission of a Premarket Approval (PMA) Application to FDA/CDRH according to the following schedule:

Final Report Submission: June 2019

3213-4 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid-based *in vitro* diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are microsatellite instability high.

The timetable you submitted on May 18, 2017, states that you will support the submission of a Premarket Approval (PMA) Application to FDA/CDRH according to the following schedule:

Final Report Submission: June 2019

Submit all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved prescribing information (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.S.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

PATRICIA KEEGAN
05/23/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KEYTRUDA safely and effectively. See full prescribing information for KEYTRUDA.

KEYTRUDA® (pembrolizumab) for injection, for intravenous use
KEYTRUDA® (pembrolizumab) injection, for intravenous use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	05/2017
Dosage and Administration (2)	05/2017
Warnings and Precautions (5)	05/2017

----------INDICATIONS AND USAGE----------

KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated in:

Melanoma

- for the treatment of patients with unresectable or metastatic melanoma. (1.1)

Non-Small Cell Lung Cancer (NSCLC)

- as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. (1.2)
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. (1.2)
- in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.2)

Head and Neck Squamous Cell Cancer (HNSCC)

- for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.3)

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.4)

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.5)
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.5)

Microsatellite Instability-High Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
  - o solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
  - o colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.6)
- Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. (1.6)

----------DOSAGE AND ADMINISTRATION----------

- Melanoma: 200 mg every 3 weeks. (2.2)
- NSCLC: 200 mg every 3 weeks. (2.3)
- HNSCC: 200 mg every 3 weeks. (2.4)
- cHL: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.5)
- Urothelial Carcinoma: 200 mg every 3 weeks. (2.6)
- MSI-H Cancer: 200 mg every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for children. (2.7)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

----------DOSAGE FORMS AND STRENGTHS----------

- For injection: 50 mg lyophilized powder in single-dose vial for reconstitution (3)
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Immune-mediated Pneumonitis: Withhold for moderate, and permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated Colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated Hepatitis: Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue. (5.3)
- Immune-mediated Endocrinopathies (5.4):
  - o Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  - o Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or life-threatening hyperthyroidism.
  - o Type 1 diabetes mellitus: Monitor for hyperglycemia. Withhold KEYTRUDA in cases of severe hyperglycemia.
- Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis. (5.5)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.7)
- Complications of allogeneic HSCT after KEYTRUDA: Monitor for hepatic veno-occlusive disease, grade 3-4 acute GVHD including hyperacute GVHD, steroid-requiring febrile syndrome, and other immune-mediated adverse reactions. Transplant-related mortality has occurred. (5.8)
- Embryofetal toxicity: KEYTRUDA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.9)

----------ADVERSE REACTIONS----------

Most common adverse reactions (reported in ≥20% of patients) were fatigue, pruritus, diarrhea, decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Discontinue nursing or discontinue KEYTRUDA. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*.

1.2 Non-Small Cell Lung Cancer

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.2)]*.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA *[see Clinical Studies (14.2)]*.

KEYTRUDA, in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC *[see Clinical Studies (14.2)]*. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.3 Head and Neck Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy *[see Clinical Studies (14.3)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.4 Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy *[see Clinical Studies (14.4)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.5 Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy *[see Clinical Studies (14.5)].*

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.5)].*

1.6 Microsatellite Instability-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan *[see Clinical Studies (14.5)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of NSCLC

Select patients for treatment of metastatic NSCLC with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression *[see Clinical Studies (14.2)]*. Information on FDA-approved tests for the detection of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage for Melanoma

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*.

2.3 Recommended Dosage for NSCLC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.2)]*.

When administering KEYTRUDA in combination with chemotherapy, KEYTRUDA should be administered prior to chemotherapy when given on the same day *[see Clinical Studies (14.2)]*. See also the Prescribing Information for pemetrexed and carboplatin.

2.4 Recommended Dosage for HNSCC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.3)]*.

2.5 Recommended Dosage for cHL

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.4)]*.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.6 Recommended Dosage for Urothelial Carcinoma

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.5)]*.

2.7 Recommended Dosage for MSI-H Cancer

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.5)].*

The recommended dose of KEYTRUDA in children is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.8 Dose Modifications

Withhold KEYTRUDA for any of the following:

- Grade 2 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 2 or 3 colitis *[see Warnings and Precautions (5.2)]*
- Grade 3 or 4 endocrinopathies *[see Warnings and Precautions (5.4)]*
- Grade 4 hematological toxicity in cHL patients
- Grade 2 nephritis *[see Warnings and Precautions (5.5)]*
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction *[see Warnings and Precautions (5.6)]*

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA for any of the following:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy, or hematological toxicity in patients with cHL)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity *[see Warnings and Precautions (5.1)]*
- Grade 3 or 4 nephritis *[see Warnings and Precautions (5.5)]*
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions *[see Warnings and Precautions (5.7)]*
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of KEYTRUDA

- Any severe or Grade 3 treatment-related adverse reaction that recurs *[see Warnings and Precautions (5.6)]*

2.9 Preparation and Administration

Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Reconstituted and Diluted Solutions

The product does not contain a preservative.

Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

Administration

- Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg lyophilized powder in a single-dose vial for reconstitution
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)].*

Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), Grade 2 (1.3%), Grade 3 (0.9%), Grade 4 (0.3%), and Grade 5 (0.1%) pneumonitis. The median time to onset was 3.3 months (range: 2 days to 19.3 months), and the median duration was 1.5 months (range: 1 day to 17.2+ months). Sixty-three (67%) of the 94 patients received systemic corticosteroids, with 50 of the 63 receiving high-dose corticosteroids for a median duration of 8 days (range: 1 day to 10.1 months) followed by a corticosteroid taper. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation (2.9%). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 (59%) of the 94 patients.

5.2 Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)].*

Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.4%), Grade 3 (1.1%), and Grade 4 (<0.1%) colitis. The median time to onset was 3.5 months (range: 10 days to 16.2 months), and the median duration was 1.3 months (range: 1 day to 8.7+ months). Thirty-three (69%) of the 48 patients received systemic corticosteroids, with 27 of the 33 requiring high-dose corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 (85%) of the 48 patients.

5.3 Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)].*

Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.4%), and Grade 4 (<0.1%) hepatitis. The median time to onset was 1.3 months (range: 8 days to 21.4 months), and the median duration was 1.8 months (range: 8 days to 20.9+ months). Thirteen (68%) of the 19 patients received systemic corticosteroids, with 12 of the 13 receiving high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 (79%) of the 19 patients.

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

KEYTRUDA can cause hypophysitis. Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis and withhold or

discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)].*

Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), Grade 3 (0.3%), and Grade 4 (<0.1%) hypophysitis. The median time to onset was 3.7 months (range: 1 day to 11.9 months), and the median duration was 4.7 months (range: 8+ days to 12.7+ months). Sixteen (94%) of the 17 patients received systemic corticosteroids, with 6 of the 16 receiving high-dose corticosteroids. Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 (41%) of the 17 patients.

Thyroid Disorders
KEYTRUDA can cause thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)].*

Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months), and the median duration was 2.1 months (range: 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 (74%) of the 96 patients.

Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and Grade 3 (0.1%) hypothyroidism. The median time to onset was 3.5 months (range: 1 day to 18.9 months), and the median duration was not reached (range: 2 days to 27.7+ months). Hypothyroidism led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Hypothyroidism resolved in 48 (20%) of the 237 patients. The incidence of new or worsening hypothyroidism was higher in patients with HNSCC occurring in 28 (15%) of 192 patients receiving KEYTRUDA, including Grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of hypothyroidism.

Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. The median time of onset was 1.2 months (range: 0.5 to 3.5 months).

Type 1 Diabetes mellitus
KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)]*.

5.5 Immune-Mediated Nephritis and Renal Dysfunction
KEYTRUDA can cause immune-mediated nephritis. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)].*

Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis. The median time to onset was 5.1 months (range: 12 days to 12.8 months), and the median duration was 3.3 months (range: 12 days to 8.9+ months). Eight (89%) of the 9 patients received systemic corticosteroids, with 7 of the 8 receiving high-dose corticosteroids for a

median duration of 15 days (range: 3 days to 4.0 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 (56%) of the 9 patients.

5.6 Other Immune-Mediated Adverse Reactions

KEYTRUDA can cause other clinically important immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)].*

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients treated with KEYTRUDA: arthritis (1.5%), exfoliative dermatitis, bullous pemphigoid, rash (1.4%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. In addition, myelitis and myocarditis were reported in other clinical trials, including cHL, and post-marketing use.

5.7 Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.8)]*.

5.8 Complications of Allogeneic HSCT after KEYTRUDA

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA. Of 23 patients with cHL who proceeded to allogeneic HSCT after treatment with KEYTRUDA on any trial, 6 patients (26%) developed graft-versus-host-disease (GVHD), one of which was fatal, and 2 patients (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning, one of which was fatal. Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

5.9 Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA *[see Use in Specific Populations (8.1, 8.3)].*

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)].*
- Immune-mediated colitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated hepatitis *[see Warnings and Precautions (5.3)]*.
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.4)]*.
- Immune-mediated nephritis and renal dysfunction *[see Warnings and Precautions (5.5)]*.
- Other immune-mediated adverse reactions *[see Warnings and Precautions (5.6)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.7)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to KEYTRUDA in 2799 patients in three randomized, open-label, active-controlled clinical trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001) which enrolled 655 patients with melanoma and 550 patients with NSCLC. In addition, these data reflect exposure to KEYTRUDA in a non-randomized, open-label, multi-cohort trial (KEYNOTE-012) which enrolled 192 patients with HNSCC and 241 cHL patients in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087). Across all studies, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among the 2799 patients, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

The data described in this section were obtained in five randomized, open-label, active-controlled clinical trials (KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-021, and KEYNOTE-045) in which KEYTRUDA was administered to 912 patients with melanoma, 741 patients with NSCLC, and 542 patients with urothelial carcinoma, and three non-randomized, open-label trials (KEYNOTE-012, KEYNOTE-087, and KEYNOTE-052) in which KEYTRUDA was administered to 192 patients with HNSCC, 210 patients with cHL, and 370 patients with urothelial carcinoma. In these trials, KEYTRUDA was administered at 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks.

Melanoma

Ipilimumab-Naive Melanoma

The safety of KEYTRUDA for the treatment of patients with unresectable or metastatic melanoma who had not received prior ipilimumab and who had received no more than one prior systemic therapy was investigated in Study KEYNOTE-006. KEYNOTE-006 was a multicenter, open-label, active-controlled trial where patients were randomized (1:1:1) and received KEYTRUDA 10 mg/kg every 2 weeks (n=278) or KEYTRUDA 10 mg/kg every 3 weeks (n=277) until disease progression or unacceptable toxicity or ipilimumab 3 mg/kg every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity (n=256) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA 10 mg/kg every 2 or 3 weeks, respectively, for ≥6 months. No patients in either arm received treatment for more than one year.

The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 32% had an elevated lactate dehydrogenase (LDH) value at baseline, 65% had M1c stage disease, 9% with history of brain metastasis, and approximately 36% had been previously treated with systemic therapy which included a BRAF inhibitor (15%), chemotherapy (13%), and immunotherapy (6%).

In KEYNOTE-006, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both KEYTRUDA arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions (reported in at least 20% of patients) were fatigue and diarrhea. Table 1 and Table 2 summarize the incidence of selected adverse reactions and laboratory abnormalities that occurred in patients receiving KEYTRUDA.

Table 1: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-006

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
Adverse Reaction	**All Grades† (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	28	0.9	28	3.1
Skin and Subcutaneous Tissue Disorders				
Rash‡	24	0.2	23	1.2
Vitiligo§	13	0	2	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	0.4	10	1.2
Back pain	12	0.9	7	0.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	7	0.4
Dyspnea	11	0.9	7	0.8
Metabolism and Nutrition Disorders				
Decreased appetite	16	0.5	14	0.8
Nervous System Disorders				
Headache	14	0.2	14	0.8

* Adverse reactions occurring at same or higher incidence than in the ipilimumab arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and exfoliative rash.
§ Includes skin hypopigmentation

Other clinically important adverse reactions occurring in ≥10% of patients receiving KEYTRUDA were diarrhea (26%), nausea (21%), and pruritus (17%).

Table 2: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-006

	KEYTRUDA 10 mg/kg every 2 or 3 weeks		Ipilimumab	
Laboratory Test†	**All Grades‡ %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	45	4.2	45	3.8
Hypertriglyceridemia	43	2.6	31	1.1
Hyponatremia	28	4.6	26	7
Increased AST	27	2.6	25	2.5
Hypercholesterolemia	20	1.2	13	0
Hematology				
Anemia	35	3.8	33	4.0
Lymphopenia	33	7	25	6

* Laboratory abnormalities occurring at same or higher incidence than in ipilimumab arm

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: KEYTRUDA n=429 and ipilimumab n=183; hypercholesterolemia: KEYTRUDA n=484 and ipilimumab n=205.

‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were increased hypoalbuminemia (27% all Grades; 2.4% Grades 3-4), increased ALT (23% all Grades; 3.1% Grades 3-4), and increased alkaline phosphatase (21% all Grades, 2.0% Grades 3-4).

Ipilimumab-Refractory Melanoma

The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Study KEYNOTE-002. KEYNOTE-002 was a multicenter, partially blinded (KEYTRUDA dose), randomized (1:1:1), active-controlled trial in which 528 patients received KEYTRUDA 2 mg/kg (n=178) or 10 mg/kg (n=179) every 3 weeks or investigator's choice of chemotherapy (n=171), consisting of dacarbazine (26%), temozolomide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%) *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease, severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 16.6 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 16.8 months). The data described below reflect exposure to KEYTRUDA 2 mg/kg in 36% of patients exposed to KEYTRUDA for ≥6 months and in 4% of patients exposed for ≥12 months. In the KEYTRUDA 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA for ≥6 months and 6% of patients were exposed to KEYTRUDA for ≥12 months.

The study population characteristics were: median age of 62 years (range: 15 to 89 years), 61% male, 98% White, 41% with an elevated LDH value at baseline, 83% with M1c stage disease, 73% received two or more prior therapies for advanced or metastatic disease (100% received ipilimumab and 25% a BRAF inhibitor), and 15% with history of brain metastasis.

In KEYNOTE-002, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving

KEYTRUDA; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). The most common adverse reactions (reported in at least 20% of patients) of KEYTRUDA were fatigue, pruritus, rash, constipation, nausea, diarrhea, and decreased appetite.

Table 3 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 3: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-002

	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks n=357		Chemotherapy† n=171	
Adverse Reaction	**All Grades‡ (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Pyrexia	14	0.3	9	0.6
Asthenia	10	2.0	9	1.8
Skin and Subcutaneous Tissue Disorders				
Pruritus	28	0	8	0
Rash§	24	0.6	8	0
Gastrointestinal Disorders				
Constipation	22	0.3	20	2.3
Diarrhea	20	0.8	20	2.3
Abdominal pain	13	1.7	8	1.2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	18	0	16	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	14	0.6	10	1.2

* Adverse reactions occurring at same or higher incidence than in chemotherapy arm
† Chemotherapy: dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin
‡ Graded per NCI CTCAE v4.0
§ Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (43%), nausea (22%), decreased appetite (20%), vomiting (13%), and peripheral neuropathy (1.7%).

Table 4: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-002

	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks		Chemotherapy	
Laboratory Test†	**All Grades‡ %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	49	6	44	6
Hypoalbuminemia	37	1.9	33	0.6
Hyponatremia	37	7	24	3.8
Hypertriglyceridemia	33	0	32	0.9
Increased Alkaline Phosphatase	26	3.1	18	1.9
Increased AST	24	2.2	16	0.6
Bicarbonate Decreased	22	0.4	13	0
Hypocalcemia	21	0.3	18	1.9
Increased ALT	21	1.8	16	0.6

* Laboratory abnormalities occurring at same or higher incidence than in chemotherapy arm.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 320 to 325 patients) and chemotherapy (range: 154 to 161 patients); hypertriglyceridemia: KEYTRUDA n=247 and chemotherapy n=116; bicarbonate decreased: KEYTRUDA n=263 and chemotherapy n=123.
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were anemia (44% all Grades; 10% Grades 3-4) and lymphopenia (40% all Grades; 9% Grades 3-4).

NSCLC

Previously Treated NSCLC

The safety of KEYTRUDA was investigated in Study KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations. A total of 991 patients received KEYTRUDA 2 mg/kg (n=339) or 10 mg/kg (n=343) every 3 weeks or docetaxel (n=309) at 75 mg/m^2 every 3 weeks. Patients with autoimmune disease, medical conditions that required systemic corticosteroids or other immunosuppressive medication, or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.5 months (range: 1 day to 22.4 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 3.5 months (range 1 day to 20.8 months). The data described below reflect exposure to KEYTRUDA 2 mg/kg in 31% of patients exposed to KEYTRUDA for ≥6 months. In the KEYTRUDA 10 mg/kg arm, 34% of patients were exposed to KEYTRUDA for ≥6 months.

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 years or older, 61% male, 72% white and 21% Asian, 8% with advanced localized disease, 91% with metastatic disease, and 15% with history of brain metastases. Twenty-nine percent received two or more prior systemic treatments for advanced or metastatic disease.

In KEYNOTE-010, the adverse reaction profile was similar for the 2 mg/kg and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=682). Treatment was discontinued for adverse reactions in 8% of patients receiving KEYTRUDA. The most common adverse events resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.8%). Adverse reactions leading to interruption of KEYTRUDA occurred in 23% of patients; the most common (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%).

Table 5 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA.

Table 5: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-010

	KEYTRUDA 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m^2 every 3 weeks n=309	
Adverse Reaction	**All Grades† (%)**	**Grade 3-4 (%)**	**All Grades† (%)**	**Grade 3-4 (%)**
Metabolism and Nutrition Disorders				
Decreased appetite	25	1.5	23	2.6
Gastrointestinal Disorders				
Nausea	20	1.3	18	0.6
Constipation	15	0.6	12	0.6
Vomiting	13	0.9	10	0.6
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	23	3.7	20	2.6
Cough	19	0.6	14	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	11	1.0	9	0.3
Back pain	11	1.5	8	0.3
Skin and Subcutaneous Tissue Disorders				
Rash‡	17	0.4	8	0
Pruritus	11	0	3	0.3

* Adverse reactions occurring at same or higher incidence than in docetaxel arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (25%), diarrhea (14%), asthenia (11%) and pyrexia (11%).

Table 6: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving KEYTRUDA in KEYNOTE-010

	KEYTRUDA 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
Laboratory Test†	**All Grades‡ %**	**Grades 3-4 %**	**All Grades‡ %**	**Grades 3-4 %**
Chemistry				
Hyponatremia	32	8	27	2.9
Alkaline phosphatase increased	28	3.0	16	0.7
Aspartate aminotransferase increased	26	1.6	12	0.7
Alanine aminotransferase increased	22	2.7	9	0.4

* Laboratory abnormalities occurring at same or higher incidence than in docetaxel arm.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 631 to 638 patients) and docetaxel (range: 274 to 277 patients).
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were hyperglycemia (44% all Grades; 4.1% Grades 3-4), anemia (37% all Grades; 3.8% Grades 3-4), hypertriglyceridemia (36% all Grades; 1.8% Grades 3-4), lymphopenia (35% all Grades; 9% Grades 3-4), hypoalbuminemia (34% all Grades; 1.6% Grades 3-4), and hypercholesterolemia (20% all Grades; 0.7% Grades 3-4).

Previously Untreated Nonsquamous NSCLC, in Combination with Chemotherapy

The safety of KEYTRUDA in combination with pemetrexed and carboplatin was investigated in a randomized (1:1) open-label cohort in Study KEYNOTE-021. Patients with previously untreated, metastatic nonsquamous NSCLC received KEYTRUDA 200 mg with pemetrexed and carboplatin (n=59), or pemetrexed and carboplatin alone (n=62). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible *[see Clinical Studies (14.2)]*.

The median duration of exposure to KEYTRUDA was 8 months (range: 1 day to 16 months). Sixty-eight percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA 200 mg for ≥6 months. The study population characteristics were: median age of 64 years (range: 37 to 80), 48% age 65 years or older, 39% male, 87% White and 8% Asian, 97% with metastatic disease, and 12% with brain metastases.

KEYTRUDA was discontinued for adverse reactions in 10% of patients. The most common adverse reaction resulting in discontinuation of KEYTRUDA (≥ 2%) was acute kidney injury (3.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 39% of patients; the most common (≥ 2%) were fatigue (8%), neutrophil count decreased (8%), anemia (5%), dyspnea (3.4%), and pneumonitis (3.4%).

Table 7 summarizes the adverse reactions that occurred in at least 20% of patients treated with KEYTRUDA. KEYNOTE-021 was not designed to demonstrate a statistically significant difference in adverse reaction rates for pembrolizumab plus chemotherapy, as compared to chemotherapy alone, for any specified adverse reaction listed in Table 7.

Table 7: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE-021

	KEYTRUDA Pemetrexed Carboplatin n=59		Pemetrexed Carboplatin n=62	
Adverse Reaction	**All Grades* (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	71	3.4	50	0
Peripheral Edema	22	0	18	0
Gastrointestinal Disorders				
Nausea	68	1.7	56	0
Constipation	51	0	37	1.6
Vomiting	39	1.7	27	0
Diarrhea	37	1.7	23	1.6
Skin and Subcutaneous Tissue Disorders				
Rash†	42	1.7	21	1.6
Pruritus	24	0	4.8	0
Alopecia	20	0	3.2	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	39	3.4	21	0
Cough	24	0	18	0
Metabolism and Nutrition Disorders				
Decreased Appetite	31	0	23	0
Nervous System Disorders				
Headache	31	0	16	1.6
Dizziness	24	0	16	0
Dysgeusia	20	0	11	0
Psychiatric Disorders				
Insomnia	24	0	15	0
Infections and Infestations				
Upper respiratory tract infection	20	0	3.2	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	15	0	24	1.6

* Graded per NCI CTCAE v4.0

† Includes rash, rash generalized, rash macular, rash maculo-papular, and rash pruritic.

Table 8: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients in KEYNOTE-021

	KEYTRUDA Pemetrexed Carboplatin		Pemetrexed Carboplatin	
Laboratory Test*	**All Grades† %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	74	9	61	5
Lymphocytes decreased	53	23	60	28
Aspartate aminotransferase increased	51	3.5	46	1.7
Hypertriglyceridemia	50	0	43	0
Alanine aminotransferase increased	40	3.5	32	1.7
Creatinine increased	34	3.4	19	1.7
Hyponatremia	33	5	35	3.5
Hypoalbuminemia	32	0	31	0
Hypocalcemia	30	5	19	1.7
Hypokalemia	29	5	22	1.7
Hypophosphatemia	29	5	24	11
A kaline phosphatase increased	28	0	9	0
Hematology				
Hemoglobin decreased	83	17	84	19
Neutrophils decreased	47	14	43	8
Platelets decreased	24	9	36	10

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA pemetrexed carboplatin (range: 56 to 58 patients) and pemetrexed carboplatin (range: 55 to 61 patients).

† Graded per NCI CTCAE v4.0

HNSCC

Among the 192 patients with HNSCC enrolled in Study KEYNOTE-012, the median duration of exposure to KEYTRUDA was 3.3 months (range: 1 day to 27.9 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for KEYNOTE-012. The median age of patients was 60 years (range: 20 to 84), 35% were age 65 years or older, 83% were male, 77% were White, 15% were Asian, and 5% were Black. Sixty-one percent of patients had two or more lines of therapy in the recurrent or metastatic setting, and 95% had prior radiation therapy. Baseline ECOG PS was 0 (30%) or 1 (70%) and 86% had M1 disease.

KEYTRUDA was discontinued due to adverse reactions in 17% of patients. Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); these data were pooled. The most common adverse reactions (occurring in ≥ 20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism *[see Warnings and Precautions (5.4)]*.

cHL

Among the 210 patients with cHL enrolled in Study KEYNOTE-087 *[see Clinical Studies (14.4)]*, the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). KEYTRUDA was discontinued due to adverse reactions in 5% of patients, and treatment was interrupted due to adverse reactions in 26%. Fifteen percent (15%) of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, pyrexia, dyspnea, graft versus host disease and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

Table 9 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA.

Table 9: Adverse Reactions in ≥10% of Patients with cHL in KEYNOTE-087

	KEYTRUDA 200 mg every 3 weeks N=210	
Adverse Reaction	All Grades* (%)	Grade 3 (%)
General Disorders and Administration Site Conditions		
Fatigue[†]	26	1.0
Pyrexia	24	1.0
Respiratory, Thoracic and Mediastinal Disorders		
Cough[‡]	24	0.5
Dyspnea[§]	11	1.0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[¶]	21	1.0
Arthralgia	10	0.5
Gastrointestinal Disorders		
Diarrhea[#]	20	1.4
Vomiting	15	0
Nausea	13	0
Skin and Subcutaneous Tissue Disorders		
Rash[Þ]	20	0.5
Pruritus	11	0
Endocrine Disorders		
Hypothyroidism	14	0.5
Infections and Infestations		
Upper respiratory tract infection	13	0
Nervous System Disorders		
Headache	11	0.5
Peripheral neuropathy[β]	10	0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes cough, productive cough
§ Includes dyspnea, dyspnea exertional, wheezing
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
# Includes diarrhea, gastroenteritis, colitis, enterocolitis
Þ Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, dermatitis acneiform, dermatitis contact, rash erythematous, rash macular, rash papular, rash pruritic, seborrhoeic dermatitis, dermatitis psoriasiform
β Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

Other clinically important adverse reactions that occurred in less than 10% of patients on KEYNOTE-087 included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), myelitis and myocarditis (0.5% each).

Table 10: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of cHL Patients Receiving KEYTRUDA in KEYNOTE-087

	KEYTRUDA 200 mg every 3 weeks	
Laboratory Test*	All Grades† (%)	Grade 3-4 (%)
Chemistry		
Hypertransaminasemia‡	34%	2%
Alkaline phosphatase increased	17%	0%
Creatinine increased	15%	0.5%
Hematology		
Anemia	30%	6%
Thrombocytopenia	27%	4%
Neutropenia	24%	7%

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 208 to 209 patients)
† Graded per NCI CTCAE v4.0
‡ Includes elevation of AST or ALT

Hyperbilirubinemia occurred in less than 15% of patients on KEYNOTE-087 (10% all Grades, 2.4% Grade 3-4).

Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The safety of KEYTRUDA was investigated in Study KEYNOTE-052, a single-arm trial that enrolled 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression. The median duration of exposure to KEYTRUDA was 2.8 months (range: 1 day to 15.8 months).

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, decreased appetite, constipation, rash and diarrhea. KEYTRUDA was discontinued due to adverse reactions in 11% of patients. Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with KEYTRUDA experienced sepsis which led to death, and three patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

Immune-related adverse reactions that required systemic glucocorticoids occurred in 8% of patients, use of hormonal supplementation due to an immune-related adverse reaction occurred in 8% of patients, and 5% of patients required at least one steroid dose ≥ 40 mg oral prednisone equivalent.

Table 11 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 11: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

	KEYTRUDA 200 mg every 3 weeks N=370	
Adverse Reaction	**All Grades* (%)**	**Grades 3 – 4 (%)**
All Adverse Reactions	96	49
Blood and Lymphatic System Disorders		
Anemia	17	7
Gastrointestinal Disorders		
Constipation	21	1.1
Diarrhea†	20	2.4
Nausea	18	1.1
Abdominal pain‡	18	2.7
Elevated LFTs§	13	3.5
Vomiting	12	0
General Disorders and Administration Site Conditions		
Fatigue¶	38	6
Pyrexia	11	0.5
Weight decreased	10	0
Infections and Infestations		
Urinary tract infection	19	9
Metabolism and Nutrition Disorders		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain#	24	4.9
Arthralgia	10	1.1
Renal and Urinary Disorders		
Blood creatinine increased	11	1.1
Hematuria	13	3.0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	14	0
Dyspnea	11	0.5
Skin and Subcutaneous Tissue Disorders		
Rashᵖ	21	0.5
Pruritis	19	0.3
Edema peripheral	14	1.1

* Graded per NCI CTCAE v4.0

† Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements

‡ Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper

§ Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, transaminases increased, hyperbilirubinemia, blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzymes increased, liver function tests increased

¶ Includes fatigue, asthenia

\# Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain

ᵖ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized

Previously Treated Urothelial Carcinoma

The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in Study KEYNOTE-045. KEYNOTE-045 was a multicenter, open-label, randomized (1:1), active-controlled trial in which 266 patients received KEYTRUDA 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) *[see Clinical Studies (14.5)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. The median duration of exposure was 3.5 months (range: 1 day to 20 months) in patients who received KEYTRUDA and 1.5 months (range: 1 day to 14 months) in patients who received chemotherapy.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). The most common adverse reactions (occurring in at least 20% of patients who received KEYTRUDA) were fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea and rash. Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis.

Table 12 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA. Table 13 summarizes the incidence of laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 12: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

	KEYTRUDA 200 mg every 3 weeks n=266		Chemotherapy* n=255	
Adverse Reaction	**All Grades† (%)**	**Grade 3-4 (%)**	**All Grades† (%)**	**Grade 3-4 (%)**
Gastrointestinal Disorders				
Nausea	21	1.1	29	1.6
Constipation	19	1.1	32	3.1
Diarrhea‡	18	2.3	19	1.6
Vomiting	15	0.4	13	0.4
Abdominal pain	13	1.1	13	2.7
General Disorders and Administration Site Conditions				
Fatigue§	38	4.5	56	11
Pyrexia	14	0.8	13	1.2
Infections and Infestations				
Urinary tract infection	15	4.9	14	4.3
Metabolism and Nutrition Disorders				
Decreased appetite	21	3.8	21	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain¶	32	3.0	27	2.0
Renal and Urinary Disorders				
Hematuria#	12	2.3	8	1.6
Respiratory, Thoracic and Mediastinal Disorders				
CoughÞ	15	0.4	9	0
Dyspneaß	14	1.9	12	1.2
Skin and Subcutaneous Tissue Disorders				
Pruritus	23	0	6	0.4
Rasha	20	0.4	13	0.4

* Chemotherapy: paclitaxel, docetaxel, or vinflunine
† Graded per NCI CTCAE v4.0
‡ Includes diarrhea, gastroenteritis, colitis, enterocolitis
§ Includes asthenia, fatigue, malaise lethargy
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
# Includes blood urine present, hematuria, chromaturia
Þ Includes cough, productive cough
ß Includes dyspnea, dyspnea exertional, wheezing
à Includes rash maculo-papular, rash genital rash, rash erythematous, rash papular, rash pruritic, rash pustular, erythema, drug eruption, eczema, eczema asteatotic, dermatitis contact, dermatitis acneiform, dermatitis, seborrhoeic keratosis, lichenoid keratosis

Table 13: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045

	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
Laboratory Test*	**All Grades† %**	**Grades 3-4 %**	**All Grades† %**	**Grades 3-4 %**
Chemistry				
Glucose increased	52	8	60	7
Hemoglobin decreased	52	13	68	18
Lymphocytes decreased	45	15	53	25
A bumin decreased	43	1.7	50	3.8
Sodium decreased	37	9	47	13
A kaline phosphatase increased	37	7	33	4.9
Creatinine increased	35	4.4	28	2.9
Phosphate decreased	29	8	34	14
Aspartate aminotransferase increased	28	4.1	20	2.5
Potassium increased	28	0.8	27	6
Calcium decreased	26	1.6	34	2.1

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 240 to 248 patients) and chemotherapy (range: 238 to 244 patients); phosphate decreased: KEYTRUDA n=232 and chemotherapy n=222.

† Graded per NCI CTCAE v4.0

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks, 26 (2.0%) of 1289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies. Among the 26 patients who tested positive for treatment emergent anti-pembrolizumab antibodies, only 4 patients were tested for neutralizing antibodies and one was positive. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding antibody development.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to KEYTRUDA with the incidences of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue *[see Data]*. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. There are no available human data informing the risk of embryo-fetal toxicity. Apprise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development, but an assessment of the effects on reproduction was provided. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

8.2 Lactation

Risk Summary

It is not known whether KEYTRUDA is excreted in human milk. No studies have been conducted to assess the impact of KEYTRUDA on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for at least 4 months following the final dose.

8.4 Pediatric Use

There is limited experience with KEYTRUDA in pediatric patients. In a study, 40 pediatric patients (16 children ages 2 years to less than 12 years and 24 adolescents ages 12 years to 18 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumors were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range 1-17 doses), with 34 patients (85%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The safety profile in these pediatric patients was similar to that seen in adults treated with pembrolizumab; toxicities that occurred at a higher rate (≥15% difference) in pediatric patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), hypertransaminasemia (28%) and hyponatremia (18%).

Efficacy for pediatric patients with cHL or MSI-H cancers is extrapolated from the results in the respective adult populations *[see Clinical Studies (14.4, 14.5)].*

8.5 Geriatric Use

Of 3991 patients with melanoma, NSCLC, HNSCC, cHL or urothelial carcinoma who were treated with KEYTRUDA in clinical studies, 46% were 65 years and over and 16% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

10 OVERDOSAGE

There is no information on overdosage with KEYTRUDA.

11 DESCRIPTION

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

KEYTRUDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.2 Pharmacodynamics

Based on dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks in patients with melanoma or NSCLC.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2841 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Pembrolizumab clearance (CV%) is approximately 21% lower [geometric mean, 196 mL/day (41%)] at steady state than that after the first dose [249 mL/day (38%)]; this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for volume of distribution at steady state is 6.0 L (21%) and for terminal half-life ($t_{1/2}$) is 22 days (32%).

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-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.

Specific Populations: The following factors had no clinically important effect on the CL of pembrolizumab: age (range: 15 to 94 years), sex, race (94% White), renal impairment (eGFR greater than or equal to 15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or tumor burden. There is insufficient information to determine whether there are clinically important differences in the CL of pembrolizumab in patients with moderate or severe hepatic impairment. Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients (2 to 17 years) are comparable to those of adults at the same dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

14 CLINICAL STUDIES

14.1 Melanoma

Ipilimumab-Naive Melanoma

The safety and efficacy of KEYTRUDA were evaluated in Study KEYNOTE-006 (NCT01866319), a randomized (1:1:1), open-label, multicenter, active-controlled trial. Patients were randomized to receive KEYTRUDA at a dose of 10 mg/kg every 2 weeks or 10mg/kg every 3 weeks as an intravenous infusion until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg every 3 weeks as an intravenous infusion for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors [RECIST v1.1]). Additional efficacy outcome measures were overall response rate (ORR) and response duration.

A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease , 69% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor.

The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab (Table 14 and Figure 1).

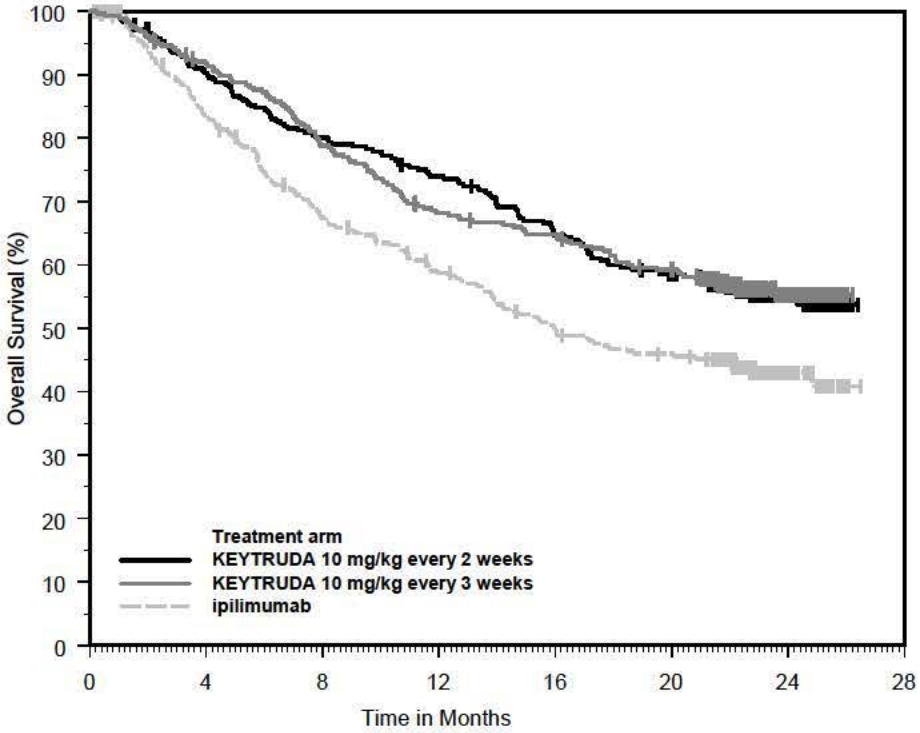
Table 14: Efficacy Results in KEYNOTE-006

	KEYTRUDA 10 mg/kg every 3 weeks n=277	**KEYTRUDA 10 mg/kg every 2 weeks n=279**	**Ipilimumab 3 mg/kg every 3 weeks n=278**
OS			
Deaths (%)	92 (33%)	85 (30%)	112 (40%)
Hazard ratio* (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value (stratified log-rank)	0.004	<0.001	---
PFS by BICR			
Events (%)	157 (57%)	157 (56%)	188 (68%)
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Hazard ratio* (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Best overall response by BICR			
ORR (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response rate	6%	5%	1%
Partial response rate	27%	29%	10%

* Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model

Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to KEYTRUDA 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months.

Figure 1: Kaplan-Meier Curve for Overall Survival in KEYNOTE-006*



Number at Risk								
KEYTRUDA 10 mg/kg every 2 weeks:	279	249	221	202	176	156	44	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	251	215	184	174	156	43	0
ipilimumab:	278	213	170	145	122	110	28	0

**based on the final analysis with an additional follow-up of 9 months (total of 383 deaths as pre-specified in the protocol)*

Ipilimumab-Refractory Melanoma

The safety and efficacy of KEYTRUDA were evaluated in Study KEYNOTE-002 (NCT01704287), a multicenter, randomized (1:1:1), active-controlled trial. Patients were randomized to receive one of two doses of KEYTRUDA in a blinded fashion or investigator's choice chemotherapy. The treatment arms consisted of KEYTRUDA 2 mg/kg or 10 mg/kg intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens: dacarbazine 1000 mg/m^2 intravenously every 3 weeks (26%), temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 plus paclitaxel 175 mg/m^2 every 3 weeks (25%), paclitaxel 175 mg/m^2 intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 intravenously every 3 weeks (8%). Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. Patients received KEYTRUDA until unacceptable toxicity; disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumor status was performed at 12 weeks after randomization, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced progression of disease were offered KEYTRUDA. The major efficacy outcomes were progression-free survival (PFS) as assessed by BICR per RECIST

v1.1 and overall survival (OS). Additional efficacy outcome measures were confirmed overall response rate (ORR) as assessed by BICR per RECIST v1.1 and duration of response.

The treatment arms consisted of KEYTRUDA 2 mg/kg (n=180) or 10 mg/kg (n=181) every 3 weeks or investigator's choice chemotherapy (n=179). Among the 540 randomized patients, the median age was 62 years (range: 15 to 89 years), with 43% age 65 or older; 61% male; 98% White; and ECOG performance score was 0 (55%) and 1 (45%). Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease.

The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm (Table 15). There was no statistically significant difference between KEYTRUDA 2 mg/kg and chemotherapy or between KEYTRUDA 10 mg/kg and chemotherapy in the OS analysis in which 55% of the patients who had been randomized to receive chemotherapy had crossed over to receive KEYTRUDA.

Table 15: Efficacy Results in KEYNOTE-002

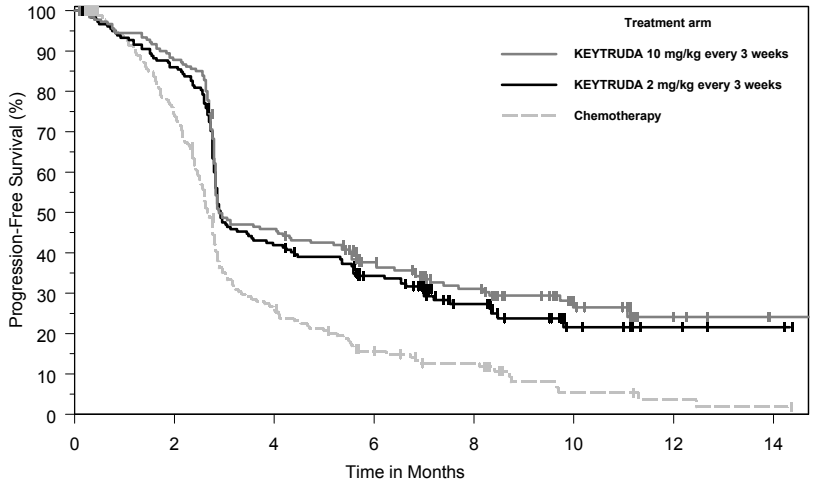
	KEYTRUDA 2 mg/kg every 3 weeks n=180	**KEYTRUDA 10 mg/kg every 3 weeks n=181**	**Chemotherapy n=179**
Progression-Free Survival			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
P Value (stratified log-rank)	<0.001	<0.001	---
Hazard ratio* (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
Overall Survival[†]			
Deaths (%)	123 (68%)	117 (65%)	128 (72%)
Hazard ratio* (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value (stratified log-rank)	0.117	0.011[‡]	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Objective Response Rate			
ORR (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response rate	2%	3%	0%
Partial response rate	19%	23%	4%

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

† With additional follow-up of 18 months after the PFS analysis

‡ Not statistically significant compared to multiplicity adjusted significance level of 0.01

Figure 2: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-002



Number at Risk								
KEYTRUDA 10 mg/kg:	181	158	82	55	39	15	5	1
KEYTRUDA 2 mg/kg:	180	153	74	53	26	9	4	2
Chemotherapy:	179	128	43	22	15	4	2	1

Among the 38 patients randomized to KEYTRUDA 2 mg/kg with an objective response, response durations ranged from 1.3+ to 11.5+ months. Among the 46 patients randomized to KEYTRUDA 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months.

14.2 Non-Small Cell Lung Cancer

First-line treatment of metastatic NSCLC as a single agent

Study KEYNOTE-024 (NCT02142738) was a randomized, multicenter, open-label, active-controlled trial in patients with metastatic NSCLC, whose tumors had high PD-L1 expression [tumor proportion score (TPS) of 50% or greater] by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx Kit, and had not received prior systemic treatment for metastatic NSCLC. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. Randomization was stratified by ECOG performance status (0 vs. 1), histology (squamous vs. nonsquamous), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of any of the following platinum-containing chemotherapy regimens:

- Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m^2 on Days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for nonsquamous histologies).

Treatment with KEYTRUDA continued until RECIST 1.1-defined progression of disease as determined by an independent radiology committee, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving

clinical benefit by the investigator. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression.

Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measure was PFS as assessed by a blinded independent central radiologists' (BICR) review according to RECIST 1.1. Additional efficacy outcome measures were OS and ORR as assessed by the BICR according to RECIST 1.1.

A total of 305 patients were randomized: 154 patients to the KEYTRUDA arm and 151 to the chemotherapy arm. The study population characteristics were: median age of 65 years (range: 33 to 90), 54% age 65 or older; 61% male; 82% white and 15% Asian; 65% ECOG performance status of 1; 18% with squamous and 82% with nonsquamous histology and 9% with history of brain metastases. A total of 66 patients in the chemotherapy arm received KEYTRUDA at the time of disease progression.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared with chemotherapy. Additionally, a pre-specified interim OS analysis at 108 events (64% of the events needed for final analysis) also demonstrated statistically significant improvement of OS for patients randomized to KEYTRUDA as compared with chemotherapy. Table 16 summarizes key efficacy measures for KEYNOTE-024.

Table 16: Efficacy Results in KEYNOTE-024

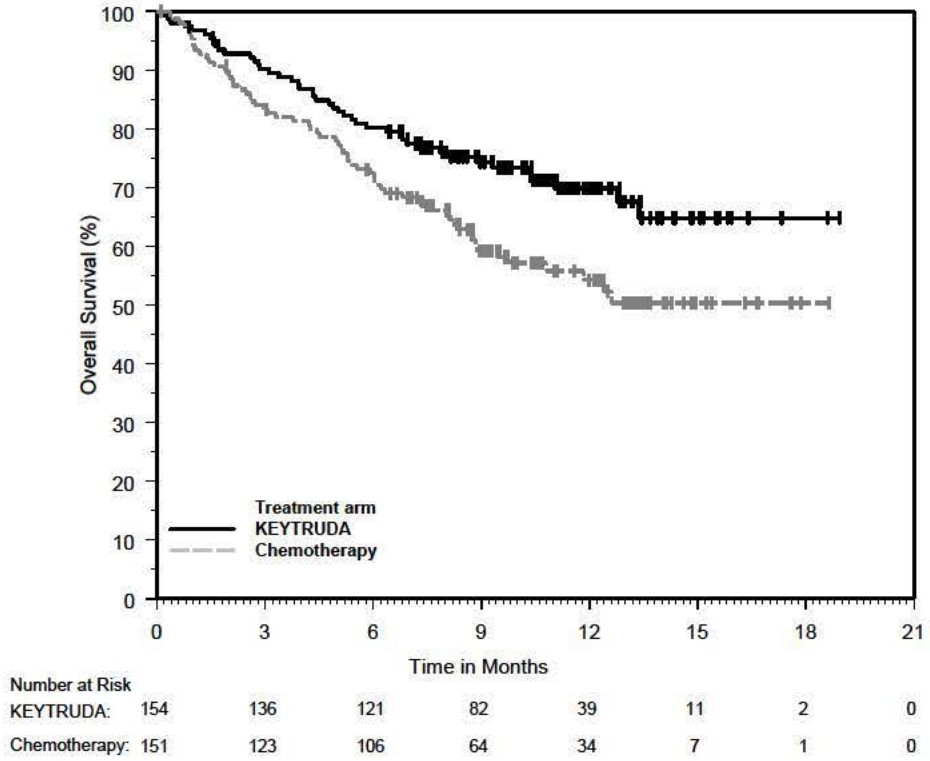
Endpoint	**KEYTRUDA 200 mg every 3 weeks n=154**	**Chemotherapy n=151**
PFS		
Number (%) of patients with event	73 (47%)	116 (77%)
Median in months (95% CI)	10.3 (6.7, NR)	6.0 (4.2, 6.2)
Hazard ratio* (95% CI)	0.50 (0.37, 0.68)	
p-Value (stratified log-rank)	<0.001	
OS		
Number (%) of patients with event	44 (29%)	64 (42%)
Median in months (95% CI)	NR (NR, NR)	NR (9.4, NR)
Hazard ratio* (95% CI)	0.60 (0.41, 0.89)	
p-Value (stratified log-rank)	0.005†	
Objective Response Rate		
ORR (95% CI)	45% (37, 53)	28% (21, 36)
Complete response rate	4%	1%
Partial response rate	41%	27%
p-Value (Miettinen-Nurminen)	0.001	
Median duration of response in months (range)	NR (1.9+, 14.5+)	6.3 (2.1+, 12.6+)

* Based on the stratified Cox proportional hazard model

† P-value is compared with 0.0118 of the allocated alpha for this interim analysis.

NR = not reached

Figure 3: Kaplan-Meier Curve for Overall Survival in KEYNOTE-024



First-line treatment of metastatic nonsquamous NSCLC in combination with pemetrexed and carboplatin
The efficacy of KEYTRUDA was investigated in patients enrolled in an open-label, multicenter, multi-cohort study, Study KEYNOTE-021 (NCT02039674); the efficacy data are limited to patients with metastatic nonsquamous NSCLC randomized within a single cohort (Cohort G1). The key eligibility criteria for this cohort were locally advanced or metastatic nonsquamous NSCLC, regardless of tumor PD-L1 expression status, and no prior systemic treatment for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by PD-L1 tumor expression (TPS <1% vs. TPS ≥1%). Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg, pemetrexed 500 mg/m^2, and carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles followed by KEYTRUDA 200 mg intravenously every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Pemetrexed 500 mg/m^2 and carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles.

At the investigator's discretion, maintenance pemetrexed 500 mg/m^2 every 3 weeks was permitted in both treatment arms.

Treatment with KEYTRUDA continued until RECIST 1.1-defined progression of disease as determined by blinded independent central review (BICR), unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

Patients on chemotherapy were offered KEYTRUDA as a single agent at the time of disease progression.

Assessment of tumor status was performed every 6 weeks through Week 18 and every 9 weeks thereafter. The major efficacy outcome measure was objective response rate (ORR) as assessed by

BICR using RECIST 1.1. Additional efficacy outcome measures were progression-free survival (PFS) as assessed by BICR using RECIST 1.1, duration of response, and overall survival (OS).

A total of 123 patients were randomized: 60 patients to the KEYTRUDA and chemotherapy arm and 63 to the chemotherapy arm. The study population characteristics were: median age of 64 years (range: 37 to 80); 48% age 65 or older; 39% male; 87% White and 8% Asian; ECOG performance status of 0 (41%) and 1 (56%); 97% had metastatic disease; and 12% had brain metastases. Thirty-six percent had tumor PD-L1 expression TPS <1%; no patients had sensitizing EGFR or ALK genomic aberrations. A total of 20 (32%) patients in the chemotherapy arm received KEYTRUDA at the time of disease progression and 12 (19%) additional patients received a checkpoint inhibitor as subsequent therapy.

In Cohort G1 of KEYNOTE-021, there was a statistically significant improvement in ORR in patients randomized to KEYTRUDA in combination with pemetrexed and carboplatin compared with pemetrexed and carboplatin alone (see Table 17).

Table 17: Efficacy Results in Cohort G1 of KEYNOTE-021

Endpoint	KEYTRUDA Pemetrexed Carboplatin n=60	Pemetrexed Carboplatin n=63
Overall Response Rate		
Overall Response Rate	55%	29%
(95% CI)	(42, 68)	(18, 41)
Complete Response	0%	0%
Partial Response	55%	29%
p-value*	0.0032	
Duration of Response		
% with duration ≥ 6 months†	93%	81%
Range (months)	1.4+ to 13.0+	1.4+ to 15.2+
PFS		
Number of events (%)	23 (38%)	33 (52%)
Progressive Disease	15 (25%)	27 (43%)
Death	8 (13%)	6 (10%)
Median in months (95% CI)	13.0 (8.3, NE)	8.9 (4.4, 10.3)
Hazard ratio‡ (95% CI)	0.53 (0.31, 0.91)	
p-value§	0.0205	

* Based on Miettinen-Nurminen method stratified by PD-L1 status (TPS <1% vs. TPS ≥1%).
† Based on Kaplan-Meier estimation
‡ Based on the Cox proportional hazard model stratified by PD-L1 status (TPS <1% vs. TPS ≥1%).
§ Based on the log-rank test stratified by PD-L1 status (TPS <1% vs. TPS ≥1%).
NE = not estimable

Exploratory analyses for ORR were conducted in subgroups defined by the stratification variable, PD-L1 tumor expression (TPS <1% and TPS ≥1%). In the TPS <1% subgroup, the ORR was 57% in the KEYTRUDA-containing arm and 13.0% in the chemotherapy arm. In the TPS ≥1% subgroup, the ORR was 54% in the KEYTRUDA-containing arm and 38% in the chemotherapy arm.

Previously treated NSCLC

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx Kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS=1-49%), ECOG performance scale (0 vs. 1), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1:1) to receive KEYTRUDA 2 mg/kg intravenously every 3 weeks, KEYTRUDA 10 mg/kg intravenously every 3 weeks or docetaxel intravenously 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue until disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or confirmation of progression at 4 to 6 weeks with repeat imaging or for up to 24 months without disease progression.

Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measures were OS and PFS as assessed by the BICR according to RECIST 1.1 in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%. Additional efficacy outcome measures were ORR and response duration in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%.

A total of 1033 patients were randomized: 344 to the KEYTRUDA 2 mg/kg arm, 346 patients to the KEYTRUDA 10 mg/kg arm, and 343 patients to the docetaxel arm. The study population characteristics were: median age 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG performance status 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease.

Tables 18 and 19 summarize key efficacy measures in the subgroup with TPS ≥50% population and in all patients, respectively. The Kaplan-Meier curve for OS (TPS ≥1%) is shown in Figure 4.

Table 18: Efficacy Results of the Subgroup of Patients with TPS ≥50% in KEYNOTE-010

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=139	KEYTRUDA 10 mg/kg every 3 weeks n=151	Docetaxel 75 mg/m^2 every 3 weeks n=152
OS			
Deaths (%)	58 (42%)	60 (40%)	86 (57%)
Median in months (95% CI)	14.9 (10.4, NR)	17.3 (11.8, NR)	8.2 (6.4, 10.7)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	89 (64%)	97 (64%)	118 (78%)
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Objective response rate			
ORR† (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 16.8+)	NR (2.1+, 17.8+)	8.1 (2.1+, 8.8+)

* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† All responses were partial responses

NR = not reached

Table 19: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

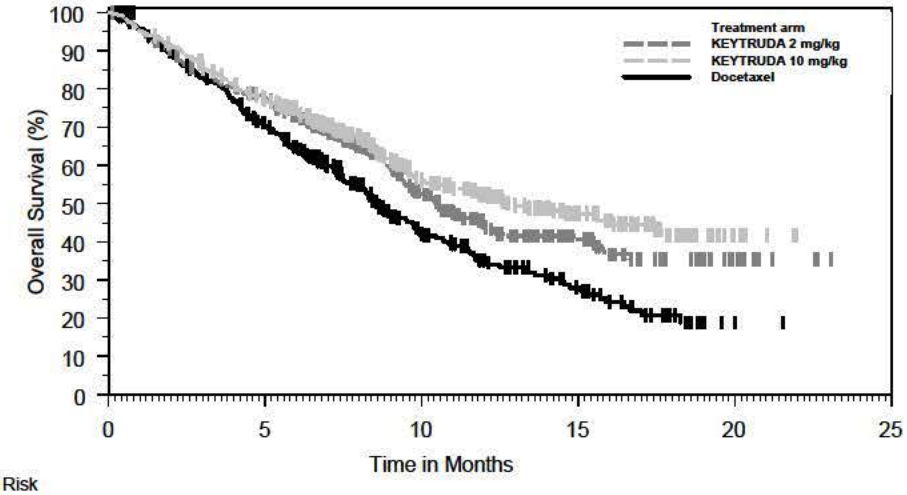
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	266 (77%)	255 (74%)	257 (75%)
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value (stratified log-rank)	0.068	0.005	---
Objective response rate			
ORR† (95% CI)	18% (14, 23)	19% (15, 23)	9% (7, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 20.1+)	NR (2.1+, 17.8+)	6.2 (1.4+, 8.8+)

* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† All responses were partial responses

NR = not reached

Figure 4: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-010 (TPS ≥1%)



Number at Risk						
KEYTRUDA 2 mg/kg:	344	259	115	49	12	0
KEYTRUDA 10 mg/kg:	346	255	124	56	6	0
Docetaxel:	343	212	79	33	1	0

14.3 Head and Neck Cancer

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-012 (NCT01848834), a multicenter, non-randomized, open-label, multi-cohort study that enrolled 174 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy. Patients with active autoimmune disease, a medical condition that required immunosuppression, evidence of interstitial lung disease, or ECOG PS ≥2 were ineligible.

Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=53) or 200 mg every 3 weeks (n=121) until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 174 patients, the baseline characteristics were median age 60 years (32% age 65 or older); 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumors; 63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; and the median number of prior lines of therapy administered for the treatment of HNSCC was 2.

The ORR was 16% (95% CI: 11, 22) with a complete response rate of 5%. The median follow-up time was 8.9 months. Among the 28 responding patients, the median duration of response had not been reached (range 2.4+ to 27.7+ months), with 23 patients having responses of 6 months or longer. The ORR and duration of response were similar irrespective of dosage regimen (10 mg/kg every 2 weeks or 200 mg every 3 weeks) or HPV status.

14.4 Classical Hodgkin Lymphoma

The efficacy of KEYTRUDA was investigated in 210 patients with relapsed or refractory cHL, enrolled in a multicenter, non-randomized, open-label study (KEYNOTE-087; NCT02453594). Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or greater than 5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Patients received KEYTRUDA at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months in patients that did not progress. Disease assessment was performed every 12 weeks. The major efficacy outcome measures (ORR, CRR, and duration of response) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria.

Among the 210 patients, the baseline characteristics were: median age of 35 years (range: 18 to 76), 9% age 65 or older; 54% male; 88% White; 49% had an ECOG performance status (PS) of 0 and 51% had an ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range 1 to 12). Fifty-eight percent were refractory to the last prior therapy, including 35% with primary refractory disease and 14% whose disease was chemo-refractory to all prior regimens. Sixty-one percent of patients had undergone prior auto-HSCT, 83% had received prior brentuximab vedotin and 36% of patients had prior radiation therapy.

Efficacy results for KEYNOTE-087 are summarized in Table 20.

Table 20: Efficacy Results in KEYNOTE-087

	KEYNOTE-087*
Endpoint	N=210
Overall Response Rate	
ORR %, (95% CI)	69% (62, 75)
Complete Remission	22%
Partial Remission	47%
Response Duration	
Median in months (range)	11.1 (0.0+, 11.1)†

* Median follow-up time of 9.4 months

† Based on patients (n=145) with a response by independent review

14.5 Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-052 (NCT02335424), a multicenter, open-label, single-arm trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Tumor response assessments were performed at 9 weeks after the first dose, then every 6 weeks for the first year, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST 1.1 as assessed by independent radiology review and duration of response.

In this trial, the median age was 74 years, 77% were male, and 89% were White. Eighty-seven percent had M1 disease, and 13% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 19% of patients had a primary tumor in the upper tract. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Reasons for cisplatin ineligibility included: 50% with baseline creatinine clearance of <60 mL/min, 32% with ECOG performance status of 2, 9% with ECOG 2

and baseline creatinine clearance of <60 mL/min, and 9% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

The median follow-up time for 370 patients treated with KEYTRUDA was 7.8 months (range 0.1 to 20 months). Efficacy results are summarized in Table 21.

Table 21: Efficacy Results in KEYNOTE-052

Endpoint	KEYTRUDA 200 mg every 3 weeks n=370
Objective Response Rate	
ORR (95% CI)	29% (24, 34)
Complete Response Rate	7%
Partial Response Rate	22%
Duration of Response	
Median in months (range)	NR (1.4+, 17.8+)

\+ Denotes ongoing
NR = not reached

Previously Treated Urothelial Carcinoma
The efficacy of KEYTRUDA was evaluated in Study KEYNOTE-045 (NCT02256436), a multicenter, randomized (1:1), active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients were randomized to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (n=87). Treatment continued until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed at 9 weeks after randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy outcomes were OS and PFS as assessed by BICR per RECIST 1.1. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST 1.1 and duration of response.

Among the 542 randomized patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 42% ECOG status of 0 and 56% ECOG performance status of 1; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumor in the lower tract and 14% had a primary tumor in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

Table 22 and Figure 5 summarize the key efficacy measures for KEYNOTE-045. The study demonstrated statistically significant improvements in OS and ORR for patients randomized to KEYTRUDA as compared to chemotherapy. There was no statistically significant difference between KEYTRUDA and

chemotherapy with respect to PFS. The median follow-up time for this trial was 9.0 months (range: 0.2 to 20.8 months).

Table 22: Efficacy Results in KEYNOTE-045

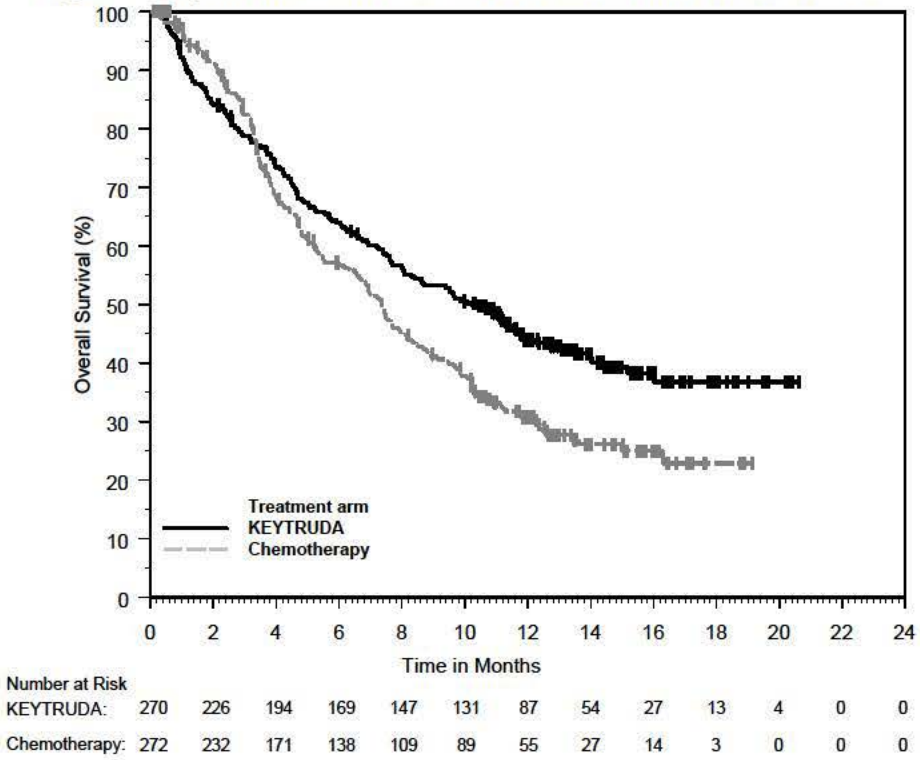
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
Hazard ratio* (95% CI)	0.98 (0.81, 1.19)	
p-Value (stratified log-rank)	0.833	
Objective Response Rate		
ORR (95% CI)	21% (16, 27)	11% (8, 16)
Complete Response Rate	7%	3%
Partial Response Rate	14%	8%
p-Value (Miettinen-Nurminen)	0.002	
Median duration of response in months (range)	NR (1.6+, 15.6+)	4.3 (1.4+, 15.4+)

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

\+ Denotes ongoing

NR = not reached

Figure 5: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



14.6 Microsatellite Instability-High Cancer

The efficacy of KEYTRUDA was evaluated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by blinded independent central radiologists' (BICR) review according to RECIST 1.1 and duration of response.

Table 23: MSI-H Trials

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

A total of 149 patients with MSI-H or dMMR cancers were identified across the five clinical trials. Among these 149 patients, the baseline characteristics were: median age 55 years (36% age 65 or older); 56% male; 77% White, 19% Asian, 2% Black; and ECOG PS 0 (36%) or 1 (64%). Ninety-eight percent of patients had metastatic disease and 2% had locally advanced, unresectable disease. The median number of prior therapies for metastatic or unresectable disease was two. Eighty-four percent of patients with metastatic CRC and 53% of patients with other solid tumors received two or more prior lines of therapy.

The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR

test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.

Efficacy results are summarized in Table 24.

Table 24: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	n=149
Objective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4
Partial response rate	32.2
Response duration	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

NR = not reached

Table 25: Response by Tumor Type

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA for injection (lyophilized powder): carton containing one 50 mg single-dose vial (NDC 0006-3029-02).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

KEYTRUDA injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02)

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
- Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.
- Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.4)].*
- Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes *[see Warnings and Precautions (5.4)].*
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*.

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7)]*.
- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.8)].*
- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.3, 5.4, 5.5)]*.
- Advise females that KEYTRUDA can cause fetal harm. Instruct females of reproductive potential to use highly effective contraception during and for 4 months after the last dose of KEYTRUDA *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)]*.
- Advise nursing mothers not to breastfeed while taking KEYTRUDA and for 4 months after the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
U.S. License No. 0002

For KEYTRUDA for injection, at:
MSD International GmbH,
County Cork, Ireland

For KEYTRUDA injection, at:
MSD Ireland (Carlow)
County Carlow, Ireland

For patent information: www.merck.com/product/patent/home.html

uspi-mk3475-iv-1705f011

MEDICATION GUIDE

KEYTRUDA® (key-true-duh)
(pembrolizumab)
for injection

KEYTRUDA® (key-true-duh)
(pembrolizumab)
injection

What is the most important information I should know about KEYTRUDA?

KEYTRUDA is a medicine that may treat certain cancers by working with your immune system. KEYTRUDA can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

Call or see your doctor right away if you develop any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Symptoms of pneumonitis may include:
- shortness of breath
- chest pain
- new or worse cough

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:
- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:
- yellowing of your skin or the whites of your eyes
- nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine
- feeling less hungry than usual
- bleeding or bruising more easily than normal

Hormone gland problems (especially the thyroid, pituitary, adrenal glands, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:
- rapid heart beat
- weight loss or weight gain
- increased sweating
- feeling more hungry or thirsty
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- muscle aches
- dizziness or fainting
- headaches that will not go away or unusual headache

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:
- change in the amount or color of your urine

Problems in other organs. Signs of these problems may include:
- rash
- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness
- low red blood cells (anemia)
- shortness of breath, irregular heartbeat, feeling tired, or chest pain (myocarditis)

Infusion (IV) reactions, that can sometimes be severe and life-threatening. Signs and symptoms of infusion reactions may include:
- chills or shaking

- shortness of breath or wheezing
- itching or rash
- flushing
- dizziness
- fever
- feeling like passing out

Complications of stem cell transplantation that uses donor stem cells (allogeneic) after treatment with KEYTRUDA. These complications can be severe and can lead to death. Your doctor will monitor you for signs of complications if you are an allogeneic stem cell transplant recipient.

Getting medical treatment right away may help keep these problems from becoming more serious.
Your doctor will check you for these problems during treatment with KEYTRUDA. Your doctor may treat you with corticosteroid or hormone replacement medicines. Your doctor may also need to delay or completely stop treatment with KEYTRUDA, if you have severe side effects.

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat:

- a kind of skin cancer called melanoma that has spread or cannot be removed by surgery (advanced melanoma).
- a kind of lung cancer called non-small cell lung cancer (NSCLC).
  - KEYTRUDA may be used alone when your lung cancer:
    - has spread (advanced NSCLC) **and,**
    - tests positive for "PD-L1" **and,**
      - as your first treatment if you have not received chemotherapy to treat your advanced NSCLC and your tumor does not have an abnormal "EGFR" or "ALK" gene,

      or
      - you have received chemotherapy that contains platinum to treat your advanced NSCLC, and it did not work or it is no longer working, **and**
      - if your tumor has an abnormal "EGFR" or "ALK" gene, you have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.
  - KEYTRUDA may be used with the chemotherapy medicines pemetrexed and carboplatin as your first treatment when your lung cancer:
    - has spread (advanced NSCLC) **and**
    - is a type of lung cancer called "nonsquamous".
- a kind of cancer called head and neck squamous cell cancer (HNSCC) that:
    - has returned or spread **and**
    - you have received chemotherapy that contains platinum and it did not work or is no longer working.
- a kind of cancer called classical Hodgkin lymphoma (cHL) in adults and children when:
    - you have tried a treatment and it did not work **or**
    - your cHL has returned after you received 3 or more types of treatment.
- a kind of bladder and urinary tract cancer called urothelial carcinoma. KEYTRUDA may be used when your bladder or urinary tract cancer:
    - has spread or cannot be removed by surgery (advanced urothelial cancer) **and**,
    - you are not able to receive chemotherapy that contains a medicine called cisplatin, **or**
    - you have received chemotherapy that contains platinum, and it did not work or is no longer working.
- a kind of cancer that is shown by a laboratory test to be a microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumor. KEYTRUDA may be used in adults and children to treat:
    - cancer that has spread or cannot be removed by surgery (advanced cancer), **and**
    - has progressed following treatment, and you have no satisfactory treatment options, **or**
    - you have colon or rectal cancer, and you have received chemotherapy with fluoropyrimidine, oxaliplatin, and irinotecan but it did not work or is no longer working.

  It is not known if KEYTRUDA is safe and effective in children with MSI-H cancers of the brain or spinal cord (central nervous system cancers).

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical problems
- are pregnant or plan to become pregnant
  - KEYTRUDA can harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during and for at least 4 months after the final dose of KEYTRUDA. Talk to your doctor about birth control methods that you can use during this time.
  - Tell your doctor right away if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed.
  - It is not known if KEYTRUDA passes into your breast milk.
  - Do not breastfeed during treatment with KEYTRUDA and for 4 months after your final dose of KEYTRUDA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive KEYTRUDA?

- Your doctor will give you KEYTRUDA into your vein through an intravenous (IV) line over 30 minutes.
- KEYTRUDA is usually given every 3 weeks.
- Your doctor will decide how many treatments you need.
- Your doctor will do blood tests to check you for side effects.
- If you miss any appointments, call your doctor as soon as possible to reschedule your appointment.

What are the possible side effects of KEYTRUDA?

KEYTRUDA can cause serious side effects. See "What is the most important information I should know about KEYTRUDA?"

Common side effects of KEYTRUDA when used alone include: feeling tired, itching, diarrhea, decreased appetite, rash, fever, cough, shortness of breath, pain in muscles, bones or joints, constipation, and nausea.

In children, feeling tired, vomiting and stomach-area (abdominal) pain, and increased levels of liver enzymes and decreased levels of salt (sodium) in the blood are more common than in adults.

These are not all the possible side effects of KEYTRUDA. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of KEYTRUDA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about KEYTRUDA, talk with your doctor. You can ask your doctor or nurse for information about KEYTRUDA that is written for healthcare professionals. For more information, go to www.keytruda.com.

What are the ingredients in KEYTRUDA?

Active ingredient: pembrolizumab

Inactive ingredients:

KEYTRUDA for injection: L-histidine, polysorbate 80, and sucrose. May contain hydrochloric acid/sodium hydroxide.

KEYTRUDA injection: L-histidine, polysorbate 80, sucrose, and Water for Injection, USP.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For KEYTRUDA for injection, at:
MSD International GmbH, County Cork, Ireland
For KEYTRUDA injection, at:
MSD Ireland (Carlow), County Carlow, Ireland
U.S. License No. 0002
For patent information: www.merck.com/product/patent/home.html

usmg-mk3475-iv-1705r010

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

SUMMARY REVIEW

Division Director Summary Review

Date	May 23, 2017
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
BLA Supplement #	BLA 125514/S-014
Applicant Name	Merck, Sharp & Dohme Corp.
Date of Submission	September 8, 2016
Date of Major Amendment	March 9, 2017
PDUFA Goal Date	June 8, 2017
Proprietary Name / Established (USAN) Name	Keytruda/ pembrolizumab
Dosage Forms / Strength	For injection: 100 mg/4 mL in single-use vials. Injection: 50 mg in single use vials
Proposed Indication	KEYTRUDA is indicated for the treatment of (b) (4) This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials
Approved Indication	for the treatment of adult and pediatric patients with: • unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or • colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [see Clinical Studies (14.5)]. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Health Project Manager Review	Sharon Sickafuse
Medical Officer Review	Leigh Marcus
Statistical Review	Weishi Yuan
CMC Review/OBP Review	Mark Paciga
Clinical Pharmacology Review	Brian Furmanski & Hongshan Li
OPDP	Nicholas Senior
OSI	Lauren Iacono-Connors
CDTL Review	Steve Lemery
Patient Labeling Team	Sharon R. Mills

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

Division Directory Summary Review

1. Introduction

This efficacy supplements sought approval under the provisions of 21 CFR 601.41 (accelerated approval) for pembrolizumab (Keytruda; Merck, Sharp & Dohme Corp. (Merck)) for the proposed indication of (b) (4)

Pembrolizumab, a humanized, programmed death receptor-1 (PD-1)-blocking monoclonal antibody, was approved on September X, 2014, and is currently approved for the treatment of the following cancers: patients with unresectable or metastatic melanoma, metastatic; PD-L1-positive, non-small cell lung cancer; recurrent or metastatic head and neck squamous cell carcinoma; adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL) or who have relapsed after 3 or more prior lines of therapy: and patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy or with disease progression disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Merck requested approval of pembrolizumab for the treatment of tumors arising in any primary site, where there is evidence in the tumor of impaired DNA repair, as detected by protein expression by immunohistochemistry (IHC) of four mismatch repair (MMR) proteins (MLH1/MSH2/MSH6/PMS2) or by detection of 3 to 5 tumor microsatellite loci using a polymerase chain reaction (PCR) assay.

Data supporting this approval was derived by pooling data from patients with metastatic, previously treated, solid tumors, enrolled in five single-arm, multicenter trials and selected for inclusion in the pooled dataset based on MSI-H or dMMR tumor testing. The studies differed in eligibility criteria [(pre-specified requirement for MSI-H or dMMR tumor vs. pre-specified testing for PD-L1 status/retrospective testing for MSI-H or dMMR); extent of prior therapy(≥ 1 prior line of therapy vs. specified prior treatment regimens for a specific cancer type); primary cancer (limited to colorectal cancer vs. multiple primary cancers)], use of local vs. central laboratory to determine MSI-H/dMMR status, pembrolizumab dosage regimen (10 mg/kg every 2 weeks vs. 200 mg every 3 weeks). Based on discussions with FDA, approximately 150 patients were to be assessed for overall response rate (ORR) by an independent review committee according to RECIST v1.1, with adequate duration of follow-up to characterize duration of response. The goal of the analysis was to estimate the point estimate for ORR and articulate 95% confidence intervals.

The database contained 149 patients, the median age was 55 years, 56% were male, and 77% were White, 19% Asian, 2% Black. The majority (98%) had metastatic disease at study entry; 60% had colorectal cancer and of the 40% with non-colorectal cancers, the most common primary cancers in descending order were: endometrial cancer (24%), biliary tract

cancer (19%), gastric or gastroesophageal cancers (15%), small intestinal cancers (13%), and pancreatic cancers (10%). The median number of prior lines of therapies administered for the treatment of metastatic or unresectable disease was 2, with 84% of patients with metastatic colorectal cancer and 53% of patients with other solid tumors ≥2 prior lines of therapy. Across all 149 patients, 40% (n=60) had tumors identified as MSI-H using a PCR-based assay, 32% (n=47) had tumors identified as dMMR using an IHC assay, and 28% (n=42) were determined to be eligible for inclusion using both assays. For 91% (135/149) of the population, the presence of MSI-H or dMMR was determined prior to study entry based on local laboratory assessment.

In the pooled dataset of 149 patients, the ORR was 39.6% (95% confidence intervals (CI): 31.7, 47.9) with 78%of responding patients experiencing a duration of response of more than 6 months. The ORR was similar among patients with colorectal cancers [ORR 36% (95% CI: 26, 46) and non-colorectal cancers [ORR 46% (95% CI: 33, 59)]. Based on updated efficacy and safety data submitted in a major amendment, the median duration of response was not estimable; however, 78% of responding patients had response durations of ≥ 6 months. While there was a dose-related, numerically higher response rate for the subgroup of patients receiving pembrolizumab 10 mg/kg every 2 weeks as compared to 200 mg every 3 weeks, interpretation of this difference was confounded by differential follow-up (shorter follow-up in studies using the 200 mg dosage regimen) and possible differences across studies with regard to patient characteristics (e.g., primary tumor type, proportion of patients with ECOG PS 1, number of prior lines of therapy) as well as unknown factors. In light of the relatively flat exposure-response curve across multiple disease-specific indications, a dosage regimen of 200 mg every 3 weeks was included in product labeling.

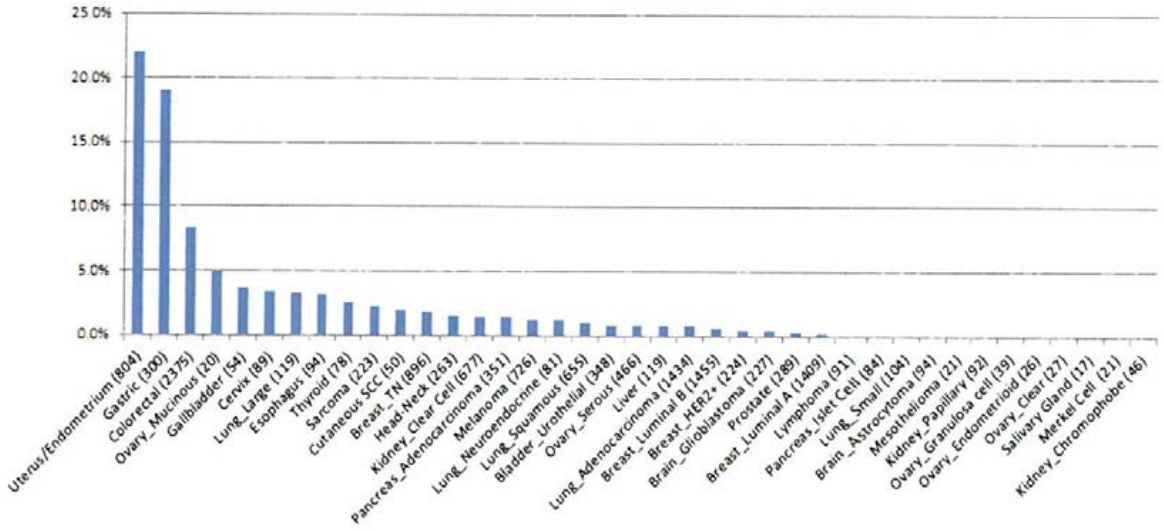
There were no new safety signals observed in this patient population; no updates were made to Sections 5 and 6 of the package insert based on the extensive prior safety experience and single arm nature of these studies.

Four major issues were considered during review of this supplement:

- Whether the presence of MSI-H or dMMR in tumors predicted similar efficacy across different primary tumors, such that this phenotype identified a “tissue agnostic” phenotype sufficient to identify patients who will derive similar benefit (overall response rate of sufficient magnitude and durability) from treatment with pembrolizumab;
- Whether one or more companion diagnostic devices were required to select the indicated patient population in order to ensure safe and effective use of pembrolizumab; and
- Whether the observed differences in response rate observed in subgroups defined by the pembrolizumab dosage regimen administered provided evidence of a differential dose-response relationship.
- Extrapolation of the efficacy results to pediatric patients with MSI-H cancers.

2. Background

Indicated Population and Available Therapy
There is insufficient information to accurately characterize the incidence of the indicated population, patients with MSI-H or dMMR across all solid tumors; however, the most detailed assessment was provided by Moffitt database.[1] .



In the retrospective screening of 415 patients with available tumor samples enrolled KEYNOTE-012, KEYNOTE-028, or rare-tumor cohorts in the KEYNOTE-158-studies, the incidence of MSI-H or dMMR tumors was 3.4% (95% CI: 1.9, 5.6).

Based on published literature[2], patients with MSI-H or MMR-deficient colorectal cancers appear to have a more favorable prognosis than MSS (microsatellite stable) colorectal cancers; the extent to which this holds true in patients receiving third-line therapy for metastatic disease is unclear. The indication being sought is limited to patients with MSI-H/dMMR cancers that are both metastatic and have progressed following standard treatment. In general, this population would be considered to have no FDA-approved therapy. Since the two most common cancers in this pooled dataset were colorectal and endometrial cancers, a summary of the outcomes with potentially available treatments are summarized below, for context.

Available therapies for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy include the following drugs:

Regorafenib was approved September 27, 2012, for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-

[1] Figure 6: Moffitt Cancer Center database estimates of MSI-H frequency (BLA 125514/S-014)
[2] *Journal of Clinical Oncology* 23, no. 3 (January 2005) 609-618.

and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. This approval was based on demonstration of improved overall survival [HR 0.77 (0.64, 0.94); p=0.01], supported by an improvement in progression-free survival (PFS) [HR 0.49 (0.42, 0.58)], in an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial enrolling 760 patients with previously treated metastatic colorectal cancer. The overall response rate (ORR) with regorafenib was 1% (5/505).

Trifluridine/tipiracil was approved on September 22, 2015 for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. This approval was based on demonstration of a clinically important and statistically significant improvement in overall survival [hazard ratio (HR) 0.68 (95% confidence interval (CI): 0.58, 0.81); p<0.001], supported by an improvement in PFS [HR 0.47 (95% CI: 0.40, 0.55); p<0.001], in a randomized, placebo-controlled trial conducted in 800 patients. The ORR to with trifluridine/tipiracil was 1.5% (8/534).

Metastatic endometrial cancer

Megestrol acetate is the only drug that is FDA- approved for the treatment of endometrial cancer. The approved indication is states "Megace is indicated for the palliative treatment of advanced carcinoma of the endometrium (i.e., recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, or chemotherapy." The basis for this approval is not described in product labeling.

The NCCN Practice Guidelines[3] make the following recommendations for hormonal therapy and chemotherapy for the treatment of recurrent or metastatic endometrial cancer based on Category 2A evidence (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate):

Hormonal therapy, consisting of megestrol alternating with tamoxifen, progestational agents, aromatase inhibitors, and tamoxifen, "may be used for lower grade endometrioid histologies only, preferably in patients with small tumor volume or an indolent growth pace."

Multi-agent chemotherapy regimens (carboplatin/paclitaxel, cisplatin/doxorubicin, and cisplatin/doxorubicin/paclitaxel) are preferred, if tolerated. Single agent chemotherapeutic options may include cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, and paclitaxel). Bevacizumab may be considered for use in patients who have progressed on prior cytotoxic chemotherapy. Reported response rates with single agent chemotherapies ranges from 31-81% with short duration of response. Reported response rates with first-line combination chemotherapy, e.g., carboplatin and paclitaxel, range from 40-62%.

However for patients progressing following first line chemotherapy, treatment options are limited to investigational and off-label therapies with responses of generally less than 20%,

[3] https://www.nccn.org/professionals/physician_gls/pdf/uterine_blocks.pdf

with the exception of a reports of temsirolimus plus bevacizumab (ORR 24%) and everolimus plus letrozole (ORR 32%).[4]

Pre-Submission Regulatory History
The clinical investigation and FDA interactions for pembrolizumab for the treatment of patients with MSI-H or dMMR metastatic solid tumors were conducted primarily under IND 123482, submitted to FDA on November 21, 2014 for the investigation of pembrolizumab for the treatment of various gastrointestinal malignancies. As noted below, clinical studies supporting this application were also discussed under INDs 110080 and 127548.

On May 12, 2015, a Type B meeting was held to discuss the adequacy of the design of Protocol KEYNOTE (KN)-164 entitled "A Phase IIB Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Unresectable Locally Advanced or Metastatic Microsatellite Instability-High Colorectal Adenocarcinoma" to support an expanded indication for pembrolizumab (b) (4)

The proposed development program was based on the preliminary results of the KEYNOTE-016 trial, entitled, "A Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors," which is an investigator-initiated multi-institutional study conducted by Johns Hopkins University. The preliminary results were that 4 of 10 (40%; 95% CI: 12, 74) "evaluable" patients with metastatic MSI-H colorectal cancer, 5 of 7 (71%; 95% CI: 29, 96) "evaluable patients with MSI-H non-colorectal cancers but none of 18 patients with microsatellite stable (MSS) colorectal cancer achieved RECIST-defined responses. Key agreements reached:

- FDA agreed that an ORR that exceeded that observed with regorafenib in patients with metastatic colorectal cancer who had progressed following at least two lines of approved standard therapies, which must include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS wild type), if approved in the respective country, could support accelerated approval for patients with MSI-H colorectal cancer.
- FDA recommended that KN-164 be designed to rule out an ORR of <15% based on the lower bound of the 95% confidence interval around the observed response rate. FDA agreed that in the population to be studied, (b) (4)
- FDA encouraged Merck to enroll patients with MSI-H small intestinal cancer and other gastrointestinal malignancies in a dedicated protocol in order to expedite development of pembrolizumab for these patient populations.

On July 10, 2015, a meeting was held between FDA and Merck under IND 110080 to discuss the design of KEYNOTE-158, a study that was initially intended to enroll patients across ten different primary tumors based on PD-1 tumor expression, microsatellite instability, or a specific gene expression profile signature (using Nanostring-based RNA analysis). The

[4] *The Lancet* 387: 1094-1108, 2016. https://doi.org/10.1016/S0140-6736 (15)00130-0

meeting package indicated that Merck would use the Promega MSI Analysis System to identify patients as MSI-H in KEYNOTE-158.

On September 29, 2015, under new IND 127548, Merck requested FDA's agreement with a proposal to (b) (4) . On October 27, 2015, FDA responded by email that the Agency did not agree with the proposal based on (b) (4) . FDA stated that an alternative to central testing would be required to ensure the same reagents, protocol, and result reporting are used at all testing sites. On February 16, 2016, Merck submitted an amendment to IND 127548 containing a proposal stating that MSI-H testing could be performed using IHC or one of two specific PCR assays. Merck stated that the case report forms would collect information about methodology used to identify MSI-H status, including reagents, assay protocols, and results.

On October 29, 2015, FDA granted Breakthrough Therapy designation for pembrolizumab for the treatment of patients with microsatellite instability high (MSI-H) metastatic colorectal cancer.

On November 30, 2015, FDA issued an Agreed Initial Pediatric Study Plan for pembrolizumab (b) (4) .

On April 15, 2016, a teleconference was held at FDA's request to discuss the update provided by Merck on their development program in MSI-H colorectal and non-colorectal cancers, in order to facilitate development of pembrolizumab for the Breakthrough Therapy designated program. Merck stated that based on rapid enrollment, with a 3 week-interval between the 40th subject and the 61st patient enrolled, they planned to include the entire study population of 61 subjects in the interim analysis on or around July 15, 2016. Merck said at the time of submission of the planned efficacy supplement, the application would contain efficacy data from approximately 90 patients with metastatic, MSI-H colorectal cancer and 60 patients with metastatic, MSI-H, non-colorectal cancer patients, however the maturity of response data for the latter group was not certain. FDA stated that the most important data would be the response information, including a central review of scans, given the extensive information available regarding the safety of pembrolizumab. FDA advised that the Agency would consider a proposal for a "tissue-agnostic" indication for refractory, metastatic cancers, but noted that this likely require discussion with CDER's Office of Medical Policy.

On July 13, 2016, a pre-sBLA meeting was held to discuss the content of the planned efficacy supplement intended to support a new indication for the treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) cancers with disease progression following prior therapy.

On August 1, 2016, FDA granted Breakthrough Therapy designation for pembrolizumab for the treatment of patients with unresectable or metastatic non-colorectal MSI-H-positive

cancers who have disease progression on or who have no satisfactory alternative treatments.

Submission Regulatory History
On September 8, 2016, BLA 125514/S-014 was submitted.

On February 13, 2017, FDA met with Merck to discuss concerns regarding an apparent dose-response relationship suggesting greater efficacy with the 10 mg/kg every 2 week regimen as compared with the 200 mg every 3 weeks dosage regimen. Merck proposed submission of additional data supporting Merck's proposed dosage regimen of 200 mg every 3 weeks.

On March 8, 2017, a major amendment was submitted (received March 9, 2017), containing: additional follow-up for duration of response for patients enrolled in the KEYNOTE-164 and KEYNOTE-158 studies, new clinical data for 65 patients MSI-H/dMMR solid tumors who received the 200 mg dosage regimen of pembrolizumab; and additional justification for the proposed dosage regimen of 200 mg every 3 weeks as compared with 10 mg/kg every 3 weeks.

3. CMC

There are no outstanding CMC issues that preclude approval. The CMC information submitted in this supplement was limited to information regarding the drug product administered across these trials and a request for waiver from the assessment of categorical exclusion. The claim of categorical exclusion from the environmental assessment was accepted and the quality reviewer determined that the investigational pembrolizumab drug product used in these studies was comparable for to the marketed product.

The supplement did not propose use with a companion diagnostic test for identification of MSI-H or dMMR tumor status. The Division consulted the Center for Devices and Radiologic Health regarding use of laboratory developed test for determination of MSI-H and dMMR tumor status, for which regulatory discretion has been exercised and pre-market applications have not been required. Dr. Donna Roscoe (CDRH) stated that during the Office of Medical Policy meeting that there are a variety of tests for dMMR (immunohistochemistry (IHC)) and MSI-H (PCR-based) used in the community. These tests are primarily laboratory developed tests (LDTs) and that the major concerns with these LDTs are false-positives in IHC tests for dMMR and false-negatives in PCR tests for MSI-H. The College of American Pathology conducted an assessment of MSI-H testing performance across104 laboratories in 2012, where a "correct" result was considered the consensus result of the laboratories. Using this criterion, the College of American Pathology stated that the "correct" result was obtained in >95% of cases. Despite this, there remains uncertainty regarding the performance characteristics across all laboratories which may be performing these tests, including whether performance characteristics may differ by primary cancer. Given these uncertainties, agreed-upon postmarketing studies will be conducted to assess and establish the performance characteristics of MSI-H and dMMR tests.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Pharmacogenomics

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

The supplement contained following clinical pharmacology information:

- A pooled comparative analysis of pembrolizumab exposure and clearance across multiple tumor types was conducted.

- A pooled comparative analysis of the immunogenicity rate of pembrolizumab across multiple tumor types was submitted.

The population pharmacokinetic parameters were comparable between patients with MSI-H cancers (n=79) and patients in which the MSI-H status was unknown ((n=2189). The population exposure of 200 mg Q3W was numerically higher than 2 mg/kg Q3W dose, but significantly lower than 10 mg/kg Q2W and Q3W doses. This factor was considered in the interpretation of the efficacy results in which the ORR is consistently higher across trials for the 10 mg/kg Q2W regimen [69 patients; ORR 51% (95% CI: 38, 63)] than the 200 mg Q3W regimen [80 patients; ORR 21% (95% CI: 17, 37)]. Based on this difference, the pharmacology reviewers also reviewed prior submissions in which the effects on survival among randomized, dose-ranging studies were noted to favor the higher dose.

FDA discussed this issue with Merck in February 2017 and requested that Merck provide additional data to support the proposed dosage regimen of 200 mg every 3 weeks. In their response, Merck noted that the duration of follow-up was unequal across studies. In KEYNOTE-016, -012, and -028, the median duration of follow-up was ≥6 months, whereas in KEYNOTE-164 and -158, the median duration of follow-up was <6 months in the original submission. Therefore, in the major amendment, updated information was provided for KEYNOTE-164 and -158; the duration of follow-up was extended to ≥54 weeks (from ≥27 weeks in the original submission) and ≥36 weeks (from ≥18 weeks in the original submission), respectively. With additional follow-up, the response rate increased modestly among patients receiving pembrolizumab 200 mg every 3 weeks [ORR 30.0% (95% CI: 20, 41)]; however, the ORR with the 10 mg/kg every 2 week regimen remained numerically higher.

The clinical pharmacology reviewers initially recommended that the recommended dose be 10 mg/kg every 2 weeks, with reductions to "as low as" 200 mg every 3 weeks based on patient tolerability and safety, given the consistently higher ORR. However, after internal discussion and review of data contained in the major amendment, as well as a re-assessment of survival

information in randomized, dose-ranging trials, the clinical pharmacology team made the following recommendations:

- Both the 2 mg/kg Q3W and 10 mg/kg Q2W dosing regimens should be available for the treatment of MSI-H patients given the effectiveness of both regimens and incremental benefit of the higher dose. Since no baseline patient-specific factors are identified to determine which starting regimen should be recommended. In the absence of identified baseline factors, OCP recommends the starting dose regimen be left to the discretion of the practitioner without explicit recommendations in labeling.

- Further evaluation of accumulating data to determine whether both dose regimens should be made available for approved indications including melanoma and NSCLC.

The clinical review team did not concur with this recommendation for the reasons discussed in Section 7 of this review.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The data from one clinical study site enrolling 20 patients in Cohort A of Study KEYNOTE-016 were inspected. No significant deviations were noted and the data were deemed reliable in support of this efficacy supplement.

Based upon agreements with Merck prior to submission, FDA agreed to review a pooled dataset comprising data from patients enrolled in multiple clinical trials, four of which were sponsored by Merck and one conducted by a sponsor investigator, in which all patients with adequate follow-up for assessment of response and response duration were evaluated for response by an independent review committee, masked to investigator assessment of response. Response was based on RECIST v1.1, in which all responses were required to have confirmed durability of at least 4 weeks.

Key details of the differences in trial design are summarized below, which included differences in dosage regimen, timing and method of identification of MSI-H/dMMR solid tumors, and eligibility criteria with regard to presence of PD-L1 overexpression. For patients who were determined at the time of enrollment to have MSI-H/dMMR tumors (Studies KEYNOTE-016, KEYNOTE-164, and MSI-H/dMMR positive tumor cohorts within KEYNOTE-158), that determination was made primarily on laboratory developed tests, whereas for patients with MSI-H/dMMR tumors identified through retrospective of available tumor (Studies KEYNOTE-012, KEYNOTE-028, and rare-tumor cohorts within KEYNOTE-158), the determination was made based on central testing.

Overview of Clinical Studies Comprising Efficacy Dataset

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated, multi-center • CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified. PD-L1-positive, MSI-H/dMMR gastric, bladder, or triple-negative breast cancers	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified PD-L1-positive, MSI-H/dMMR esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective, multi-center MSI-H/dMMR non-CRC • retrospectively identified MSI-H/dMMR rare, non-CRC tumors	19 `	local PCR or IHC central PCR for rare tumor non-CRC	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

Results

There were 149 patients identified with MSI-H or dMMR solid tumors across five clinical trials, which comprise the pooled efficacy dataset.

In this supplement, Merck used the terms microsatellite instability-high (MSI-H) and MMR-deficient interchangeably, stating that "tumors are classified as MSI-H (including MMR-deficient) when expression of at least 1 of 4 MMR proteins is not detectable by IHC, or when at least 2 allelic size shifts among 3 to 5 analyzed microsatellite markers are detected by PCR." As support for pooling data across the study population, regardless of the test used for identification of patients, Merck cites the NCCN guidelines regarding screening of patients with colorectal cancer, which state that "IHC for MMR and PCR for MSI are different assays measuring the same biological effect" because "patients determined to have defective MMR status are biologically the same population as those with MSI-H status."

For 91% (135/149) of the population, the presence of MSI-H or dMMR was determined prior to study entry based on local laboratory assessment a polymerase chain reaction (PCR) tests to detect MSI-H or immunohistochemistry (IHC) tests to detect dMMR. The remaining 14 patients (9%) in the pooled dataset were identified retrospectively in a central laboratory by screening available tumor samples from 415 patients enrolled in the KEYNOTE-012,

KEYNOTE-028, or rare-tumor cohorts in the KEYNOTE-158-studies. The incidence of MSI-H or dMMR tumors identified retrospectively was 3.4% (95% CI: 1.9, 5.6) across the three trials.

The baseline characteristics of the pooled dataset are a median age 55 years (36% were 65 years or older); 56% male; 77% White, 19% Asian, 2% Black; and ECOG PS 0 (36%) or 1 (64%); 98% had metastatic disease and 2% had locally advanced, unresectable disease at study entry. With regard to underlying primary cancer, 60% of the population had colorectal cancer. Of the remaining 40% (59 patients) with non-colorectal cancers, the most common primary cancers in descending order were: endometrial cancer (24%), biliary tract cancer (19%), gastric or gastroesophageal cancers (15%), small intestinal cancers (13%), and pancreatic cancers (10%). The median number of prior lines of therapies administered for the treatment of metastatic or unresectable disease was 2; 84% of patients with metastatic colorectal cancer and 53% of patients with other solid tumors ≥2 prior lines of therapy. Among the 149 patients in the pooled efficacy dataset, 40% (n=60) had tumors identified as MSI-H using a PCR-based assay, 32% (n=47) had tumors identified as dMMR using an IHC assay, and 28% (n=42) were determined to be eligible for inclusion using both assays.

The overall response rates and duration of response for the pooled population and by primary cancer are summarized in the following tables:

Efficacy Results for Pooled Dataset

Endpoint	**n=149**
Overall response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4
Partial response rate	32.2
Response duration	
Response Duration (range in months)	1.6+, 22.7+
% with duration ≥6 months	78%

NR = not reached

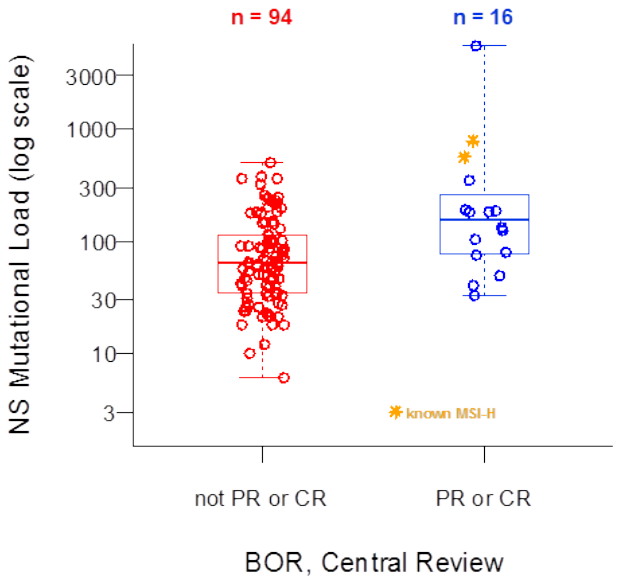
Efficacy Results by Primary Cancer

Primary Cancer	Number of Patients	Response Rate (95% CI)	Response Duration (range in months)
Colorectal Cancers	90	36% (32/90) (26, 46)	1.6+, 22.7+
Non-Colorectal Cancers	59	46% (27/59) (33, 59)	1.9+, 22.1+
Endometrial cancer	14	36% (5/14) (13, 65)	4.2+, 17.3+
Biliary cancer	11	27% (3/11) (6, 61)	11.6+, 19.6+
Gastric or GE junction cancer	9	56% (5/9) (21, 86)	5.8+, 22.1+
Small intestinal cancer	8	38% (3/9) (9, 76)	1.9+, 9.1+
Pancreatic cancer	6	83% (5/6) (36, 100)	2.6+, 9.2+
Breast cancer	2	PR, PR	7.6, 15.9
Prostate cancer	2	PR, SD	9.8+
Bladder cancer	1	NE	
Esophageal cancer	1	PR	18.2+
Sarcoma	1	PD	
Thyroid cancer	1	NE	
Retroperitoneal adenocarcinoma	1	PR	7.5+
Small cell lung cancer	1	CR	8.9+
Renal cell cancer	1	PD	

The key question raised by this application is whether the presence of MSI-H/dMMR represents a unique biomarker that predicts response to pembrolizumab and is consistent in this predictability across tumor types. Features associated with MSI-H/dMMR that are common across primary cancers include increased lymphocytic infiltration and an increased mutational tumor burden with non-synonymous mutations. Both of these factors have been identified as correlating with an increased likelihood of response to checkpoint inhibitors in tumors that have not been assessed for MSI-H or dMMR. For example, the primary cancers first identified as responsive to checkpoint inhibitors, melanoma and non-small cell lung cancer, are also cancers with the highest mutational burdens. Merck presented data from

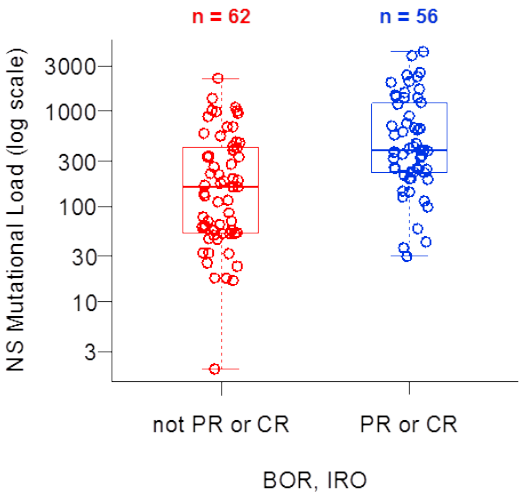
Studies KEYNOTE-012 and -028, involving 110 patients with 20 different primary cancers in which the likelihood of response was greater in those with a higher mutational burden.

KN012 and 028;
N=110; 20 tumor types

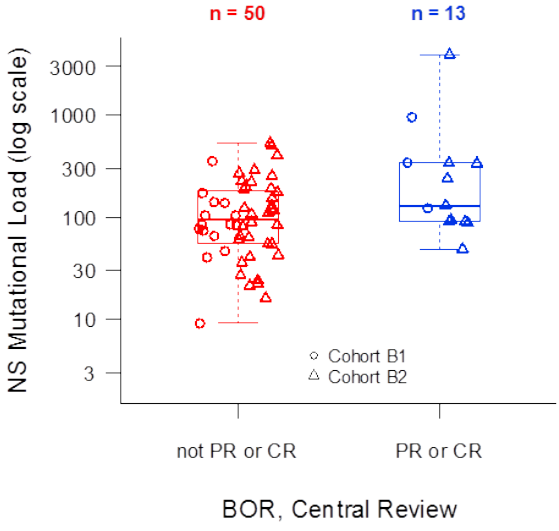


Similar results were observed in specific primary cancers, as displayed below.

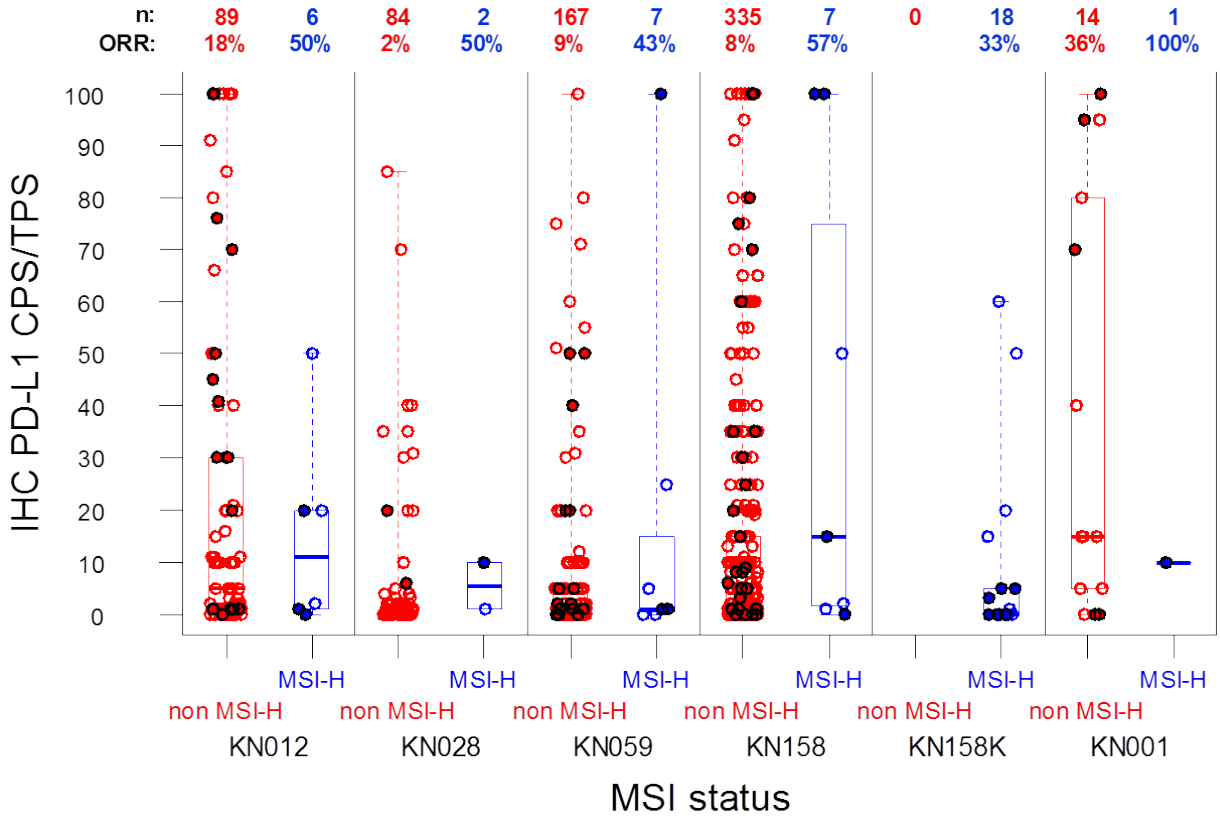
Melanoma
(KN 001, 002 and 006; N=118)



Head & Neck Cancer
(KN012 B and B2 cohorts; N=63)



Merck also presented data indicating that the higher ORR observed in patients with MSI-H tumors as compared to the ORR in patients with microsatellite stable (MSS) tumors, did not appear to be the result of a higher PD-L1 tumor expression score for MSI-H tumors compared with MSS tumors.



Based on the similarity common histologic feature of tumor infiltration and high mutational burden across MSI-H tumors and absence of an alternative explanation for the higher response rates seen in MSI-H vs. non-MSI-H tumors, specifically, differences in PD-L1 tumor expression, I concur that the biomarker of MSI-H/dMMR across primary cancers appears to identify a specific subpopulation of patients with cancer who are likely to derive clinical benefit from pembrolizumab, as requested in the proposed indication.

With regard to dosing, I concur with the clinical review team that the observed differences in ORR by dosage regimen are not compelling, based on cross-study comparisons where the differences observed may reflect differences in the study populations (including unknown factors) and chance. I also concur that dose-related differences in response may be present but cannot be addressed outside of a randomized trial comparing dosage regimens. Further, the recommendation is not consistent with prior recommendations based on relatively flat exposure: response and exposure: toxicity relationships observed in other trials; however, a more comprehensive investigation of these effects involving multiple rather than within an individual randomized, dose-ranging trial may be more informative. One specific concern with this approach is to determine the extent to which other factors (specifically PD-L1 tumor

expression) may play a role in the dose-response relationship in specific primary cancers, which may not be a factor in MSI-H/dMMR solid tumors. Pending further elucidation of this relationship to determine if 10 mg/kg every 2 weeks is actually superior to 200 mg every 3 weeks, I concur with the decision of the clinical review team that the Merck's proposed dosage regimen is both safe and effective.

8. Safety

Size of the database: The characterization of the most serious adverse drug reactions of pembrolizumab were evaluated in 2799 pembrolizumab-treated patients, of whom 41% were exposed to pembrolizumab for ≥ 6 months and 21% were exposed to pembrolizumab for ≥ 12 months, which was revised as part of previous supplemental approvals. The most common adverse reactions of pembrolizumab were evaluated in 5 randomized trials enrolling 2195 pembrolizumab-treated patients and 3 single arm trials enrolling 772 pembrolizumab-treated patients. This clinical experience in these supplements was adequate to characterize the safety for both dosage regimens (10 mg/kg every 3 weeks and 200 mg every 3 weeks) in randomized, controlled clinical trials. Thus, the limited size of the safety database in this supplement was not of concern as the adverse reaction profile of pembrolizumab is known.

Major safety concerns related to labeling: The serious adverse reactions of pembrolizumab resulting from pembrolizumab are autoimmune reactions against healthy organs and tissues. The most commonly affected organs are the endocrine system, colon, lungs, and liver. With the exception of immune-related endocrinopathies, which are generally not reversible and require hormone replacement due to loss of endocrine function, immune-related adverse reactions of other organs can be reversed with termination of pembrolizumab if mild and high-dose corticosteroids with or without additional immunosuppression if moderate or more severe. No unexpected serious adverse reactions were observed in patients with MSI-H/dMMR solid tumors.

Postmarketing data: In published literature, there are limited reports of outcomes in children with congenital mismatch repair deficiency syndromes who received checkpoint inhibitors for treatment of primary CNS tumors. While activity was observed in two patients, a third experienced neurologic deterioration and death, possibly attributable to lymphocytic tumor infiltration. Given the very limited experience, and in light of the potential for benefit, additional studies were required to further assess the safe use of pembrolizumab in this setting.

REMS
I concur with the clinical review team that no new safety signals were identified and the risk: benefit profile in the indicated population did not require REMS to ensure safe and effective use in this population.

PMRs and PMCs
A required PMR under 21 CFR 601.41 was required to further characterize the clinical benefit of pembrolizumab in adults with common solid tumors (e.g., breast cancer, prostate cancer) with MSI-H/dMMR and in pediatric patients with MSI-H/dMMR solid tumors.

A required PMR under 505(o) was required to further characterize the safety in pediatric patients MSI-H/dMMR, primary CNS tumors.

9. Advisory Committee Meeting

This efficacy supplement was not referred to the Oncologic Drugs Advisory Committee since the safety profile is acceptable for the indicated population and the trial design and endpoint are similar to prior accelerated approvals. However, use of a biomarker to define the indicated population is novel and use of this approach was discussed with the Office of Medical Policy (OMP) on February 24, 2017. The OMP agreed that the rationale for a "tissue agnostic" population was supported by the data provided by Merck.

10. Pediatrics

The Pediatric Review Committee (PeRC) confirmed their agreement (b) (4) in the Agreed Initial Pediatric Study Plan (iPSP) during the meeting held on April 19, 2017. At the time of this review, the proposed indication had been modified to (b) (4)

The clinical review team considered that MSI-H/dMMR solid tumors do occur in children, particularly those with Lynch syndrome or with rare congenital bi-allelic genetic defects, and extended the indication to these patients by extrapolation of the efficacy in adults to children with MSI-H/dMMR tumors. The recommended dose in children was based on the results of studies in pediatric patients (previously reviewed by FDA under the supplement supporting approval in classic Hodgkin lymphoma) characterizing a reasonably safe dose in children less than 12 years of age and the predicted pharmacokinetics in adolescents (i.e., same as in adult population with the recommended adult dose).

The only caveat to this extrapolation was the specific situation of CNS malignancies with mis-match repair deficiencies which are more likely to occur in children. The potential risks of lymphocytic infiltration (the suspected cause of "tumor flare" with these immunologic agents) occurring in a closed space are likely to increase the risk of herniation. Recent published reports of both responses and patient death in three pediatric patients support the potential for this risk. Thus, pending additional clinical experience, FDA requested that product labeling carry a limitation of use for this population pending the results of further studies, which will be conducted under postmarketing requirements.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Physician labeling
  - Indication and Usage: the proposed indication and usage was modified to include pediatric patients with MSI-H/dMMR solid tumors and revised to clarify the indication with regard to colorectal cancer, comprising 60% of the study population. In addition, a limitation of use was added for pediatric primary CNS cancers with MSI-H/dMMR, based on published reports of a fatality in this setting, possibly resulting from lymphocytic infiltration. It is anticipated that this limitation of use may be revised when additional data are obtained in this population in required postmarketing trials.
  - Dosage and Administration: The recommended in adults, as proposed by Merck, was retained; however, recommended doses for adolescents and for pediatric patients less than 12 years of age were added, based on results of pharmacokinetic assessments in pediatric patients previously reviewed under the supplement supporting approval of classic Hodgkin lymphoma.
  - Warnings and Precautions: Subsection 5.6 (other Immune-Mediated Adverse Reactions) was modified to include the sentence "These immune-mediated reactions may involve any organ system." This addition was to clarify for prescribers that reactions other than those listed in this section may occur with pembrolizumab.
  - Adverse Reactions: Adverse reactions observed in the pooled efficacy population were not included in the adverse reaction section given the extensive safety experience with pembrolizumab and the single arm nature of the "trial" which precluded a comparison against background events attributable to underlying disease.
  - Use in Specific Populations: The pediatric use subsection was edited for brevity and clarity. In addition, the extrapolation of efficacy data for MSI-H/dMMR solid tumors in adults to pediatric patients was described.
  - Clinical Pharmacology: Updated to include the results of the most recent population pharmacokinetic analysis, which incorporated data from patients with MSI-H/dMMR solid tumors.
  - Clinical Studies: Revised to provide greater detail regarding the design of the five clinical studies contributing patients to the pooled population, tabular results for the pooled population and data by primary cancer type. The latter is provided for information to prescribers but is not intended to suggest differences in ORR by primary cancers.

- Patient labeling/Medication guide: The Medication Guide was modified to reflect the new indication

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  Unresectable, locally advanced or metastatic cancers that have progressed following two or more available therapies have a poor prognosis, regardless of primary cancer and, with few exceptions, will have 5-year survival rates of less than 10%. In this supplement, 84% of patients with metastatic colorectal cancer and 53% of patients with other solid tumors had received two or more prior lines of therapy. With available treatment for the most common cancers in this population, overall response rates with available therapy are low (1% with regorafenib and 1.5% with trifluridine/tipiracil for third-line treatment of colorectal cancer and 24-32% with MTOR-based chemotherapy as second-line treatment of endometrial cancer).

  In the pooled dataset of 149 patients, the ORR was 39.6% (95% confidence intervals (CI): 31.7, 47.9) with 78%of responding patients experiencing a duration of response of more than 6 months. The ORR was similar among patients with colorectal cancers [ORR 36% (95% CI: 26, 46) and non-colorectal cancers [ORR 46% (95% CI: 33, 59)]. The point estimates for response rates and response durations far exceed that expected with available and commonly accepted third-line chemotherapeutic options. The risks of pembrolizumab are acceptable in light of the magnitude and durability of response. At this time, I concur with the clinical review team that there is insufficient evidence to state that the higher dosage regimen employed (10 mg/kg every 2 weeks) provides superior results to the lower dosage regimen (200 mg every 3 weeks) based on the differences across studies with regard to patient population (e.g., ECOG status, extent of prior treatment, and potential unknown confounding factors) and follow-up for observation of responses. This question should be re-assessed across the totality of the randomized, dose-ranging trials in all cancers to determine the extent, if any, of a dose-response relationship. However, data obtained in studies where response may also be driven by other factors (i.e., presence or extent of PD-L1 tumor expression) may not be relevant for this population, where MSI-H/dMMR appears to be the strongest predictive factor for response.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  In concur with the findings of the clinical review team that, in light of the agreed-upon labeling which includes a limitation of use for pediatric patients with MSI-H/dMMR central nervous system cancers, risk evaluation and mitigation strategies (REMS) are not required for this new indication for pembrolizumab, which has been marketed without REMS since 2014.

- Recommendation for other Postmarketing Requirements (PMR) and Commitments (PMC)
  Given the relatively limited clinical experience with treatment of patients with MSI-H/dMMR solid tumors other than metastatic colorectal cancer and endometrial cancer, a

post-marketing commitment was required to further verify and characterize the efficacy (ORR and duration of response) of pembrolizumab across MSI-H/dMMR tumors arising in other primary sites, including primary tumors occurring primarily in pediatric patients. Therefore, FDA will require the following PMR under the provisions of 21 CFR 601.41.

3213-1 Submit the final report, including datasets, from trials conducted to verify and describe the clinical benefit of pembrolizumab 200 mg intravenously every three weeks in patients with microsatellite instability high or mismatch repair deficient tumors including at least 124 patients with colorectal cancer enrolled in Merck-initiated trials; at least 300 patients with non-colorectal cancer, including a sufficient number of patients with prostate cancer, thyroid cancer, small cell lung cancer; and ovarian cancer; and 25 children. In order to characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

A PMR will also be required under the provisions of 505(o) to investigate the safe use of pembrolizumab for the treatment of patients with MSI-H/dMMR, central nervous system tumors that have progressed following accepted standard of care. This primary tumor site presents unique risks based on its location in an enclosed space (cranium/spinal column) and the potential for serious, potentially fatal adverse reactions due to lymphocytic infiltration resulting in an increase in tumor volume.

3213-2 Conduct a trial that will characterize the safety of pembrolizumab administered intravenously at 2 mg/kg up to a maximum of 200 mg intravenously every three weeks or to determine a reasonably safe dosage regimen in an adequate number of children with primary central nervous system malignancies that are mismatch repair deficient or microsatellite instability high. Submit a final report and datasets for pediatric patients with primary CNS malignancies.

Finally, two agreed-upon PMCs will be conducted to develop and support approval of analytically valid tests for identification of patients with MSI-H or dMMR solid tumors. While the study population in several of the trials were enrolled based on commercially available, laboratory-developed tests (LDTs), the use of such tests has been by the medical community has been evaluated primarily in colorectal cancer, based on current practice guidelines.

3213-3 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry based *in vitro* diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are mismatch repair deficient.

3213-4 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid-based *in vitro* diagnostic device that is essential to the safe and

effective use of pembrolizumab for patients with tumors that are microsatellite instability high.

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

/s/

PATRICIA KEEGAN
05/23/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

OFFICER/EMPLOYEE LIST

Officer/Employee List
BLA 125514/S-14

The following officers or employees of FDA participated in the decision to approve this supplement and consented to be identified:

Ayalew, Kassa
Fuller, Barbara
Furmanski, Brian
Griffiths, LaShawn
Keegan, Patricia
Lemery, Steven
Li, Hongshan
Liu, Jiang
Marcus, Leigh
Mills, Sharon
Rodriguez, Lisa
Senior, Nicholas
Sridhara, Rajeshwari
Thompson, Susan
Yuan, Lisa
Zhao, Hong

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	22 May 2017
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
BLA #	Supplement 14, BLA-125514
Applicant	Merck & Co., Inc. (Merck)
Date of Submission	8 Sep 2016
PDUFA Goal Date	8 Mar 2017 (June 9, 2017, following major amendment)
Proprietary Name / Established Name	Keytruda / pembrolizumab
Proposed Dosing Regimen	200 mg intravenously every three weeks
Proposed Indication(s)	(b) (4)
Recommended:	*Accelerated approval*

Table of Contents

Table of Figures

Table of Tables

1. Introduction

FDA received Supplement 14 to Biologics License Application (BLA) 125514 from Merck on 8 Sep 2016 requesting marketing authorization (accelerated approval) for pembrolizumab (Keytruda) (b) (4) The proposal was based on the results of data obtained from patients enrolled in one of five clinical trials.

This will be the first application approved for the treatment of patients independent of cancer type and based solely on the identification of a biomarker within that patient's tumor. Testing for microsatellite instability (i.e., microsatellite instability-high or MSI-H) or mismatch repair deficiency (MMRd) will likely now occur in all patients with cancer and this testing (in patients with cancers outside of colorectal or endometrial cancer) will be performed *because* of the therapy approved as part of this application.

Disclaimer: Any data or information described below that Merck does not own (for example, summary data from other drugs or literature reports) is included for descriptive purposes only. This information was not necessary to make a decision regarding this application.

2. Background

This section of the review will focus on the pertinent regulatory topics related to this submission (sBLA), with the exception of the clinical data supporting the site agnostic indication (Section 7), pembrolizumab dosing regimen (Section 7), and the risk-benefit assessment (Section 13).

2.1 Does the biology of microsatellite instability / deficient mismatch repair support a site or tissue agnostic indication?

Molecular characterization of MSI-H/MMRd cancers

A deficiency in the DNA mismatch repair (MMRd) pathway is associated with microsatellite instability and an increased number of somatic mutations in MSI-H tumors compared to microsatellite stable (MSS) tumors.[1-5] In general, MSI-H/MMRd occurs in the setting of loss of function of one or more of the mismatch repair proteins (MLH1, MSH2, MSH6, or PMS2).[6] In colon cancer, the MSI-H phenotype is generally associated with MLH1 promotor hypermethylation or with mutations in one or more of the mismatch repair genes [e.g., as can occur in Lynch syndrome (a hereditary condition that increases one's risk for cancer)].[6] Rarely, deletions of 3' exons of TACSTD1 (EPCAM) can result in inactivation of MSH2 and the development of Lynch syndrome.[7,8]

Most hypermutated colorectal cancer tumors are MMRd with the remainder associated with POLE mutations (which can also test positive for MSI-H).[2] Like colon cancer, MSI-H/MMRd gastric and endometrial cancers have an increased rate of somatic mutations.[9,10] Furthermore, in an analysis of gliomas in patients with *biallelic* mismatch repair deficiency (a highly penetrant childhood cancer syndrome), mutational load was markedly elevated as compared to

sporadic pediatric gliomas, other brain tumors, melanoma, lung cancer, or even microsatellite unstable gastrointestinal cancers.[11]

The following figures, copied from manuscripts by Ludmil Alexandrov (Nature, 2013) and Bert Vogelstein (Science, 2013), show tumor types with the highest mutational loads. Both lung cancer and melanoma (tumors for which anti-PD-1 drugs are approved) have high mutational loads (likely related to smoking and UV exposure, respectively).[12,13] The figure below (red box added by this author) shows the mutational prevalence across different tumors. Although the figure did not specify which tumors were MSI-H, there clearly is a subset of patients with uterine, gastric, and colorectal adenocarcinoma with increased somatic mutations (suggesting MSI-H). Furthermore, the report by Dr. Alexandrov described a unique signature with very large numbers of substitutions and small indels, consistent with microsatellite instability at nucleotide repeats in subsets of patients with colorectal, uterine, liver, kidney, prostate, esophageal, and pancreatic cancers.[13]

Figure 1: Somatic mutations across human cancer types (copied from Alexandrov et al., 2013)

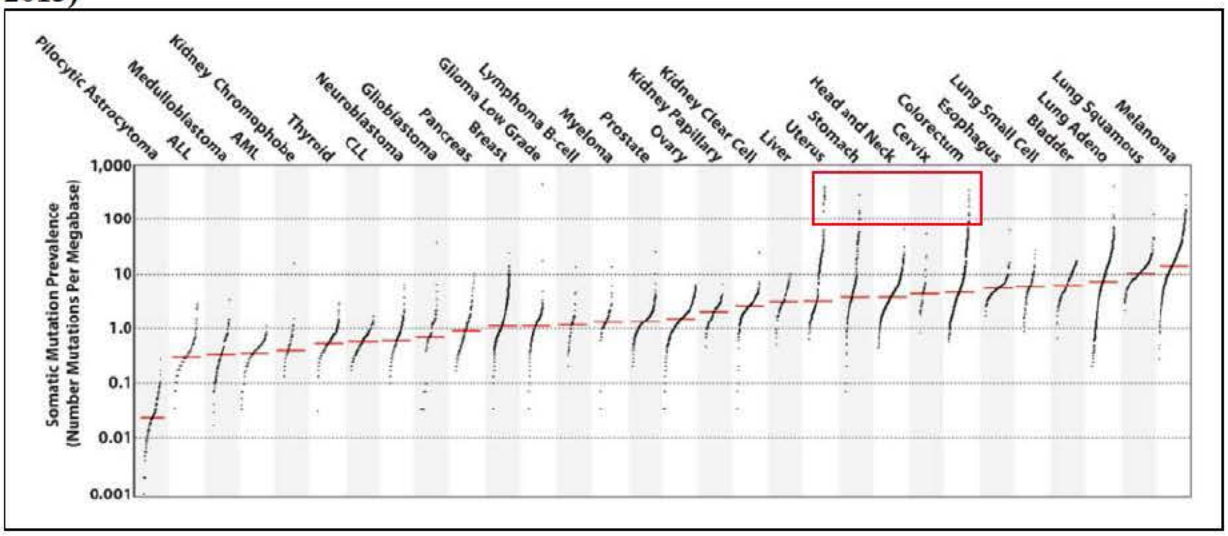
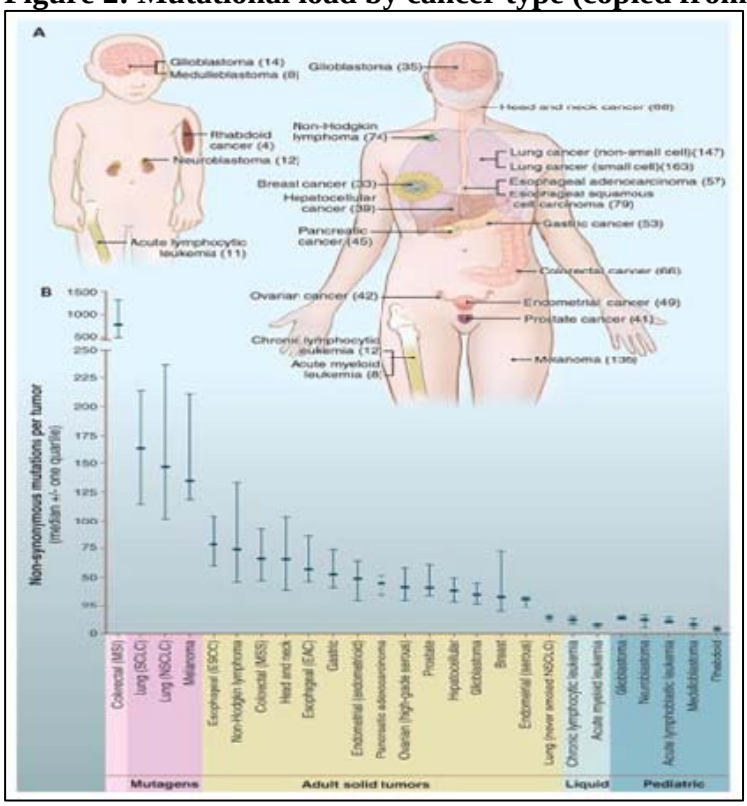


Figure 2 (below) shows that patients with MSI-H/MMRd colorectal cancer have a higher mutational load compared to patients with lung cancer or melanoma (two indications for which pembrolizumab is currently approved).

Figure 2: Mutational load by cancer type (copied from Vogelstein et al., 2013)



Increased neoantigen load/burden is postulated as the link between hypermutability and potential for susceptibility to immunotherapy because some of the mutations can lead to tumor-specific neoantigens. Non-clinical studies have shown how these tumor-specific neoantigens appear to be important targets of the immune system and that checkpoint inhibition can result in a functional T-cell attack against these neoantigen targets.[14,15] Data from MSI-H leukemia/lymphoma cell lines suggest that peptides caused by frameshift mutations due to microsatellite instability can result in tumor-specific antigens.[16] Earlier research found that unique peptides from missense mutations can be presented in unique HLA epitopes.[17] The algorithm described in the report predicted that approximately one new epitope would be generated for every 10 mutations [this may be an underestimate because the research did not assess all candidate major histocompatibility complex (MHC) molecules].[17] Mathematically, this research would predict that MSI-H tumors would generally have more neoantigens than corresponding MSS tumors (acknowledging that some tumors including melanoma and lung cancer have a high neoantigen burden due to other causes).

Additional scientific data supports the link between response to checkpoint inhibition and MSI-H/MMRd status. Howitt et al., found an approximate eight fold higher neoantigen load in patients with endometrial cancer who were MSI-H as compared to microsatellite-stable tumors (the highest mutational load was in patients with POLE tumors).[18] MSI-H/MMRd colorectal cancers also harbor an increased neoantigen load.[19] Despite the presence of neo-antigens, cancer cells may escape from the immune system through one or more checkpoints including the programmed death-ligand 1 (PD1/PD-L1) system. Howitt et al., found higher numbers of CD3+ and CD8+ tumor-infiltrating lymphocytes (TILs) in MSI-H tumors. Llosa et al., found

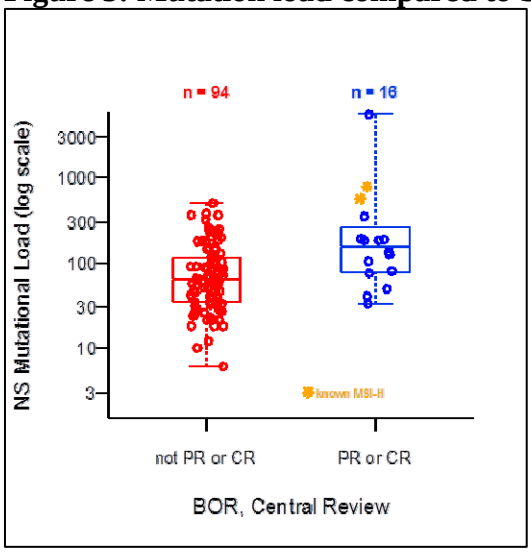
that the immune microenvironment of DNA repair-deficient MSI colorectal cancer cells contained a strong Th1 and CTL component not found in most other DNA repair-sufficient (MSS) tumors; however, multiple checkpoints including PD-1 and PD-L1 were highly upregulated in MSI-H tumors relative to MSS tumors.[20]

The link between MSI-H/MMRd and response to checkpoint inhibition was first identified at Johns Hopkins University following an early assessment of checkpoint inhibition in patients with colorectal cancer across two clinical trials. Only one patient out of 33 responded in these two trials.[5,21,22] The authors hypothesized that this patient had MSI-H CRC with a high mutation burden based on data that the responding tumors up to that date (melanoma and lung cancer) had a high mutation burden.[5] This hypothesis was correct, and this patient with MSI-H/MMRd colorectal cancer experienced a complete response for at least three years (to nivolumab).[5,23] Based on this data, the investigators at Johns Hopkins initiated a clinical trial (KEYNOTE-016 or KN16) assessing the effects of pembrolizumab in patients with MSI-H/MMRd cancer.[5]

Analyses of clinical data in other settings suggest a link between mutation and neoantigen burden and sensitivity to checkpoint inhibitors. Rizvi et al., found higher response rates and progression free survival (PFS) following pembrolizumab treatment in two independent cohorts of patients with non-small cell lung cancer (NSCLC) with higher non-synonymous mutation burden and with a higher neoantigen burden (efficacy was also correlated with DNA repair pathway mutations in this study).[24] A different study of tumor tissue from patients (in discovery and validation cohorts) with melanoma treated with a CTLA-4 inhibitor (a different checkpoint pathway inhibitor) suggested that neoantigen burden was associated with clinical benefit (but not sufficient to predict benefit) to CTLA-4 inhibition.[25] An earlier investigation of 100 patients with melanoma treated with a CTLA-4 inhibitor also identified an association between mutational load (and neoantigen load) and clinical benefit.[26] Finally, mutation load has been positively correlated with response in patients with locally advanced or metastatic urothelial carcinoma treated with an anti PD-L1 checkpoint inhibitor.[27,28]

Merck, based on their own data, also identified an association between mutation load and response to pembrolizumab across tumor types. The following plot (Figure 3) of data from patients with different tumor types enrolled in KN12 or KN28 (n=110) show that responses appear more likely to occur in patients with a higher non-synonymous mutational load. High mutational load is not the sole predictor for response; however, there *may* be a mutation threshold where a response is less likely to occur (similar analyses were provided by Merck across 118 patients enrolled in melanoma studies and in 63 patients enrolled in a specific head and neck cohort of KN12). Reasons for lack of response despite high mutational load may be related to lack of MHC restriction of the specific antigens or to other immune system-related factors.[15] Preliminary Merck data suggest that an "inflamed" tumor microenvironment may be an additional factor related to response (with PD-L1 positivity being one marker of an inflamed environment).

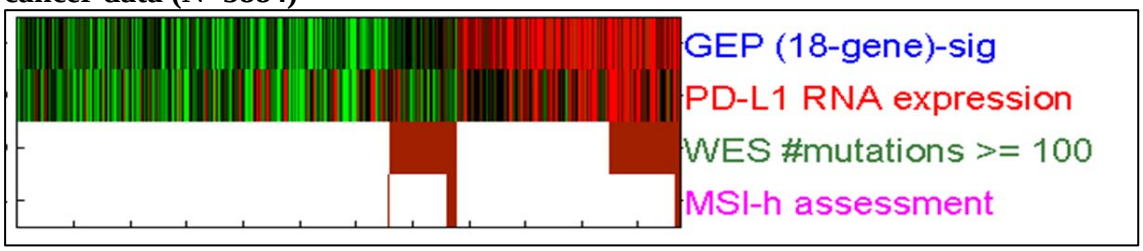
Figure 3: Mutation load compared to best response (KN12 and 28)



*copied from Merck's submission

In Merck's supportive analyses of TCGA (The Cancer Genome Atlas) data, there appeared to be a low correlation between an 18 gene "inflammation" signature and high mutation load (or MSI-H status). Merck provided this data to show that mutational load/MSI-H appears independent of inflammation or PD-L1 expression.

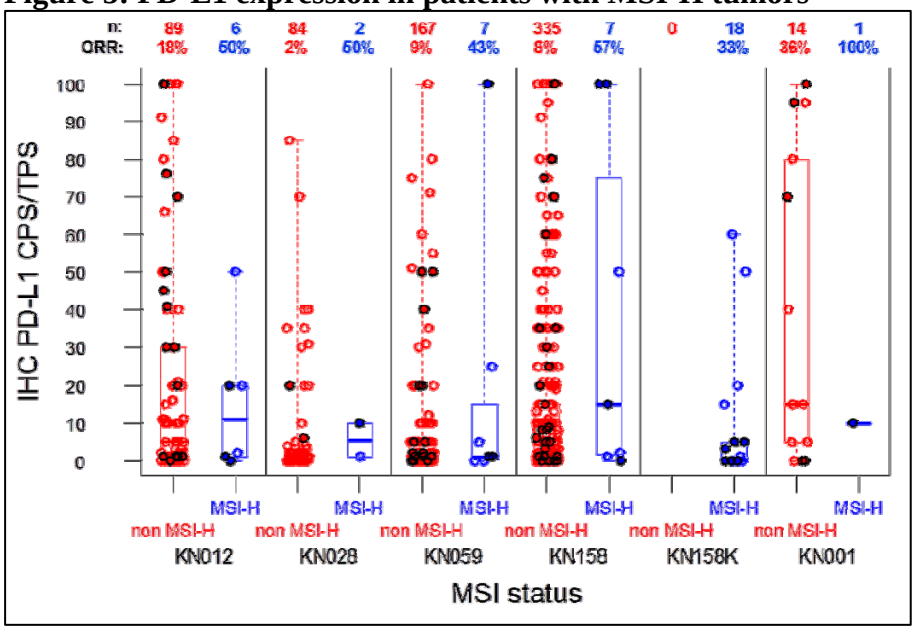
Figure 4: Mutational load versus gene expression profile signature based on TCGA, pan cancer data (N=5884)



*Green on the left is considered T-cell "non-inflamed"; right is considered T-cell "inflamed"; figure copied from Merck's submission

Data submitted by Merck (Figure 5) appear to show that although patients with MSI-H/MMRd tumors can have PD-L1-positive disease, that most patients have lower levels of expression and responses have been observed in patients with very low PD-L1 levels (including patients with PD-L1 levels less than 1%).

Figure 5: PD-L1 expression in patients with MSI-H tumors



*copied from Merck's submission; filled in circles represent responders [for KN001, PD-L1 measured by tumor proportion score (TPS); for other protocols by combined positive score (CPS)]

Merck's summary data across trials appeared to show that MSI-H/MMRd was a better predictor for response than PD-L1 (when assessed at the 1% cut-off). Prevalence of MSI-H is lower across tumors compared to PD-L1-positivity (at the 1% cut-off using Merck's assay). Across five trials [KN1, KN12, KN28, KN59, and KN158 (excluding 18 patients in a dedicated MSI-H cohort)], 712 patients had test results for both MSI-H and PD-L1 (CPS or TPS). Of these patients, the prevalence of MSI-H was 3% whereas the prevalence of PD-L1 positivity was 63%. Merck stated that the positive predictive value (PPV) for MSI-H for response was 52% whereas the PPV was 15% for PD-L1-positive disease.

Histopathological characterization of MSI-H/MMRd tumors

MSI-H/MMRd tumors across cancer types appear to share histopathological features in addition to having shared molecular features (i.e., high mutation and neoantigen burden). Multiple studies have demonstrated increased lymphocytes in MSI-H/MMRd colorectal cancer tumors[29-32] and that histopathologic features were similar in MSI-H/MMRd tumors irrespective of whether the tumors arose sporadically (e.g., through MLH-1 hypermethylation) or as part of the Lynch Syndrome.[30] In addition to being more frequently diagnosed on the right side of the colon, other histopathological findings of MSI-H/MMRd colorectal cancer (CRC) include medullary-type histology and poor differentiation.[29-31]

Like colorectal cancer, reports of MSI-H/MMRd endometrial cancer describe poor differentiation, medullary-type patterns, and increased tumor-infiltrating lymphocytes (TILs).[33] Increased lymphocytic infiltrates have also been identified in diverse MSI-H/MMRd tumor-types including pancreatic cancer[34] where medullary/poorly differentiated tumors have been described[35]; gastric cancer (which is typically intestinal type)[36,37]; ampullary cancer[38,39]; breast cancer[40]; and prostate cancer[41]. Poor differentiation has been described in MSI-H ovarian cancer.[42]

In summary, common molecular-biological characteristics exist among different MSI-H/MMRd tumors. Such common features among MSI-H/MMRd tumors underscore the rationale as to why a checkpoint inhibitor is expected to benefit patients with MSI-H/MMRd tumors irrespective of tumor histology. This strong biological rationale supporting the role of MSI-H/MMRd in immunotherapy has been elucidated through decades of scientific investigation.[43] The scientific work related to mutation burden, neo-antigens, and immune response has been replicated across different tumor types and laboratory groups. This replication markedly strengthens conclusions based upon the work. Furthermore, the response rates (described below) across different tumor types further support an approval action agnostic of tumor type.

Other immunologic factors beyond MSI-H/MMRd (or neoantigen burden) may contribute to the likelihood of whether a patient responds to treatment with pembrolizumab. Merck submitted exploratory (early) summary data in the sBLA regarding immunological factors that may be predictive for response, and data regarding an "inflamed phenotype" detected by NanoString methodology has been presented in public meetings.[44,45] Immunological factors may play a role if some differences are observed in ORR (or other outcomes) following pembrolizumab treatment in patients with MSI-H/MMRd tumors across different tumor types or lines of therapy. As such, although it would be unexpected for quantitative differences to exist among tumors, subtle qualitative differences may exist (e.g., minor differences in response among refractory CRC versus other tumors) that could be influenced by prior treatment affecting immune function or other immune system-tumor interactions.

2.2 Does the therapeutic context of pembrolizumab treatment among MSI-H/MMRd cancers support an (accelerated) approval action?

Frequency of MSI-H/MMRd tumors and natural history of MSI-H/MMRd tumors

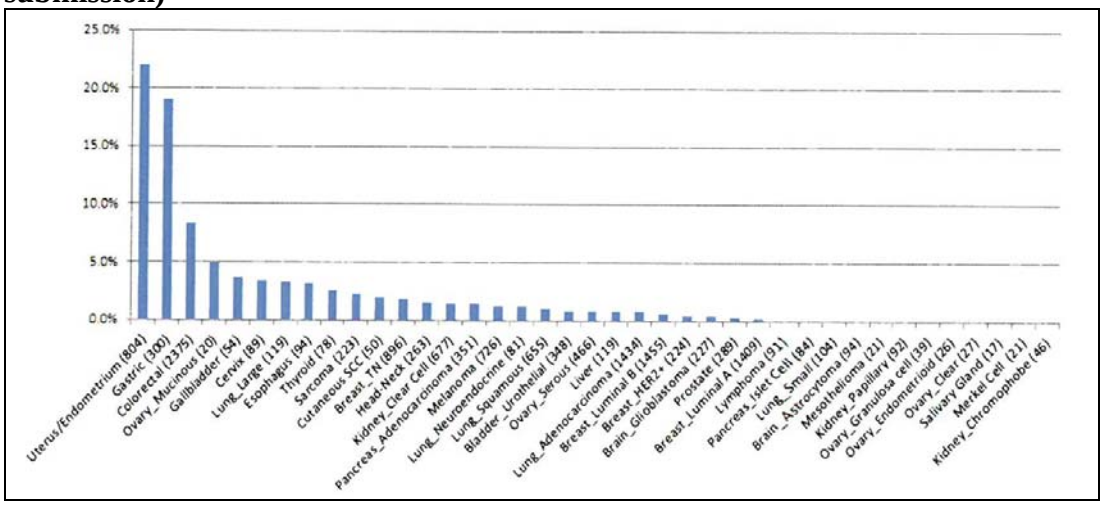
Merck provided the following estimates (Figure 6) of the percentage of MSI-H cancers from a Moffitt Cancer Center database. These estimates, however, may not reflect the frequency of MSI-H/MMRd cancers in the *metastatic* setting. For example, literature suggests that the rate of MSI-H/MMRd in patients with Stage II or III CRC is approximately 15%[46]; however, the prevalence of MSI-H/MMRd in the metastatic setting is approximately 5%.[47] Similarly, other studies have shown that the rate of MSI-H/MMRd CRC is higher in Stage II disease compared with Stage III disease (22 versus 12%).[48]

Estimates of rates of MSI-H/MMRd in other tumors is largely based on data obtained from patients who have undergone curative resection. For example, the 22% rate of MSI-H/MMRd in patients with gastric cancer described in the TCGA network database was obtained from primary gastric adenocarcinoma samples in patients who had not received any prior chemotherapy or radiation.[9] An Asian Cancer Research Group analysis of gastric cancer tumors found that the incidence of MSI-H appeared lower in advanced stage tumors: 14 of 30 (47%) Stage Ib tumors were MSI-H versus 26/97 (27%) for stage II; 19/96 (20%) for stage III; and 9/77 (12%) for stage IV.[49]

Limited data exist regarding MSI-H/MMRd in the metastatic setting for endometrial cancer. In one study investigating microsatellite instability in patients with endometrial carcinoma at

Washington University, 70 out of 229 tumors (~30%) were MSI-H; however, fewer MSI-H cases were observed in advanced stage tumors (FIGO Stage III or IV) with 9 of 53 advanced stage tumors (17%) being MSI-H.[50] Only one of 15 patients (6%) with FIGO Stage IV disease had a MSI-H-positive cancer.[50]

Figure 6: Moffitt database estimates of MSI-H frequency (copied from Merck's submission)

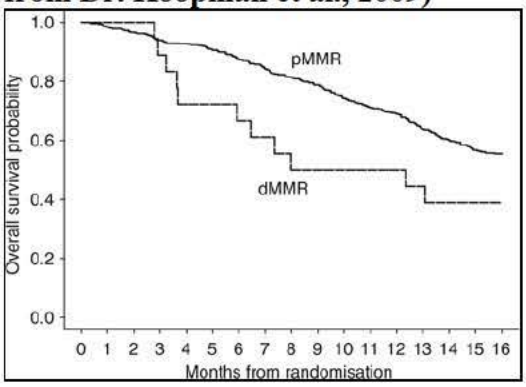


Published data regarding the natural history of MSI-H/MMRd colorectal cancer

Multiple studies, including meta-analyses have reported that MSI-H/MMRd represents a favorable prognostic marker in patients with colorectal cancer. Specifically, meta-analyses have described an association for improved overall survival (OS) and disease free survival (DFS) among patients with MSI-H disease.[51] Data, however, appear to show that this effect is restricted to patients diagnosed with early-stage disease and that the rate of tumor recurrence may be lower in these patients with early-stage MSI-H/MMRd tumors.[52]

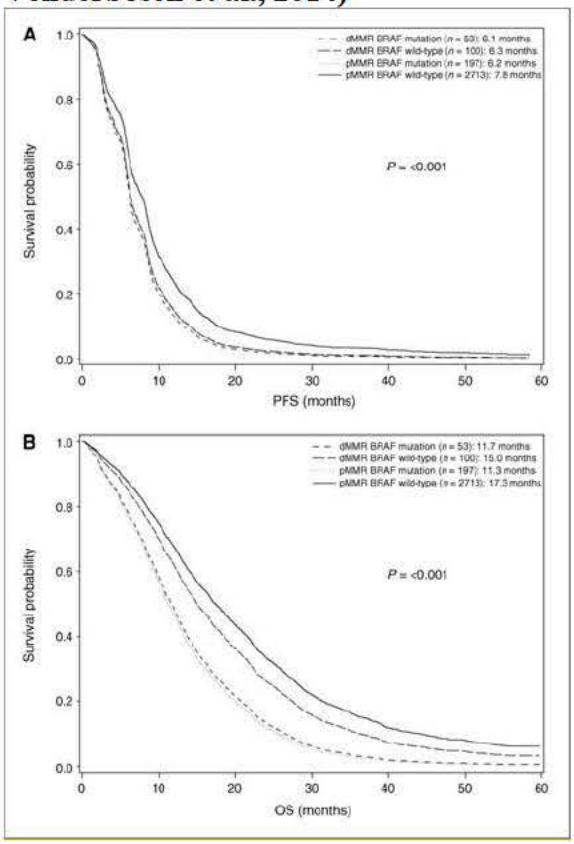
Outcomes data are more limited in the metastatic setting. Early reports either indicated that MSI-H/MMRd had no effect or conferred a favorable prognosis in patients with metastatic disease; however, the number of patients with metastatic disease in these reports was limited.[53-55] Conversely, Koopman et al., 2009, published a subgroup analysis of survival in patients with advanced (unresectable) CRC by MMR status who received treatment in the CAIRO trial of the Dutch Colorectal group. The trial identified 18 out of 515 (3.5%) evaluable patients with mismatch repair deficient tumors.[56] Acknowledging the small size of the subgroup, estimated median OS was approximately 18 months for patients with MMR-proficient tumors versus less than 10 months for patients with MMRd tumors (Figure 7 below).[56]

Figure 7: KM curves by MMR status in a subgroup analysis of the CAIRO trial (copied from Dr. Koopman et al., 2009)



In a larger, retrospective, pooled analysis of 3,063 patients treated across four first-line trials of therapy in the metastatic setting, 153 patients (or approximately 5%) were found to have MSI-H/MMRd tumors.[47] In the pooled dataset, median estimated PFS and OS appeared worse for patients with MSI-H/MMRd tumors compared with MSS/MMRp (mismatch repair proficient) tumors [HR, 1.33; 95% confidence interval (CI), 1.12–1.57 and HR, 1.35; 95% CI, 1.13–1.61, respectively)].[47] The figure below shows Kaplan-Meier (KM) curves for PFS and OS across four subgroups by MMRd and BRAF status (BRAF is a known adverse prognostic factor in patients with metastatic CRC).

Figure 8: Pooled PFS and OS results by MSI-H/MMRd (and BRAF) status (copied from Venderbosch et al., 2014)



In another smaller study, 55 patients with MSI-H metastatic colorectal cancer were identified out of 870 patients who underwent MSI testing at one of two centers.[57] Median survival from diagnosis of metastatic disease was 15.4 months (20.2 months from the date of original diagnosis).[57] The authors concluded that MSI-H does not appear to confer an improved outcome in the metastatic setting when compared to historical data. Nevertheless, median survival of patients who underwent metastasectomy in this cohort was longer (33.8 months).[57] Longer survival post metastasectomy (compared to survival in patients without oligometastatic disease), irrespective of MSI status, is expected based on clinical data in patients with CRC.[58] A report from the Mayo Clinic described similar findings based on a case-control study of 75 patients with MSI-H metastatic CRC and 75 matched controls with MSS metastatic CRC.[59]

Natural history of previously-treated metastatic colon cancer (3rd or greater-line setting), unselected for MSI-H/MMRd status

Outcomes data are available in unselected (for MSI-H/MMRd status) patients with metastatic CRC who received prior oxaliplatin, irinotecan, fluoropyrimidine, anti-VEGF, and anti-EGFR (if RAS wild-type) therapy. In a randomized clinical trial of patients receiving TAS-102, patients in the TAS-102 arm lived for a median of 7.1 months versus 5.3 months in patients who received placebo (HR 0.68; 95% CI, 0.58 to 0.81; $p < 0.001$).[60,61] Median estimated PFS was 2 months and the objective response rate was 1.5% for patients in the TAS-102 arm. Efficacy results were similar in the randomized clinical trial supporting the approval of regorafenib. Median overall survival was 6.4 months in the regorafenib arm versus 5.0 months in the placebo arm. Median estimated PFS was 2.0 months in the regorafenib arm and the objective response rate was 1% (HR 0.77; 95% CI, 0.64, 0.94; $p = 0.0102$).[62,63]

Overall survival was assessed in a randomized non-inferiority clinical trial of cetuximab versus panitumumab in patients with KRAS exon 2 wild-type metastatic CRC who received prior irinotecan, oxaliplatin, and a fluoropyrimidine. Approximately 25% of the population received prior bevacizumab. Median estimated survival was 10.4 months for patients who received cetuximab versus 10 months in patients who received panitumumab.[64] Response rates across both arms were approximately 20%; however, per the published report, duration of response in both arms was less than 6 months (3.8 months for panitumumab versus 5.4 months for cetuximab).[64] An additional factor in (historical) comparisons of EGFR-inhibitors versus PD-1 inhibition in patients with MSI-H/MMRd CRC relates to sidedness of the patients' tumors. As stated above, MSI-H/MMRd tumors are more commonly located on the right side of the colon; however, survival of patients with right sided tumors appeared shorter in cetuximab-treated patients compared to patients who received bevacizumab in a subgroup analysis of CALGB/SWOG 80405 (a large cooperative group trial).[65] Although there are limitations to post hoc subgroup analyses, similar results have been described in other studies.[66-69] Current guidelines for the treatment of colon cancer now state that "these and other data suggest that cetuximab and panitumumab confer little if any benefit to patients with metastatic colorectal cancer if the primary tumor originated on the right side."[70]

In summary, available data suggest that patients with metastatic CRC who have received irinotecan, fluoropyrimidine, and oxaliplatin-based chemotherapy have a poor prognosis, irrespective of MSI-H/MMRd status, and that response rates are low with TAS-102 and

regorafenib (standard available therapies). Although EGFR inhibitors (in patient who had not received prior EGFR inhibitors) resulted in higher response rates in patients with RAS wild-type tumors, durability of response was limited and the effect of EGFR inhibition may be blunted in patients with right sided tumors (the majority of patients with MSI-H/MMRd mCRC). Based on these data and the data supporting the use of pembrolizumab (generally in the third or greater-line settings) in patients with metastatic CRC (see Section 7 below), it is appropriate to approve pembrolizumab in patients who have received prior irinotecan, fluoropyrimidine, and oxaliplatin-based chemotherapy. The response rates (and data on response duration) in this group of patients with MSI-H/MMRd CRC support a conclusion that pembrolizumab confers a meaningful advantage over available therapy.

Natural history of MSI-H/MMRd endometrial cancer and previously-treated endometrial cancer

The following summarizes recently published studies investigating outcomes in patients with MSI-H/MMRd endometrial cancer:

- GOG conducted an analysis of patients with endometroid endometrial carcinomas and assigned 1,024 tumors to one of four MMR classes.[71] Approximately 36% of the patients were considered as MSI-H/MMRd (either through mutation or epigenetic mechanisms).[71] The paper stated that MMR status was not associated with outcomes on PFS or endometrial cancer-specific survival; however univariate analysis suggested worse PFS for women whose tumors had epigenetic defects conferring MMRd (but not MMR through probable mutation).[71] The investigation also found that MMR defects were associated with clinical features that portend poor outcomes.[71] Few patients (18) had stage IV disease in this report, including only five with MMR defects.
- A smaller Lithuanian study of 109 patients with endometrial cancer also did not find a statistically significant relationship between MSI-H status and survival in patients with endometrial cancer.[72] Like the GOG study, the majority of patients had early stage disease (~80% had Stage I) and only 4 had Stage IV disease.[72]
- A Spanish study of 212 patients with endometroid endometrial carcinomas also found no association between MMR deficiency and OS or PFS either as a whole or when analyzed by stage [I, I/II or III/IV (18 patients had Stage IV disease)].[73]
- In contrast, an earlier (2013) report stated that MMRd was associated with worse outcomes in patients with Stage III or IV high-grade endometroid carcinomas (HGEC); however the KM analyses were limited to 27 patients (12 MMRd) with Stage III or IV disease.[74]

A 2013 meta-analysis of studies investigating the effects of MMRd on outcomes in endometrial cancer concluded that "the existing literature together with data from this review is inconclusive and show that no consistent association between MSI and clinical outcome can be ascertained as of yet in endometrial cancer."[75] The meta-analysis found differences in populations studied (e.g., endometroid histology versus all histologies), assessments for MSI-H/MMRd, study designs, and outcomes across studies.[75]

Therapeutic options are limited in patients with endometrial cancer who have received prior cytotoxic chemotherapy for metastatic disease. Reported response rates have generally been

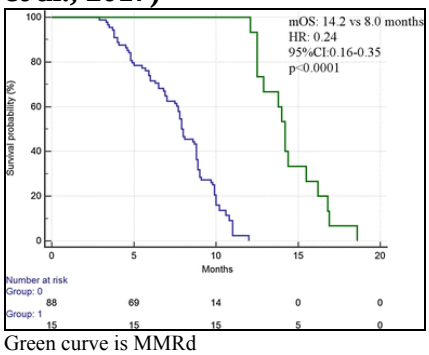
15% or less; however, one report described a 27% response rate for paclitaxel in the second-line setting.[76] Nevertheless, in the paclitaxel report with the highest reported response rate (described in a treatment-evaluable population and not an ITT population), median duration of response was only 4.2 months and median overall survival was 10.3 months.[77] Responses rates in the paclitaxel report were per the GOG response criteria and therefore may not have been comparable to other reports (and the pembrolizumab data) that used RECIST criteria.

In summary, data on MSI-H/MMRd endometrial cancer in the metastatic setting are limited. I agree with the quoted comment above that "the existing literature together with data from this review is inconclusive and show that no consistent association between MSI and clinical outcome can be ascertained as of yet in endometrial cancer." In unselected patients with previously treated metastatic endometrial cancer, survival is expected to be poor for most patients. There are no approved therapies in this setting and available therapies are generally based on uncontrolled single-arm studies. The therapy with the highest reported response rate in the second-line setting (paclitaxel) had limited durability of response and the responses may not be comparable to what would be observed in current practice (e.g., RECIST responses in an ITT or as-treated population).

Natural history of MSI-H/MMRd gastric cancer

Data regarding outcomes in patients with MSI-H/MMRd gastric cancer in the metastatic setting are limited. A recent report from Italy found that prognosis was favorable for patients with defective MMRd gastric cancer in the first-line metastatic setting; however, only 15 of the 103 patients had MMRd disease.[78] Although MMR was reported to have a favorable prognosis, median survival of the 15 patients was only 14.2 months, and the KM curves showed that all 15 patients died within 20 months.[78]

Figure 9: KM curves by MMR status, metastatic gastric cancer (copied from Giampieri et al., 2017)



Green curve is MMRd

A different Italian study of 472 patients with gastric cancer also concluded that MSI-H/MMRd was associated with better prognosis; however, most patients in this series underwent curative resection (i.e., 80% of the 111 patients with MSI-H/MMRd tumors underwent R0 resection) with only 9 (8.1%) patients with MSI-H/MMRd tumors having stage IV disease versus 77 (21.3%) patients with MSS disease (survival of patients with stage IV disease was not described).[79]

Zhu at al. (2015) performed a meta-analysis of 8 studies that enrolled 1,976 patients with gastric cancer (431 were MSI-H/MMRd).[80] The investigators found associations between MSI-H/MMRd (assessed using different numbers of microsatellite markers across studies) and fewer lymph node metastases and tumor histology (intestinal type). In the meta-analysis, patients with MSI-H tumors undergoing a surgical treatment strategy had improved survival compared to MSS gastric cancer.[80] The paper did not describe the number of patients with metastatic disease enrolled across the studies; however, the number would be expected to be low given the primary treatment strategy for patients described in the meta-analysis.

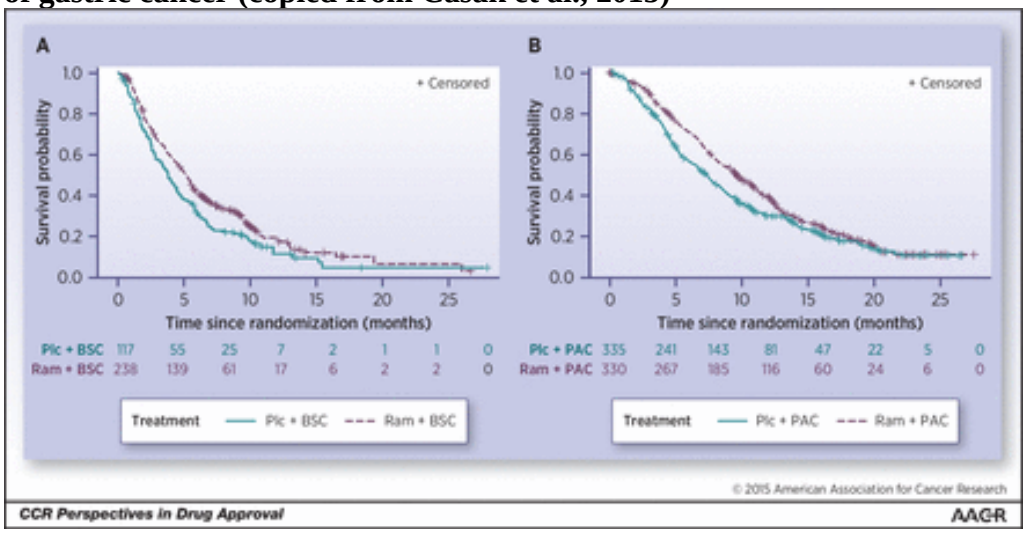
A larger meta-analysis of 5,438 patients (712 had MSI-H tumors) with gastric cancer also concluded that MSI-H was associated with a favorable prognosis (HR of 0.72 in a random effects model for OS); however, the meta-analysis found heterogeneity in the results of the studies, possibly related to differences in epidemiology or due to chemotherapy.[81] A separate analysis (by many of the same authors) of 1,276 patients with Stage II or III gastric cancer suggested that the benefits of MSI-H (for prognosis) may be attenuated by chemotherapy.[82] Again, data regarding MSI-H was largely restricted to patients undergoing curative resection.

In summary, it is difficult to articulate any conclusions regarding the natural history of patients with MSI-H/MMRd gastric cancer in the metastatic setting. MSI-H/MMRd may be a favorable prognostic marker in patients with completely resected gastric cancer; however, it is unclear if this effect persists in patients with metastatic gastric cancer.

Natural history of previously-treated metastatic gastric cancer unselected for MSI-H/MMRd status

Although data were limited regarding outcomes of patients with metastatic MSI-H/MMRd gastric cancer, survival of unselected (for MSI status) patients with previously-treated gastric cancer remains poor. Estimated median OS of patients who received ramucirumab, the drug most recently approved for gastric cancer was 5.2 months as a single agent or 9.6 months in combination with paclitaxel.[83-85] The KM curves below show that virtually all patients in both trials had died by the second year on study. Although the estimated response rate was 28% when ramucirumab was administered in combination with paclitaxel, median duration of response was 4.4 months for this combination, indicating that response duration was generally limited.[85]

Figure 10: KM curves for OS in two trials of ramucirumab for the second-line treatment of gastric cancer (copied from Casak et al., 2015)



Natural history of MSI-H/MMRd in other cancers

Data regarding the natural history of other cancers that are MSI-H/MMRd are limited or anectodal.

Biliary tract cancers

One report of 59 patients who underwent surgical resection for gall bladder cancer found that patients with MSI-H gall bladder cancer had an improved prognosis.[86] There is lack of data, however, regarding patients with MSI-H/MMRd biliary tract cancers in the metastatic setting. Survival is poor in unselected (for MSI-H/MMRd) patients with biliary tract cancers. In the trial that established gemcitabine plus cisplatin as the standard of care for patients with previously untreated biliary tract cancers, median overall survival was 11.7 months in the 204 patients who received cisplatin in combination with gemcitabine.[87] Response rates and outcomes are worse in the second-line setting. A systemic review of 25 literature reports describing effects of various second-line therapies estimated that approximately 7.7% of patients respond with a reported mean overall survival of 7.7 months.[88] The review concluded that there was insufficeint evidence to recommend any specific second-line therapy.[88]

Ovarian cancer

Limited data exist regarding the natural history of MSI-H/MMRd in patients with ovarian cancer. One report found prognosis to be worse for patients with MSI-H ovarian cancer (in early and late stage disease); however, the number of patients in the analysis was limited (n = 26 for Stage III disease).[42]

Pancreatic cancer

One study, published in abstract form, assessed MSI-H/MMRd in 109 patients with pancreatic cancer.[89] Although MSI-H-positivity was 25% or more in patients with Stages I to III pancreatic cancer, only 4% of patients with metastatic disease had MSI-H/MMRd tumors.[89] Reported median overall survival was 21.5 months in patients with MSI-H/MMRd disease compared to 20.0 months with microsatellite stable disease (the abstract did not provide stage-

specific survival).[89] Survival in patients with metastatic pancreatic cancer (unselected for MSI-H/MMRd) in the second-line setting is poor. Median OS was 6.1 months in the randomized clinical trial supporting the use of liposomal irinotecan.[90] OS was similar in patients randomized to the OFF (folinic acid, fluorouracil, oxaliplatin) regimen in the CONKO-003 trial (median 5.9 months).[91]

Small intestinal adenocarcinoma

A Korean study identified the loss of expression of MLH1, MSH2 and MSH6 in 25 (13.0%), 25 (13%) and 29 (15%) of 193 small intestinal carcinoma pathology specimens, respectively.[92] Loss of MSH2 expression was associated with retroperitoneal seeding and loss of MSH6 expression was associated with a higher frequency of pancreas invasion and a lower frequency of peritumoral edema.[92] The authors found no difference in OS in patients who were MMRd compared to patients who were MMRp.[92]

Overall, data are limited in regards to the treatment and prognosis of (unselected) patients with small intestinal adenocarcinoma. For small intestinal adenocarcinoma, most data comes from retrospective case series or small uncontrolled studies.[93] Data in the first-line metastatic setting indicate that survival generally appears to be less than two years (although even these retrospective reports may overestimate OS due to selection bias)[93] and there is no known effective treatment for patients with previously treated small intestinal cancer.

Summary of unmet medical need

Although standard treatment regimens exist for most patients with advanced or metastatic solid tumor malignancies, such treatment generally is not curative and additional treatment is needed. In settings where no treatment is available, an argument can clearly be made across MSI-H/MMRd tumor types that treatment with pembrolizumab (with the outcomes described in Section 7 below) is better than available therapy. Such arguments could also be made in settings where the clinical effects of available therapy are modest. A review of the data in the sBLA submitted by Merck indicated that patients had received appropriate therapy prior to enrolling into the clinical trials.

Unfortunately, limited data exist regarding outcomes for patients with MSI-H/MMRd tumors in the metastatic setting. Nevertheless, at least in the more common tumors that harbor MSI-H/MMRd (CRC and endometrial cancer), compelling evidence does not exist that MSI-H/MMRd confers a favorable prognosis in the metastatic setting. Due to limited numbers of patients with individual MSI-H/MMRd tumor types (outside of CRC or possibly gastric or endometrial cancer), due to lack of equipoise in settings without available therapies, and due to expected cross-over (if a clinical trial were conducted) it would not appear possible (or appropriate) to establish with certainty, i.e., a requirement to conduct a randomized controlled trial, that pembrolizumab clearly alters the overall survival of patients with these end-stage tumors. Nevertheless, the durable responses (described below) support a beneficial treatment effect and favorable risk-benefit profile of pembrolizumab in these patients with life threatening malignancies and unmet need.

2.3 How will patients with MSI-H/MMRd-positive tumors be identified and will a companion in vitro diagnostic test be needed?

Current guidelines recommend that all patients with colorectal cancer undergo an assessment of their tumor for MSI-H/MMRd with either immunohistochemistry (IHC) for MMRd or polymerase chain reaction (PCR) for MSI-H.[94,95] Further assessment for germline genetic testing (for Lynch syndrome) depends upon results observed in the initial tumor screening. For example, American Society of Clinical Oncology (ASCO) guidelines recommend testing for germline mutations if there is loss of MLH1/PMS2 and absence of a BRAF mutation or if MLH1 promotor methylation is not identified.[95] Loss of other proteins (MSH2, MSH6, or PMS2) should result in germline genetic testing for the corresponding genes.[95] Although treatment decisions have been made for years based on MSI-H/MMRd testing (e.g., initiating a cancer screening program in people with Lynch syndrome), an FDA-approved *in vitro* diagnostic test is not available in order to make these treatment decisions and different laboratory developed tests (LDTs) have been used to date.

MMR testing generally involves an immunohistochemistry assessment for one of four MMR proteins: MLH1, MSH2, MSH6, and PMS2. Different PCR tests for MSI are available in the community and generally involve testing three to five tumor microsatellite loci (referenced from Merck's submission).

Differences in IHC and PCR exist regarding test results for certain rare subgroups of patients. For example, some patients with MSH6 germline mutations lack MSI (i.e., the tumors are microsatellite stable) when assessed via PCR due to a functional redundancy in the MMR system.[96-98] There are also reports of rare patients with missense mutations (e.g., in MLH1 or MSH6) that produce non-functional proteins that stain positive (i.e., are deemed mismatch repair proficient) due to their presence when assessed by IHC; however, the tumors are MSI-H when assessed by PCR.[96-98]

Reports have described prior chemoradiation as affecting IHC results for MMR. In one study, MSH6 was reported to decrease in (stain) intensity in patients whose tumors have been subject to chemoradiation in the neoadjuvant setting (i.e., patients with rectal cancer).[99] Similar findings were described by a second group after neoadjuvant chemoradiation for rectal cancer; however, differences in IHC staining were not limited to MSH6.[100]

Although variations between IHC and PCR may exist, in general, literature reports describe high concordance (e.g., > 95%) when the same lab or group assesses both IHC and PCR.[101] Reported problems with IHC include errors in immunohistochemistry misinterpretation or technical problems with staining, fixation, or processing.[101] Additionally, false reads can occur due to staining variability within a tumor, especially if internal controls are not adequate.[102] For PCR, adequate tissue is required to perform the analysis, so discrepant results between tests could occur if there is tissue for the IHC test but inadequate tissue for PCR.

One study assessed concordance between IHC and PCR in 157 patients with endometrial cancer with tissue available from a biobank repository. In this study, both MSI and MMR could be assessed in 89 patients.[103] In all missing cases, there was insufficient tumor available for PCR testing (there was insufficient tumor for IHC testing in two cases).[103] There were 6

discordant results among the 89 cases (>93% were concordant): one due to isolated MSH6 loss (see example above); two cases with MLH1 and PMS2 loss (due to hypermethylation) but MSI result of MSI-low; and three cases that were MSI-H by PCR but all MMR proteins were present by IHC.[103] Although not described in the report, POLD and POLE mutations have been reported to be potential causes of unexplained MSI-H results in patients with endometrial cancers.[104-106]

A combined assessment of MMR protein expression and MSI status was performed in 696 patients (81%) enrolled in two endometrial cancer studies (PORTEC-1 and 2).[107] The concordance rate between IHC and PCR in this study was approximately 94%.[107] In this study, most discordant cases appeared related to loss of MMR protein expression and a MSS/MSI-L (microsatellite instability-low) phenotype which could be explained by MLH1 promoter methylation or variants of MMR proteins.[107] Additionally, the investigators found that subclonal loss of MMR protein expression was generally associated with subclonal MSI within a microdissected area of tumor.[107] Finally, in this study, there were two patients who were MSI-H who had retained expression of all four MMR proteins. These two patients were subsequently determined to have POLE mutations.[107]

Limited data are available in regards to testing results across different centers or hospitals (most of the above data were published by single groups representing academic medical centers). Different centers may use various testing platforms or methodologies. For example, certain commercially developed LDTs for MSI use seven markers including five mononucleotide repeat markers and two pentanucleotide repeat markers whereas the Bethesda panel interrogated three dinucleotide and two mononucleotide repeats.[108] Other centers have reported tests with more markers[109] and differences in sensitivity among tests have been described in the literature using different panels of markers.[110]

To assess MSI-H testing performance across laboratories, College of American Pathology MSI-H proficiency test reports from 2005 to 2012 were summarized in one publication. A total of 104 laboratories participated in 2012, up from 42 in 2005.[111] The "correct" result in the report was considered the consensus result of the laboratories. The number of laboratories using five markers increased from 63% in 2005 to 82% in 2012 [most (but not all) of the other laboratories used more than 5 markers].[111] In 2012, 65% of the laboratories reported using a single commercially available LTD to assess for MSI-H.[111] In general, "correct" analyses were reported in > 95% of laboratories, although differences existed among laboratories (which decreased over time) in tissue enrichment techniques (88% used such techniques in 2012) including microdissection or laser capture.[111] The paper stated that MSI-H may not be detected if tumor cellularity is less than 20%.[111]

In summary, PCR and IHC are different tests that are generally concordant but identify (even in the ideal scenario with 100% reproducible results) slightly different groups of patients. Patients with POLE or POLD mutations who are MSI-H might respond to checkpoint inhibition, even in the setting of negative IHC testing for MLH1, MSH2, MSH6, and PMS2. Conversely, it is unknown how an individual patient would respond to checkpoint inhibition whose tumor lacks MSH6 via IHC but is MSS by PCR; tumors from such patients may have a lower number of neoantigens and be less responsive. More difficult to interpret may be the

uncommon patient whose tumor is MMRd based on lack of staining to MLH1 and PMS2 (via hypermethylation) but MSI-L by PCR (e.g., these tumors may exhibit heterogeneity regarding MSI-H/MSI-L status).

Next-generation sequencing (NGS) is also being evaluated as a diagnostic test for MSI-H with sensitivity listed as greater than 90% in published reports.[112-116] A recent report from the Memorial Sloan Kettering Cancer Center compared IHC to a custom NGS 341-gene assay in 224 patients with CRC. All (of 193) tumors with fewer than 20 mutations were scored as MMR-proficient by IHC. Twenty-eight of the 31 tumors with 20 or more mutations were MMRd by IHC; the three remaining tumors harbored POLE mutations.[117] Challenges have been cited regarding NGS testing (compared to IHC) in that testing may require additional time, specialized resources, and different NGS panels may have different number of genes, techniques, and cut-offs for positive results (i.e., standardization does not exist).[118] Nevertheless, development of a reproducible, accurate, and clinically validated NGS test could be desirable, especially for patients with tumors that are already undergoing multiple diagnostic tests (e.g., ALK, EGFR, and ROS in lung cancer, or RAS and RAF for CRC). NGS may also allow for testing of circulating tumor or plasma cell-free DNA.[119]

In practice, it is unlikely that patients will undergo testing with all modalities. As will be described in Section 7 below, response rates were similar irrespective of whether the patient was identified using either IHC or PCR (when conducted by highly experienced laboratories). Such results are expected given that >90% of patients have concordant results when assessed by IHC and PCR. *If* sufficient tissue is available, and the test is accurate (and reproducible), PCR may have (slightly) better performance characteristics by identifying the end result (higher mutational burden) of MMR deficiency as well as identifying patients who have a high mutation burden due to POLE or POLD mutations. IHC may continue to have a role in identifying patients; however, given that results can be obtained quickly and specialized equipment may not be needed. IHC may also be the only testing method available for some patients with limited tumor obtained at biopsy.

FDA's 2014 In Vitro Companion Diagnostic Devices Guidance states the following:

> "When results from a diagnostic device are essential in patient treatment, health care professionals must be able to rely on those results. Inadequate performance of an IVD companion diagnostic device could have severe therapeutic consequences. Such a device might fail analytically (e.g., by not accurately measuring the expression level of a protein of interest), or clinically (e.g., by not identifying those patients at increased risk for a serious adverse effect). Erroneous IVD companion diagnostic device results could lead to withholding appropriate therapy or to administering inappropriate therapy. Therefore, FDA believes that use of an IVD companion diagnostic device with a therapeutic product raises important concerns about the safety and effectiveness of both the IVD companion diagnostic device and the therapeutic product."

Consideration of whether a diagnostic device is essential for the proposed indication is complicated given the breadth of the proposed tissue-agnostic indication. For some indications, knowledge of MSI-H/MMRd status could be considered as complimentary, rather

than essential. Such examples include the indications for which pembrolizumab is already approved including lung cancer, melanoma, and head and neck cancer. Other tumors; however, appear not to respond to single-agent checkpoint inhibition in the absence of microsatellite instability. For these tumor types, such as pancreatic cancer or CRC, alternative therapies may exist that could provide benefit for these patients (e.g., regorafenib or TAS-102 for patients with CRC).

FDA's IVD Guidance states that "for a novel therapeutic product for which an IVD companion diagnostic device is essential for the safe and effective use of the product, the IVD companion diagnostic device should be developed and approved or cleared contemporaneously so that it will be available for use when the therapeutic product is approved." Although FDA generally expects that the device be approved contemporaneously with the drug, FDA Guidance states that "if the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device, FDA does not intend to delay approval of changes to the labeling of the therapeutic product until the IVD companion diagnostic device is approved or cleared." Given the clear therapeutic effect described below in patients with advanced life-threatening malignancies, I recommend approval of this efficacy supplement even though a companion IVD is not available to select patients with MSI-H/MMRd cancers for treatment with pembrolizumab. Merck has agreed to support the development of diagnostic assays consistent with and in support of the approved indication (with PMAs to be tentatively submitted in 2019). Although literature generally describes concordant results between tests and across centers, most of the literature comes from centers which are highly experienced in the testing and treatment of patients with MSI-H/MMRd cancers. Ultimately, having accurate and reproducible tests to identify patients across all localities, clinics, and hospitals will promote the public health to ensure that patients who have MSI-H/MMRd cancers can receive treatment with pembrolizumab whereas patients with MSS cancers can receive alternative treatment (or enroll into a clinical trial) if appropriate.

2.4 How will Merck address accelerated approval post-marketing requirements?

Randomized trials will be challenging to conduct in the tissue-agnostic setting. Given the number of tumor types with different natural histories, it would not be scientifically appropriate to "lump" all tumor types together into a single randomized trial. Although there is a common biology (e.g., increased neoantigen burden) among MSI-H/MMRd tumors, there will be differences among patients with different types of cancer that could influence response to therapy with pembrolizumab (e.g., the degree of immunosuppression related to previous cytotoxic chemotherapy).

Accelerated approval offers the ability to bring drugs to the market earlier and could be granted if the drug effect provides a meaningful advantage over available therapy and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit *or* on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e. an intermediate clinical endpoint).[120]

When considering the data necessary for *regular approval*, the FDA considers the effect size observed in the specific population(s) and whether that effect supports regular approval. The FDA will need to consider whether it would be scientifically appropriate to require a randomized trial and whether patients would even elect to be randomized (e.g., is there equipoise?). Merck is conducting a randomized trial (KN-177) in the *first-line* metastatic colorectal cancer setting (with crossover allowed after progression on standard chemotherapy).[121] The trial will assess PFS in patients with MSI-H/MMRd metastatic CRC receiving pembrolizumab versus investigator's choice of standard-of-care chemotherapy (i.e., FOLFOX or FOLFIRI-based chemotherapy).[121] Although the trial will answer an important clinical question, it is unlikely that the trial will be adequately powered, especially in the setting of crossover, to assess whether pembrolizumab improves overall survival. Furthermore, given changes in standard treatment guidelines (which allow for the use of pembrolizumab or nivolumab in patients with MSI-H CRC)[70] it is not realistic (and probably not ethical) that a trial could be conducted in the United States that prohibits cross-over. Although response may not be entirely predictive of effects on clinical benefit, checkpoint inhibitor therapy, including pembrolizumab, has demonstrated beneficial effects on OS with similar response rates in other tumor types.[122-132]

The FDA granted regular approval to crizotinib for the treatment of ROS1-rearranged metastatic NSCLC, based on a high response rate (66%), duration of response of 18.3 months, and a favorable risk-benefit ratio with comparative clinical data also available from two randomized controlled trials in patients with *ALK*-positive NSCLC.[133-135] A recently published review from the FDA summarized that in certain circumstances, particularly in rare cancer subsets when the drug has demonstrated safety and efficacy in other settings, ORR and duration of response have been used for regular approval.[135] This application, with the observed (durable) effect on overall response rate (ORR) (including complete responses, see below) in very rare groups of patients (e.g., MSI-H/MMRd pancreatic cancer or biliary cancer), and with demonstrated safety and efficacy in other settings, highlights this approach.

Although the proposed endpoint of ORR (which is an endpoint that is "other than survival or irreversible morbidity") *may* support regular approval depending on the effect size and duration, additional data will provide data to verify and describe the ultimate clinical benefit in an expanded population.

Granting accelerated approval allows for residual uncertainty to be addressed regarding the tissue-agnostic indication. Given the totality of data (scientific and clinical) submitted in this application, I believe that such an approach is appropriate rather than requiring a large number of additional patients to be enrolled in the pre-approval setting. Data submitted post-approval will allow for increased confidence in the data across multiple tumor types, some of which have not yet been studied. During the February 13, 2017, meeting between Merck and FDA, Merck provided the following table indicating that 416 patients have received pembrolizumab for MSI-H/MMRd tumors in clinical trials. In order to support regular approval, Merck proposed submitting data from these patients across at least 20 tumor types with at least 24 months of follow-up.

Table 1: Enrollment of patients with MSI-H/MMRd tumors in Merck's development program (copied from Merck's submission)

	Enrollment by Trial (As of 21-Dec-16 and Per sBLA)															
	KN016A		KN164		KN016C		KN012		KN028		KN158		KN177		Total	
	As of 21-Dec-16	# Per sBLA	As of 21-Dec-16	# Per sBLA	As of 21-Dec-16	# Per sBLA	As of 21-Dec-16	# Per sBLA	As of 21-Dec-16	# Per sBLA	As of 21-Dec-16	# Per sBLA	As of 21-Dec-16	# Per sBLA	As of 21-Dec-16	# Per sBLA
(b) (4)																

I am generally supportive of Merck's proposed post-marketing requirement (PMR) submission. There will be a limited number of patients with certain tumor types; however, when analyzed in aggregate, the overall pattern of responses should be sufficient to support the tissue-agnostic approach. The most common MSI-H/MMRd tumor types will each have 20 or more patients enrolled (except small bowel cancer with 18 patients, acknowledging that this is a rare cancer). Lack of a response in single enrolled patients with a tumor type (e.g., testicular or salivary gland tumor) would not necessarily indicate that other patients with that tumor type would be unresponsive.

Ultimately, real world data may be useful in the unexpected scenario where there is a specific MSI-H/MMRd tumor type that may unresponsive to checkpoint inhibition.[135,136] Such an approach, either through the accelerated approval PMR or through real world data could, if necessary, facilitate revisions to labeling (e.g., to include a limitation of use with a specific tumor-type). Nevertheless, I agree with the approach to grant accelerated approval with a PMR to obtain additional data on ORR and response durability given that pembrolizumab will be approved for patients, who in essence, have no effective available therapies and who would ultimately die of their malignancy.

Merck has already enrolled the majority of patients in order to satisfy the PMR. Merck has agreed to enroll additional patients with prostate cancer, thyroid cancer, small cell lung cancer,

and ovarian cancer in order to further assess clinical effects in tumor types less commonly affected by microsatellite instability. Merck will also enroll children with MSI-H/MMRd cancers to further verify and describe the benefit of pembrolizumab across the entire spectrum of patients with MSI-H/MMRd cancers.

2.5 Pediatric considerations

Prior to submission of the sBLA, Merck and FDA reached agreement upon an initial pediatrics study plan (iPSP) (submitted on August 30, 2016) for MSI-H CRC. In the original sBLA submission for the tissue-agnostic indication, (b) (4)

Based on the mechanism of action and dose comparability of pembrolizumab in adolescents versus adults, during the review of the application, DOP2 (Division of Oncology Products 2) proposed to label pembrolizumab for the treatment of patients with eligible MSI-H/MMRd cancers aged 12 years and older (e.g., adolescents and adults). FDA took a similar approach in the approval of avelumab (a PD-L1 inhibitor) for the treatment of patients (12 years of age and older) with metastatic Merkel cell carcinoma.[137] FDA also published a review to support the derivation of adolescent dosing of drugs from data in adults and that 87 out of 92 products had identical adolescent and adult dosing.[138]

Subsequent to the decision to approve pembrolizumab for the treatment of patients with eligible MSI-H/MMRd cancers aged 12 years and older, FDA approved (March 2017) pembrolizumab (accelerated approval) for the treatment of adult and pediatric patients with classical Hodgkin lymphoma.[139] This approval provided for a dose to be used in children (2 mg/kg, up to a maximum of 200 mg every three weeks). As part of this approval, Merck is conducting a post-marketing requirement to characterize the long-term safety of pembrolizumab in pre-pubertal patients. Commensurate with this approval in patients with classical Hodgkin's lymphoma, FDA will also approve pembrolizumab for younger children with MSI-H/MMRd cancers; therefore, PREA requirements are satisfied. Based on the biology of MSI-H/MMRd malignancies, I would not expect quantitative differences in anti-tumor responses between adult and pediatric patients with MSI-H/MMRd cancers and therefore extrapolation would be appropriate. Although PREA is satisfied, Merck will study pediatric patients with advanced MSI-H/MMRd cancers as part of the Subpart E PMR in order to further verify and describe the clinical benefit of pembrolizumab.

<u>MSI-H/MMRd in pediatric cancer</u>

The overall incidence of MSI-H/MMRd cancers in pediatric patients is expected to be low. Merck estimates that fewer than 400 children per year will be diagnosed with advanced MSI-H/MMRd cancers in the U.S. based on the rates of MSI-H/MMRd across various adult tumors and based on the incidence rates of various malignancies in children.

Most published reports of MSI-H/MMRd cancers in children involve reports of constitutional mismatch repair deficiency (CMMRD) or biallelic mismatch repair deficiency (BMMRD),

respectively. In one report, twelve of 24 patients with available GI screening data developed GI malignancies and GI cancers made up 40% of the malignancy diagnoses in the overall population with BMMRD.[140] Patients without colorectal neoplasia had undergone a single baseline colonoscopy. Eight of the 24 patients developed 19 primary colorectal cancers and the age of the patients ranged from 8 to 25 years.[140] Four patients also developed five small bowel cancers.[140] The report recommended screening for CRC at age 3 to 5 and screening for small bowel adenocarcinoma at age 8.[140]

A second report described a review of records from 31 French patients with CMMRD.[141] These 31 patients developed a total of 67 tumors including 22 brain tumors, 17 hematological malignancies and 3 sarcomas.[141] The median age of onset until the first tumor was approximately 7 years.[141]

A summary of 146 patients with CMMRD has also been reported. In the report, 139 patients developed 223 malignancies (with multiple synchronous colon cancers counted as one malignancy).[142] A total of 81 brain/CNS tumors were identified in 78 patients including 34 glioblastomas.[142] The report stated that a total of 88 Lynch syndrome-associated malignancies were diagnosed in 59 patients (mostly CRC).[142] Hematologic malignancies tended to occur in young patients (mean age 6 years) whereas the mean age at brain tumor diagnosis was 9 years and the mean age for Lynch Syndrome-associated tumors (e.g., CRC) was 17 years.[142]

Development of pembrolizumab in children with cancer and in children with MSI-H/MMRd cancers

Merck has investigated the effects of pembrolizumab in an ongoing dose finding and activity estimating trial (KN51) in patients with advanced melanoma or PD-L1-positive advanced, relapsed, or refractory solid tumors or lymphomas. As described during the 2016 International Society of Paediatric Oncology (SIOP) and ASCO meetings, KN51 is enrolling patients aged 6 months to less than 18 years with advanced melanoma or with PD-L1-positive advanced, relapsed, or refractory solid tumors or lymphoma that is incurable and has progressed on prior therapy or for which standard therapy is either unavailable or inappropriate.[143,144] Patients are also required to have measurable disease per RECIST v1.1 (or MIBG-positive for neuroblastoma), known tumor PD-L1 status using IHC (prescreening), and performance score $\geq$ 50 using Lansky Play Scale (aged $\leq$ 16 years old) or Karnofsky Scale (aged > 16 years).[143] The starting dose for the trial was 2 mg/kg every three weeks with dose escalation permitted if the 2 mg/kg dose was considered safe and if exposure at the starting dose was < 50% of the adult value.[143]

During a face-to-face meeting with Merck held on February 13, 2017, Merck provided an update regarding the pediatric program which also allowed for potential investigation in patients with PD-L1-negative tumors. Merck stated that the recommended pediatric dose has been determined (2 mg/kg every three weeks) and that 83 patients had been enrolled. To support an assessement of pembrolizumab in children with MSI-H/MMRd cancers, Merck proposed enrolling a cohort of 25 pediatric patients with MSI-H/MMRd cancers (any solid tumor indication) via an amendment to KN51.

Given the clinical effects of pembrolizumab observed to date in adults with refractory MSI-H/MMRd solid tumors, I agree that pembrolizumab should be approved (for children with refractory metastatic cancers without alternative treatment options) prior to the completion of the enrollment of the pediatric MSI-H/MMRd cohort. Data regarding the effects on pre-pubertal children will be obtained via a PMR for Hodgkin lymphoma and in other patients enrolled in KN51. Data (reviewed in the classical Hodgkin lymphoma application) appear to show that the 2 mg/kg dose (every three weeks) in younger patients is comparable to exposure obtained with adult dosing regimens.[143]

Overall, there may be some differences regarding the effects of pembrolizumab in adult and pediatric patients who are MSI-H/MMRd depending on the number of patients enrolled with CMMRD tumors who are, for example, more likely to develop CNS tumors. Case reports have been published regarding the effects of nivolumab (a different anti-PD-1 inhibitor) in patients with CMMRD-CNS tumors. One report described two siblings (with POLE mutations) with recurrent multifocal GBM refractory to standard therapy who responded to nivolumab.[11] A different report; however, described severe cerebral edema in a 10 year old girl which was diagnosed after nivolumab administration.[145] After hemiparesis improved and she was discharged on dexamethasone, she developed severe edema again after a second nivolumab infusion and she subsequently died.[145] Autopsy revealed a large glioma which protruded 11.5 by 9 by 2 cm from the craniectomy site and extended down to involve the midbrain and pons. There was some necrosis but no atypical inflammation noted on histopathology.[145]

In order to assess the safety of pembrolizumab in children with MSI-H/MMRd primary CNS tumors, additional patients will be studied with these cancers as a (FDAAA) post-marketing requirement. Given the dismal prognosis of glioblastoma, it is reasonable to continue to study pembrolizumab in these patients, even with a possible risk of life threating cerebral edema. If the risk is real (it is difficult to ascertain causality or risk based on a single report), it will be worthwhile to ascertain whether any factors (e.g., tumor size or location) could mitigate this risk so that patients and parents can make an informed decision regarding therapy.

2.6 Regulatory history

The following summarizes the pertinent regulatory history and meetings held in support of this efficacy supplement.

12 May 2015 (Type B): Merck submitted this meeting request to discuss KN164 to support accelerated approval of pembrolizumab for patients with MSI-H/MMRd CRC. During the meeting, Merck provided preliminary data from KN16 from 11 patients with MSI-H CRC, 21 patients with MSS CRC, and 9 patients with MSI-H/MMRd non-CRC. No responses were observed in 18 evaluable patients with MSS CRC. Four of 10 evaluable patients with MSI-H/MMRd CRC responded and 5 of 7 patients with MSI-H/MMRd non-CRC responded. FDA stated that whether KN164 could support approval would depend on the magnitude of the response rate observed, duration of response, and the overall risk-benefit assessment. FDA recommended that Merck rule out at least a 15% response rate based on the lower bound of the 95% confidence interval of the response rate.

(b) (4)

FDA recommended that Merck consider allowing patients with HIV on HAART and an intact immune system to enroll into KN164. Additionally, FDA recommended that Merck enroll patients with (MSI-H/MMRd) small intestinal cancer and other gastrointestinal malignancies in a dedicated protocol to expedite development of pembrolizumab in these patient populations.

10 Jul 2015 (Type B): FDA and Merck met to discuss the design of KN158 which included patients with non-colorectal tumors identified as MSI-H/MMRd.

29 Oct 2015 (letter to Merck): FDA granted Breakthrough Therapy designation (BTD) to pembrolizumab for the treatment of patients with MSI-H metastatic colorectal cancer. FDA granted BTD based on Merck's submission dated 03 Sep 2015 that contained data in both patients with CRC and non-CRC (whose tumors were MSI-H).

11 Nov 2015 (letter to Merck): FDA provided agreement to a pediatric study plan that (b) (4)

13 Jul 2016 (Type B, pre-sBLA): In the meeting package and in a 6 Jul 2016 update, Merck provided an update of the clinical data from patients with MSI-H/MMRd cancers. FDA stated that pending review of the data, the application could potentially support the approval of pembrolizumab for the treatment of patients with metastatic, MSI-H/MMRd cancers, agnostic of tumor type. FDA informed Merck that the Agency would consider accelerated approval as an option given that limited data would be available from patients with certain tumor types (e.g., prostate cancer). FDA acknowledged that challenges may exist in conducting randomized trials in certain groups of patients with MSI-H/MMRd tumors and would consider what data would be necessary to support regular approval during the review of the sBLA.

During the meeting, to facilitate review of the data across trials, FDA requested submission of a single dataset containing demographic and response data. FDA also requested that Merck provide a discussion in the sBLA regarding the potential reason(s) for the differences in the response rates between KN16 and KN164 and whether it is scientifically appropriate to pool the data to provide an estimation of the ORR. FDA asked whether differences in dose could potentially account for the differences in ORR.

1 Aug 2016 (letter to Merck): FDA granted BTD to pembrolizumab for the treatment of patients with unresectable or metastatic non-colorectal MSI-H/MMRd positive cancers who have disease progression on or who have no satisfactory alternative treatments.

26 Oct 2016 (face to face Application Orientation Meeting): Merck provided an overview of the application including updated ORR and duration of response data from KN164 and KN158. Merck provided their justification for the 200 mg flat dose and information regarding MSI-H/MMRd testing methods. FDA and Merck held a discussion regarding revised pediatric

plans to address the tissue-agnostic indication and the submission of confirmatory data in the post-approval setting.

13 Feb 2017 (face to face meeting with Merck): Merck provided the following:

- Data regarding the biology of MSI-H/MMRd indicating why MSI-H/MMRd is an independent marker for response.
- Information pertaining to proposals for post-approval pediatric and confirmatory trials.
- Updated summary data from multiple clinical trials to support their position that 200 mg is a safe and effective dose for the proposed indication. This included updated data from KN164, KN158, KN59, and data from a French trial that investigated the effects of pembrolizumab in six subjects.
- Summary PK data to support their position.

FDA stated that Merck could submit this data in support of FDA's consideration regarding the Dosing and Administration section of product labeling; however, the totality of the information (and data) would likely need to be reviewed under a major amendment. Merck acknowledged FDA's position and planned to submit the data prior to the PDUFA deadline.

13 Mar 2017 (letter to Merck): FDA issued a major amendment letter based on Merck's 8 Mar 2016 submission extending the user fee goal date until 9 Jun 2017.

2.7 Application history

The following table summarizes the contents of amendments submitted to the BLA efficacy supplement.

Table 2: BLA submission history

Date of Submission	Purpose of Submission
8 Sep 2016	Submission of the efficacy supplement for MSI-H/MMRd cancers.
11 Oct 2016	Clarification of subject identifiers used in KN164 (submitted in response to an FDA information request during a telephone conference with Merck on 26 Sep 2016).
12 Oct 2016	Merck submitted datasets in Module 5.3.5.3, one containing tumor response data (with duration of response) and one containing subject-level demographic information. Merck also provided a revised study report.
12 Oct 2016	Merck provided a response regarding inconsistencies identified by FDA between the CRFs and the datasets related to investigator assessments of immune-related response criteria from KN16.
2 Nov 2016	Submission of corrected patient CRFs following Merck's interrogation of the source of inconsistencies in CRFs in KN16 (compared to the datasets) as well as actions undertaken in order to further verify data from KN16. The 12 Oct 2016 and 2 Nov 2016 submissions were in response to an FDA information request dated 23 Sep 2016 and two telephone conferences between FDA review staff and Merck.

Date of Submission	Purpose of Submission
14 Nov 2016	Response to an FDA information request dated 7 Nov 2016 for demographic data, PK data (if available), and efficacy data including ORR results per visit, OS, and PFS of patients with MSI-H/MMRd tumors in KN158, KN12, and KN28.
16 Nov 2016	Submission of revised labeling containing changes based on FDA approval of sBLAs S-8 and S-12.
21 Nov 2016	Based on a 7 Nov 2016 information request, Merck submitted sensitivity analyses to explore influences of patient characteristics, study design, and drug exposure on ORR, PFS, and OS across studies submitted to the sBLA.
23 Nov 2016	Merck provided the updated safety and efficacy reports to the sBLA with updated Modules 2.7.4 and 2.7.3. Merck also submitted updated datasets to support the reports.
30 Nov 2016	Merck provided a case report tabulation dataset package for KN158 in response to a 7 Nov 2016 FDA information request.
6 Dec 2016	Merck provided updated analyses pertinent to FDA's 7 Nov 2016 information request with data presented in the efficacy update report submitted to FDA on 23 Nov 2016.
16 Dec 2016	(b) (4) (b) (4) Merck stated that a new initial PSP will be submitted at a later date.
22 Dec 2016	Merck provided a response to a 7 Dec 2017 information request regarding MSI-H/MMRd testing status; per-subject listings of prior lines of therapy from patients in KN16C; and underlying cancer types of patients enrolled across Merck's clinical trials.
11 Jan 2017	In response to FDA's 21 Dec 2017 information request, Merck provided an exploratory analysis of ORR in patients with MSI-H/MMRd tumors by PD-L1 status. Merck also provided a summary table of ORR by type of test used to select patients.
18 Jan 2017	To facilitate discussion regarding a Subpart E confirmatory trial, FDA requested that Merck submit an update regarding the totality of patients enrolled in the MSI-H/MMRd program (including number of patients enrolled with specific types of tumors). This amendment to the sBLA provided an update of patient enrollment.
23 Jan 2017	Merck provided a summary of the known clinical effects of pembrolizumab among the predominant tumor types investigated in the MSI-H/MMRd application (comparing the results in patients with MSI-H to patients with MSS tumors).
22 Feb 2017	Merck provided response rates in patients tested by IHC alone, PCR alone, and tested by both ICH and PCR. Merck also provided response rates separately across all patients, by the 10 mg/kg dose, and by the 200 mg flat dose.
3 Mar 2017	Merck provided slides presented during the 13 Feb 2017 meeting between the FDA and Merck and a White paper describing the relationship between PD-L1 expression and MSI-H/MMRd biomarkers.
7 Mar 2017	Merck provided a response to FDA's proposed Postmarketing Requirements/Commitments and proposed milestone dates for each.

Date of Submission	Purpose of Submission
8 Mar 2017	Merck provided their justification (including new data) as to why Merck believes the 200 mg flat dose is the appropriate safe and effective dose. Merck also provided PBPK analysis datasets and their rationale to support their position that PD-1 is saturated at trough steady state concentrations of pembrolizumab at doses of 200 mg every three weeks.
22 Mar 2017	Merck provided updated datasets for KN158 and KN164 to support the updated ORR efficacy analyses.
24 Mar 2017	Merck provided updated labeling.
2 May 2017	Merck provided updated language and milestone dates for the PMCs to assess for MSI-H and MMRd.
15 May 2017	Merck submitted amended labeling following the approval of sBLA S-16.
16 May 2017	Merck submitted an amended Medication Guide.
18 May 2017	Based on an FDA information request dated 17 May 2017, Merck provided updated language and milestone dates for the PMCs to assess for MSI-H and MMRd.
22 May 2017	Merck submitted updated labeling following the approval of sBLAs S-17 and S-18.
22 May 2017	Merck provided updated language and milestone dates for the Subpart E PMR and the PMR to assess safety in pediatric patients with primary CNS malignancies.

3. CMC

Dr. Mark Paciga agreed with Merck's request for a categorical exclusion from the environmental assessment and that appropriate drug product supplies were used in the clinical trials.

According to the CMC review, the drug substance (DS) used in certain clinical trials (including KN164) was manufactured at (b) (4) which is not approved for commercial release. According to the CMC review, Merck provided data from release testing, extended characterization studies, forced degradation studies and stability studies to demonstrate that this material is comparable to the licensed product (IND 110,080, SD# 1095), and that the drug product manufactured from the (b) (4) DS is sufficiently representative of the commercial material for use in pivotal clinical studies.

According to the CMC review, it was not clear whether the DS used to manufacture the drug product (DP) in the pembrolizumab 50 mg/vial used in KN16 was manufactured at clinical (b) (4) or licensed sites. However, given that the pembrolizumab drug product manufactured from (b) (4) DS is sufficiently representative of the commercial material, the use of these products was considered acceptable.

4. Nonclinical Pharmacology/Toxicology

This section is not applicable to this efficacy supplement.

5. Clinical Pharmacology

OCP's amended review, dated May 10, 2017, provided the following recommendations: (1) both the 2 mg/kg every three week and 10 mg/kg every two week dosing regimens should be available for the treatment of MSI-H patients given the effectiveness of both regimens and incremental benefit of the higher dose; and (2) further evaluation of accumulating data to determine whether both dose regimens should be made available for approved indications including melanoma and NSCLC. The OCP recommendations were based on comparisons of ORR across trials that administered different doses of pembrolizumab to patients and on analyses of results observed in patients with melanoma and lung cancer. This reviewer's findings regarding dosing will be provided in Sections 7.2 and 7.3 of this review.

6. Clinical Microbiology

This section is not applicable to this efficacy supplement.

7. Clinical/Statistical-Efficacy

Dr. Leigh Marcus recommended accelerated approval of the sBLA, as amended, based on the safety and efficacy data submitted in the sBLA. The amended review completed on April 27, 2017, recommended approval of the 200 mg dose administered every three weeks.

Dr. Weishi (Vivian) Yuan concluded that based on the data and analyses described in the original sBLA (prior to the update), the results demonstrated a 35.6% ORR in pembrolizumab-treated patients. Dr. Yuan deferred the decision regarding the risk-benefit assessment to the clinical review team.

This section of the CDTL review will focus on the demonstration of efficacy in the clinical trials submitted in support of this application. Given that this will be the first application approved for the treatment of patients based solely on a biomarker and independent of cancer type, given Breakthrough Therapy designation status, and given delayed responses to checkpoint inhibition observed in patients with MSI-H/MMRd cancers, FDA agreed during the pre-sBLA meeting that Merck could submit updated efficacy data (November 23, 2016, efficacy update) which included confirmation of patient responses (i.e., certain patients had unconfirmed responses in the initial sBLA submission which were subsequently confirmed with additional follow-up).

FDA also accepted Merck's submission of updated response data during the review of the sBLA in order to further assess whether dose affected outcomes in patients with MSI-H/MMRd tumors. This submission was received on March 8, 2017, and was reviewed as a major amendment to the sBLA.

The efficacy review below will focus on the results of the November 23, 2016, efficacy update and the March 8, 2017, efficacy update.

7.1 Background of clinical program

The efficacy of pembrolizumab was evaluated in patients with MSI-H or MMRd solid tumors enrolled in one of five uncontrolled, open-label, multi-center, single-arm trials. The trials

enrolled 90 patients with MSI-H/MMRd CRC and 59 patients with other MSI-H/MMRd cancers.

Patients received either pembrolizumab 200 mg every 3 weeks or pembrolizumab 10 mg/kg every 2 weeks until unacceptable toxicity, or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. For regulatory purposes, the major efficacy outcome in all trials was ORR as assessed by blinded independent central radiologists' (BICR) review according to RECIST 1.1 and duration of response. The clinical trials also included investigator assessments of response and assessments of other endpoints including PFS and OS.

Clinical data from the following five trials conducted in adult patients were submitted to the sBLA. For brevity, statistical considerations and common aspects of trial design (e.g., single arm design) will not be described below (refer to clinical and statistical reviews). Merck initiated all trials except for KN16.

Table 3: Description of MSI-H/MMRd clinical trials

Trial identifier	Trial summary
KN16	• Investigator-initiated (i.e., non-commercial), 6 site trial • Population: - (KN16A) patients with mCRC who received two or more lines of systemic therapy **(n=28)** - (KN16C) patients with other tumors who received at least one prior line of systemic therapy **(n=30)** • Dose: 10 mg/kg every two weeks • MSI-H/MMRd testing: local PCR or IHC
KN164	• Population: patients with mCRC who received prior oxaliplatin, fluoropyrimidine, and irinotecan [with or without an anti-VEGF inhibitor and an EGFR inhibitor (if RAS wild-type)] **(n=61)** • Dose: 200 mg every three weeks • MSI-H/MMRd testing: local PCR or IHC
KN12	• Population: PD-L1-positive, previously treated patients with triple-negative breast cancer, urothelial cancer, gastric cancer, or head and neck cancer • Dose: 10 mg/kg every two weeks (for the 6 patients with MSI-H cancers) • MSI-H/MMRd testing: **retrospectively** identified patients who were MSI-H using a central PCR test (297 patients enrolled as of 8 Oct 2014; tissue available from 96 patients for MSI-H testing; **6 were MSI-H**)
KN28	• Population: PD-L1-positive, previously treated patients enrolled in one of 20 disease-specific cohorts • Dose: 10 mg/kg every two weeks • MSI-H/MMRd testing: **retrospectively** identified patients who were MSI-H using a central PCR test (475 patients enrolled as of 20 Jun 2016; tissue available from 265 subjects; **5 were MSI-H**)

Trial identifier	Trial summary
KN158	• Multi-cohort trial with the following populations: - Patients with MSI-H/MMRd tumors (other than CRC) assessed based on local testing (cohort K) - Separate cohorts of patients with one of 11 rare tumor types • Dose: 200 mg every three weeks • MSI-H/MMRd testing: local PCR or IHC for cohort K (n=16) **or** central MSI-H PCR testing for patients enrolled in one of the disease specific cohorts (**3 of 54** patients with available tumor samples from biliary and endometrial cancer cohorts tested positive for MSI-H).

To support the risk/benefit assessment of the 200 mg every three week pembrolizumab dosing regimen, Merck submitted efficacy data on March 8, 2017, from 58 additional patients from KN-158 with at least 18 weeks of follow-up (77 total subjects). Merck also submitted data from 7 patients with gastric cancer retrospectively identified as MSI-H using a central PCR-based test in Study KN59.[146] KN59 is a clinical trial enrolling cohorts of patients with gastric cancer. Patients received 200 mg pembrolizumab every three weeks in KN59. Merck also provided summary information from 6 patients (5 with CRC and one with small bowel cancer) enrolled in a French Temporary Authorization for Use (ATU) program. ATU is a French regulatory provision that allows for treatment of patients prior to marketing authorization (compassionate use).[147] Tumor responses in the French program were assessed by investigators, and patients received 2 mg/kg pembrolizumab every three weeks.

Although not necessary to approve this application, in order to assess consistency of results with other publically available data, I will summarize data presented at the 2017 Gastrointestinal Cancers Symposium (GI ASCO) that described the Mayo Clinic experience with pembrolizumab for the treatment of patients with MSI-H/MMRd CRC.[148] The Mayo Clinic report retrospectively identified 17 patients with MSI-H/MMRd CRC who received pembrolizumab between May 2015 and September 2016 (all patients were included if they had MSI-H/MMRd mCRC and received pembrolizumab). Thirteen of the 17 patients received at least two prior lines of therapy. All patients received 2 mg/kg every three weeks except one patient who received 200 mg every three weeks and one patient who received 10 mg/kg every two weeks. The poster report described responses determined at the time of the first imaging assessment (response criteria were not specified). The poster report also provided (uncontrolled) estimates of PFS and OS using Kaplan-Meier methodology. Other reports of responses to pembrolizumab in patients with MSI-H/MMRd cancers (including at the 200 mg dose) have been presented or published in the literature[149-151]; however, because they are limited to case reports (without denominators) or include combination regimens, they will not be further discussed in this review.

7.2 Efficacy results (Nov 2016 efficacy analysis and Mar 2017 efficacy update, limited to additional follow-up data from patients included in the November submission)

A total of 149 patients with MSI-H or MMRd cancers were identified across five clinical trials. Among these 149 patients with MSI-H/MMRd cancers, the baseline characteristics

were: median age 55 years (36% age 65 or older); 44% female; 56% male; 77% White, 19% Asian, 2% Black; and ECOG PS 0 (36%) or 1 (64%). Ninety (60%) of the 149 patients had CRC with the remainder diagnosed with other tumor types (refer to efficacy results by tumor below). Ninety-eight percent of patients had metastatic disease and 2% had locally advanced, unresectable disease. Sixty-nine (46%) patients received pembrolizumab 10 mg/kg every 2 weeks while 80 (54%) patients received pembrolizumab 200 mg every 3 weeks.

The identification of MSI-H or MMRd tumor status in the majority of patients (135/149) was prospectively determined using local laboratory-performed, investigational PCR tests for MSI-H status or IHC tests for MMRd status. Tumors from fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from patients in three trials using a central laboratory-developed PCR test. Forty-seven patients had MMRd cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.

Table 4 describes the independent radiology review (IRC)-determined overall response rates by trial per RECIST 1.1. Differences in response rates across the five trials will be discussed in Section 7.3 below. Durable responses have been observed among patients with cancers which have historically demonstrated low response rates to chemotherapy (e.g., third or greater line CRC or previously treated pancreatic cancer). In addition, complete responses have been observed in some patients across the development program. Nine complete responses were described in the Nov 2016 clinical study report. In the March efficacy update, an additional patient with CRC converted from a partial response (PR) to a complete response (CR) (unconfirmed) and two patients with non-CRC tumors enrolled in KN 158 converted from PRs to CRs. Complete and durable radiographic disappearance of cancer in patients with heavily pre-treated solid tumors is unexpected and should represent a beneficial treatment effect in these patients.

Table 4: IRC-assessed ORR results by trial

Trial/dose	**N**	**ORR % (95%CI) (N=149)**	**ORR % Update (N=149)**
		Nov 2016	*Mar 2017*
KN16A (10 mg/kg)	28	50.0 (30.6,69.4)	no update
KN16C (10 mg/kg)	30	46.7 (28.3,65.7)	no update
KN012 (10 mg/kg)	6	50.0 (11.8, 88.2)	no update
KN028 (10 mg/kg)	5	80.0 (28.4, 99.5)	no update
KN164 (200 mg)	61	24.6 (14.5, 37.3)	27.9 (17.1, 40.8)
KN158 (200 mg)	19	31.6 (12.6, 56.6)	36.8 (16.2, 61.6)
Overall	**149**	**37.6 (29.8, 45.9)**	**39.6 (31.1, 47.2)**

Table 4 shows that the response rate increased (modestly) in Studies KN164 and 158 with additional follow-up. Such an effect may occur because median time to response in patients with MSI-H/MMRd cancers is approximately three months. Among the 56 subjects with IRC-confirmed CR or PR in the Nov 2016 analysis, median time to response was 2.7 months and ranged from 1.7 months to 8.4 months (one response was identified at 10.4 months in the March update). The delayed conversion of PR to CR in KN158 also shows that responses may deepen over time.

Table 5 shows that responses have been observed across disparate tumor types supporting the hypothesis that MSI-H/MMRd can predict for response to immunotherapy regardless of the underlying malignancy. Given the limited number of patients, additional data will be obtained by Merck post approval to assess whether there are any unexpected findings related to tumor-treatment interactions. Nevertheless, durable responses have been observed in patients with late-line CRC, pancreatic cancer, and other tumors with a dismal prognosis and clear unmet medical need. Durable responses in such patients without available therapy (and with a favorable risk-benefit profile observed across other tumor types) could offer benefit and the prospect of improved outcomes.

Table 5: Response rate by tumor type (Nov submission)

	N	Responses
GI cancers		
CRC	90	30 (33%)
Biliary/ampullary	11	3 (27%)
Gastric/GEJ	9	4 (44%)
Pancreatic	6	5 (83%)
Small intestine	8	3 (38%)
Esophageal	1	PR
Non GI cancers		
Endometrial	14	5 (36%)
Breast	2	2 (100%)
Prostate	2	1 (50%)
Bladder	1	Missing
Sarcoma	1	PD
Thyroid	1	NE
Retroperitoneal	1	PR
SCLC	1	PR
Renal	1	PD

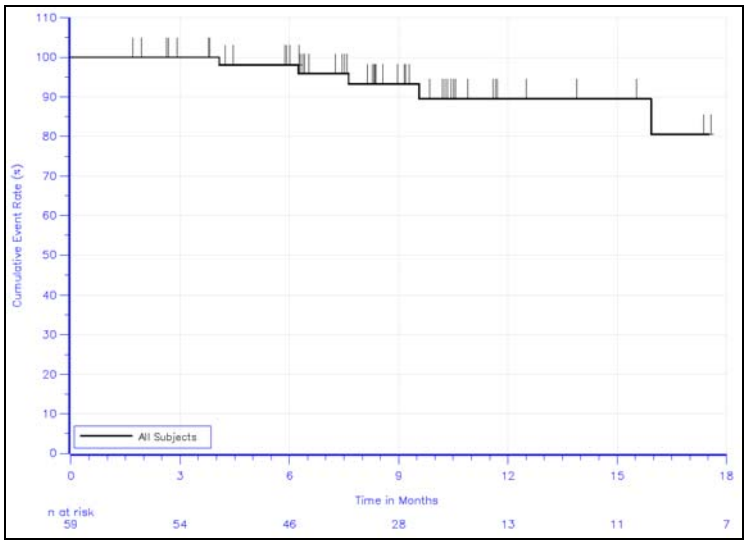
In the March update, responses were also described in patients with bladder cancer, salivary gland cancer, and sarcoma.

As indicated by Merck in a February 22, 2017, amendment to the sBLA, responses (response rate in parenthesis) were observed irrespective of whether patients were identified using immunohistochemistry (36%), PCR (33%), or both (45%). Conclusions based on these differences in ORR are limited, however, given the overall differences in ORR across the clinical trials.

Figure 11 shows that responses (for the 59 responding patients) appear durable following pembrolizumab treatment in patients with MSI-H/MMRd cancers. The median duration of response was not reached (with follow-up lasting up to 18 months); nevertheless, due to limited follow-up of patients in KN158 and KN164, additional data should be obtained to better characterize this endpoint. Response durability in the MSI-H/MMRd program, *if*

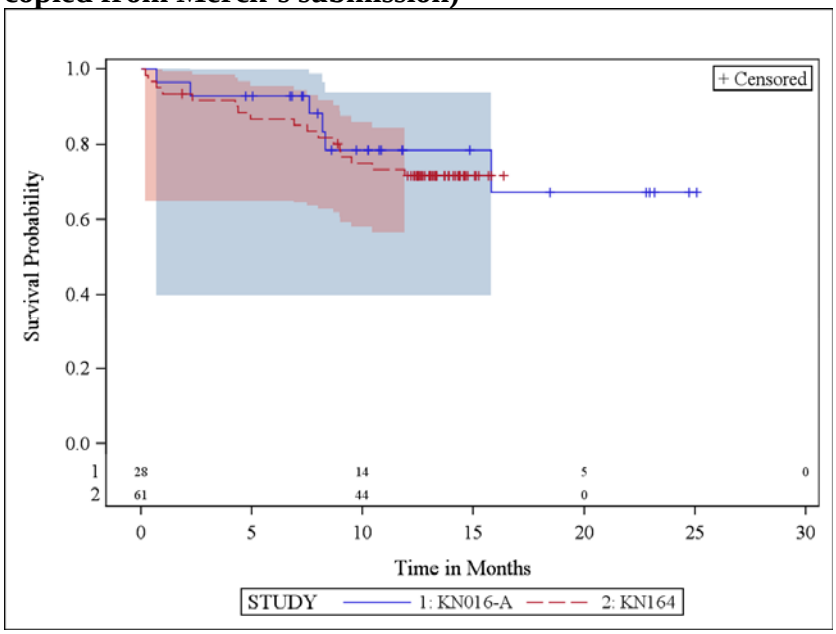
confirmed in the Subpart E PMR, would clearly be important and inconsistent with short durations of response historically observed with cytotoxic chemotherapy.

Figure 11: KM curve for duration of response (Mar 2017 update, copied from Merck's submission)



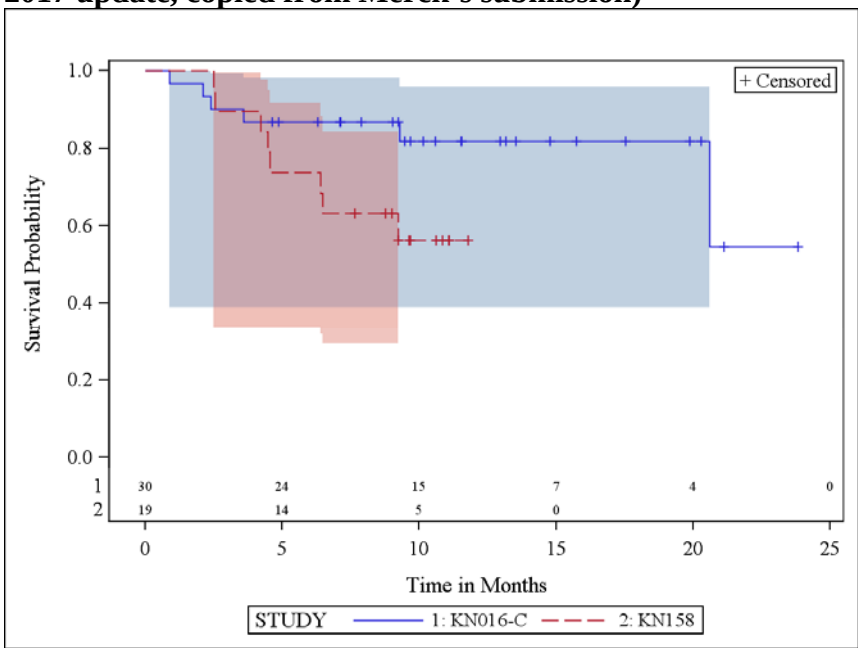
The KM curves in Figure 12 from KN164 and KN16A show that median OS has not been reached in patients with metastatic CRC treated with pembrolizumab (acknowledging limited follow-up of patients after about one year). OS observed to date is inconsistent with historical OS observed in unselected (for MSI-H/MMRd) patients with metastatic CRC treated in the third or greater line settings (where estimated median OS is 6 to 7 months). Although definitive conclusions regarding survival cannot be made in these cross-trial comparisons, results obtained to date appear encouraging, given that patients with metastatic MSI-H/MMRd CRC do not appear to have improved outcomes compared to unselected patients with metastatic CRC. Although apparent differences in exploratory analyses of ORR and PFS were observed across the two trials (Section 7.3), *at this time*, OS appeared similar between trials (acknowledging the limitations of these exploratory cross-trial comparisons and acknowledging the limited duration of follow-up).

Figure 12: KM curves for overall survival in patients with CRC (Mar 2017 update, copied from Merck's submission)



For comparison, Figure 13 below shows the KM curves for OS for patients enrolled in KN16C and KN158 (non-colorectal cancer trials). Because patients enrolled in these trials had a variety of tumor types, and due to cross-trial comparisons with a limited number of patients, interpretation of the data is limited. Nevertheless, many of the patients enrolled in these trials had previously treated gastrointestinal cancers including gastric, pancreatic, and small intestinal cancers where survival is expected to be limited.

Figure 13: KM curves for overall survival in patients with other tumors (nonCRC) (Mar 2017 update, copied from Merck's submission)



7.3 Discussion regarding dose including efficacy results submitted in the 8 Mar 2017 efficacy update

OCP's amended review, dated May 10, 2017, provided the following recommendations: (1) both the 2 mg/kg every three week and 10 mg/kg every two week dosing regimens should be available for the treatment of MSI-H patients given the effectiveness of both regimens and incremental benefit of the higher dose; and (2) further evaluation of accumulating data to determine whether both dose regimens should be made available for approved indications including melanoma and NSCLC. The amended clinical review recommended approval of the 200 mg flat dose administered every three weeks (in adults, this dose is considered to result in clinical effects consistent with the 2 mg/kg dose).

Although the 200 mg dose of pembrolizumab is described in labeling, off label prescribing of the 10 mg/kg (every two week) regimen would not be precluded based on this action (therefore, both regimens would remain available for the treatment of patients with MSI-H/MMRd cancers).

The OCP recommendations were based on comparisons of ORRs across trials that administered different doses of pembrolizumab to patients and on analyses of results observed in patients with melanoma and lung cancer. The following paragraphs will describe the updated results submitted in the major efficacy update and my rationale for recommending the 200 mg flat dose administered every three weeks. In summary, other explanations besides dose may account for cross-trial differences in ORR. These include differences in study populations, differences in study design, and chance (i.e., random "high" in an early study).

Overall response rates in the MSI-H/MMRd application

Table 4 above shows that different response rates were observed in the different trials submitted to the sBLA. *One* of the possible explanations for this difference in response rates was due to differences in doses administered across trials. Table 6 shows that the 95% confidence intervals (CIs) did not appear to overlap based on data submitted in November when patients treated with the different doses were assessed for response. Nevertheless, these differences in response cannot be considered definitive because the groups of patients who received the two doses were not randomly allocated and therefore other reasons could potentially account for differences observed between doses.

Table 6: ORR by dose (Nov 2016 submission)

Endpoint	ORR (all)	ORR 10 mg/kg	ORR 200 mg
(n)	149	69	80
% and CI	38% (30, 46)	51% (38, 63)	26% (17, 37)

As shown in Table 4 above, response rates have (modestly) increased over time in KN158 and KN164. Both studies administered the flat 200 mg dose to patients with MSI-H/MMRd cancers. Although the confidence intervals did not overlap in the November submission, the updated ORR of the 200 mg dose in the March submission is now 30% (20.3 to 41.3) with partially overlapping confidence intervals.

New data submitted in the efficacy update

In the efficacy update, Merck submitted data from additional patients enrolled in KN158 with at least 18 weeks of follow-up. Although the confirmed ORR is 30%, nearly 40% of patients have experienced either a confirmed or an unconfirmed response. As observed previously in Merck's MSI-H/MMRd development program, most patients convert from an unconfirmed to a confirmed response with additional follow-up (this is related to the delayed time to response observed following pembrolizumab treatment in patients with MSI-H/MMRd tumors).

In addition to the updated results from KN158, Merck submitted data from seven patients with gastric cancer identified as having MSI-H tumors who were enrolled in KN59. Four of these seven patients with gastric cancer experienced a response to pembrolizumab at the 200 mg dose.

Table 7: New/updated ORR results in Merck's development program

Trial	N	ORR
KN158 (confirmed ORR)	77	30%
KN158 (confirmed and unconfirmed ORR)	77	38%
KN59 (gastric)	7	57%
ATU (2mg/kg)	6 (5 colon)	33%

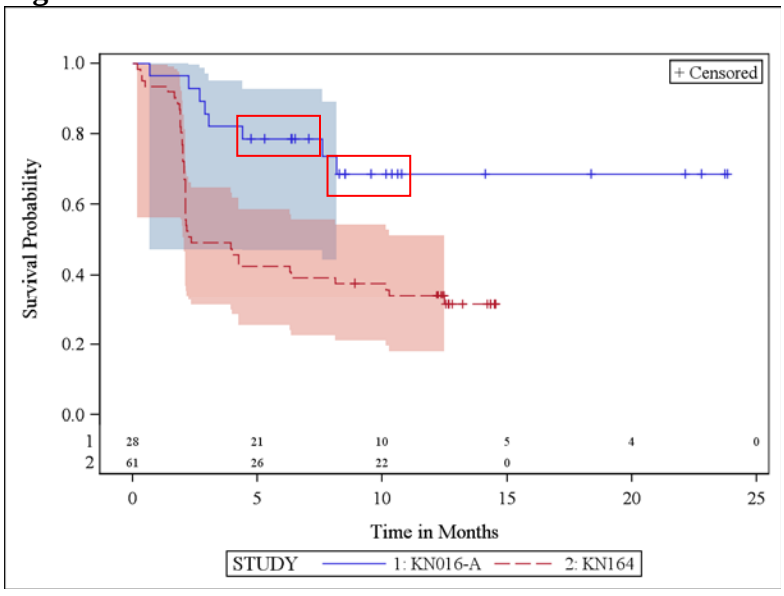
Based on this updated data, it appears that the largest differences in response rates in Merck's development program were observed in patients with *CRC* treated with the two different pembrolizumab dosing regimens. In patients with non-CRC tumors who received 10 mg/kg, the response rate was 47% in KN16C (n =30), 50% in KN12 (n=6), and 80% in KN28 (n=5).

In patients treated at the 200 mg dosing regimen, the response rate was 30 to 38% in KN158 (n=77) (this response rate *may* increase over time with increased duration of follow-up) and 57% in KN59 (n=7). Given the differences in enrolled tumor types across trials, these appear largely similar, presuming that the ORR in KN158 is confirmed to be close to 40%. Furthermore, patients identified in KN12 and KN28 were *distinct* from patients enrolled in other studies. Eligibility criteria for KN12 and KN28 required that patients have PD-L1-positive tumors; therefore, these patients had "double-positive" tumors for both PD-L1 and MSI-H/MMRd. PD-L1-positivity was not required in other trials and therefore patients' tumors could be either PD-L1-positive or negative.

Exploratory analyses of outcomes between trials in patients with mCRC

The ORR in patients with mCRC was 27.9% (95% CI: 17.1, 40.8) in the March 2017 update to the sBLA among 61 patients with mCRC in KN164 who received the 200 mg flat dosing regimen versus 50.0% (95% CI: 30.6, 69.4) in KN16A among 28 patients with mCRC who received the 10 mg/kg dosing regimen. Although OS appeared similar in the exploratory cross-trial comparison of OS (see Figure 12 above), the OCP review highlighted potential differences between KN164 and KN16 in progression free survival. The PFS KM curves, copied from Merck's submission (and similar to KM curves presented in FDA reviews), are presented in Figure 14 below. The red boxes, inserted by this reviewer, show that there were more early censored observations in the KN16 trial. In my opinion, the curves for OS and PFS are difficult to interpret in regards to the effects of pembrolizumab in patients with MSI-H/MMRd tumors given that they represent effects observed in two different trials. Interestingly, exploratory PFS curves for patients enrolled in KN16C and KN158 (non-CRC) largely overlapped (they did not separate as they did in Figure 14); nevertheless, given differences in tumor types, conclusions based on the lack of separation of these curves are limited.

Figure 14: KM curves for PFS in Studies KN16 and KN164



Differences between studies with a focus on CRC trials

Differences existed between trials and populations that, in my opinion, limit conclusions based on dose effects. Most of the data regarding ORR at the 10 mg/kg dose was derived from KN16, an investigator-initiated trial conducted at six sites, with the largest proportion of patients enrolled at Johns Hopkins University, a highly specialized referral center. The remaining 11 patients were retrospectively identified from KN12 and KN28, and were both PD-L1-positive and MSI-H.

KN16 versus KN164

KN16 was an investigator-initiated study conducted at 6 sites including Johns Hopkins, the National Institutes of Health, and Stanford (with the highest proportion of patients enrolled at Johns Hopkins). Patients enrolled at such sites may differ, for example, in their ability to travel (e.g., based on tumor burden), financial resources, or in relation to being pre-screened and referred to a study site. KN164 was an international, industry-initiated trial that enrolled patients at 21 centers across 9 countries. Although KN16 was not a single center study, literature reports have described larger treatment effects in single center studies compared to larger multi-center trials.[152,153]

The following analyses show differences among patient populations enrolled in KN16 versus KN164. The number of patients who tested positive for MSI-H/MMRd based on IHC, PCR, or both, were 25%, 25%, and 50%, respectively in KN16 versus 37%, 42%, and 22%, respectively in KN164. The racial/ethnic background of patients enrolled in KN16A and 164 also differed. KN16A enrolled 82% of patients who were White, 7% Black, 4% Asian, and 7% other or unknown whereas KN164 enrolled patients who were either White (69%) or Asian (31%). Additionally, one patient in KN164 was enrolled based on having a known germline mutation in PMS2. The patient received pembrolizumab on study; however, subsequent analysis of the patient's tumor revealed that the tumor was MMRp (this constituted a protocol deviation and the patient developed progressive disease, without response, after Cycle 3).

Differences existed among prior therapies received in the metastatic setting in KN16A and KN164 (Table 8) with a higher proportion of patients having received one or fewer lines of therapy in KN16A. An exploratory analysis of ORR by line of therapy across both studies appears to show decreasing response rates in more heavily pre-treated patients. Although definitive conclusions cannot be reached based on this analysis, it shows that factors unrelated to dose may have contributed to differences in response across trials.

Table 8: Number of prior treatment regimens (KN16A versus KN164)

Prior lines of therapy (metastatic setting)	% KN16A (n=28)	% KN164 (n=61)	ORR based on line of therapy (n=89)
0	**3.6%**	**0**	0
1	**25%**	**9.8%**	46%
2	28.6%	45.9%	39%
3	25%	21.3%	35%
4	14.3%	8.2%	22%
5 or more	3.6%	14.8%	20%

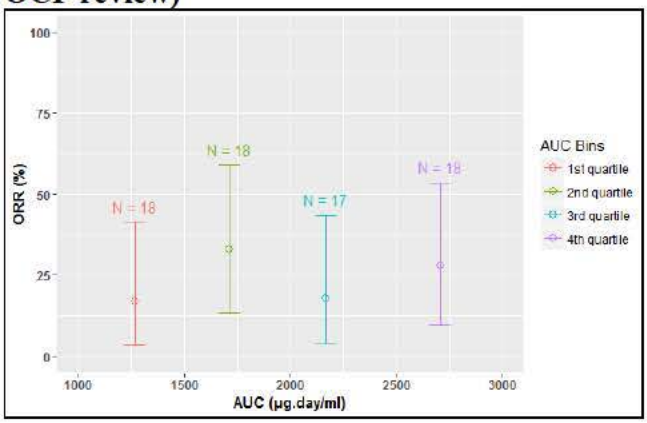
In addition to differences in prior therapy among Studies KN164 and KN16A, there were also differences in the baseline size of tumors per RECIST 1.1 among patients enrolled in KN164 and KN16A. Median tumor size was 98.7 mm (range 11.0 to 407.6) in KN164 (largest dimension among all studies) versus 83 mm (range 19.7 to 268.8) in KN16A. Although RECIST measurements are unlikely to capture overall tumor burden (e.g., it may not capture peritoneal burden), this analysis shows that tumor burden was probably higher in KN164 compared to KN16A.

Other data pertinent to dosing recommendations

Data from the Mayo Clinic (a highly specialized referral center) were presented at the 2017 Gastrointestinal Cancer Symposium.[148] These data were not included in labeling given that the assessment was a retrospective review that did not describe IRC-assessed confirmed responses and because the data were not submitted to the sBLA. Nevertheless, these data suggest that response rates can differ by site (e.g., due to differences in patient populations). Seventeen patients with MSI-H/MMRd CRC received pembrolizumab: 15 at 2 mg/kg every three weeks (comparable to 200 mg every three weeks); 1 at 200 mg every three weeks; and 1 at 10 mg/kg every 2 weeks. The response table in the poster presentation indicated that one patient experienced a CR and 7 patients experienced a PR for an overall estimated response rate of 47%. Because the poster did not indicate whether the patient at the 10 mg/kg dose experienced a response, the estimated response rate at one of the lower dosing regimens would be either 44% or 50%. This reported response rate, with a lower dose regimen (2 mg/kg or 200 mg flat dose), was consistent with the response rate of 50% in patients with CRC treated in KN16A. Like KN16A, 30% of patients received fewer than 2 prior lines of therapy. Although not conclusive, these data provide further support that factors other than dose can influence response rates.

Merck submitted exposure-response data from their two industry-initiated MSI-H/MMRd studies (KN 164 and KN158) that investigated the 200 mg every three week dosing regimen. Figure 15 shows that exposure did not appear to predict response in patients treated with the 200 mg dosing regimen. While I agree that this analysis should not be considered as conclusive evidence that clinical effects of the lower dose regimen are the same as the effects of the higher dose regimen, it provides data that there is a lack of a compelling argument to mandate labeling with the higher dose regimen. Likewise, although PK modeling data predicting target saturation (i.e., that target saturation is consistently reached at the 200 mg every three week dose) were not conclusive, the data do not suggest a compelling rationale that increasing the dose will predict for a higher response.

Figure 15: Exposure-response analyses (for ORR) in patients treated with the 200 mg every three weeks dosing regimen (copied from Merck's submission and included in the OCP review)



Summary of dosing recommendations

In summary, differences in response rates existed across trials. Potential explanations for these differences include dose, differences in trial populations, differences in trial designs, or even chance (i.e., random "high" in an early study). For comparison, as stated above, the response rates across trials of patients tested with IHC, PCR, or both tests were 36%, 33%, and 45%, respectively. Like dose, there are other factors that may account for these results independent of what tests were used. In parallel, I would not agree with a requirement that patients should undergo both tests prior to receiving pembrolizumab (given concordance rates between tests described in Section 2.3 above).

The dosing regimen that Merck requested in the application was 200 mg every three weeks. This is the same dosing regimen that the FDA approved for patients with melanoma, NSCLC, head and neck squamous cell carcinoma, classical Hodgkin's lymphoma, and is being further investigated in other Merck-sponsored studies. In the absence of compelling data (or new safety information), I do not believe that the FDA has the authority to compel Merck to include a higher dose in labeling. Likewise, the FDA could recommend but could not *require* a sponsor to submit an efficacy supplement for a new condition of use for a drug. In this application, compelling data did not exist that the higher dose provides better outcomes (i.e., that there was an incremental benefit of the higher dose). Differences in effects were only observed across trials and not within trials, and could have been caused by other factors including tumor burden or timing of treatment in the context of prior lines of therapy.

The OCP review referred to analyses of clinical effects of different dosing regimens in trials of melanoma and lung cancer in support of the higher dose regimen in patients with MSI-H/MMRd cancers. These comparisons (in Table 2 of the amended OCP S-14 review) of effects in the different dosing regimens were not statistically significant and therefore can be attributed to chance (i.e., there was insufficient evidence to reject the null hypothesis of a difference between arms/doses). Furthermore, I would not agree with an argument using a "meta-analytic" approach of combining data from both studies to require the use of the higher dose. In general, the FDA would not agree with a sponsor using such an approach to salvage a

negative clinical trial; accordingly, the FDA should not use this approach to support a scientific argument regarding the efficacy of pembrolizumab.

The FDA, including OCP, previously reviewed the data from melanoma and lung cancer trials and recommended 200 mg every three weeks as the dose to be described in product labeling. Data reviewed to support this dose included the overall clinical effects observed in these trials, dose-efficacy relationships, and exposure distributions between dosing regimens. FDA and OCP recommended the 200 mg every three week dose for S-13 and S-16, applications for melanoma and NSCLC that were reviewed and approved (on May 17, 2017 and May 10, 2017, respectively) during the review cycle for the MSI-H/MMRd application. Accordingly, it would be difficult for FDA to require a higher dose in patients with MSI-H/MMRd cancers based on differences in response rate observed across different single arm clinical trials, especially without requiring a higher dose in other tumors (noting that FDA previously reviewed the data and recommended the 200 mg flat dose regimen for every other indication).

Ultimately, I acknowledge that absolute certainty may not exist regarding dose effects. As stated above, compelling evidence does not exist that would require the Agency to mandate a higher dose of pembrolizumab in this application. This issue was discussed during a meeting with OHOP/OCE management and clinical, statistical, and clinical pharmacology reviewers on April 21, 2017, where clinical and statistical management agreed that the higher dose could not be mandated based on the results submitted in this application.

8. Safety

Discussion of primary reviewer's findings and conclusions

Analyses of safety data in this application were limited by the lack of a control arm and by limitations of the database [safety datasets were limited to data from patients enrolled in KN16A and KN164 (n = 89)]. Nevertheless, the clinical review found that the safety profile of pembrolizumab in this application was consistent with the known safety profile of pembrolizumab described in product labeling. Immune-related adverse events including Grade 3 pancreatitis, rash, and pemphigoid were observed. The rate of permanent discontinuation of pembrolizumab due to adverse events (AEs) was 5% in the MSI-H/MMRd safety population, which consisted of 2 subjects each from KN16A and KN164 (n=89). Anemia occurred more frequently in patients with colon cancer compared to the reference safety population; however, these results were difficult to interpret given the lack of a control arm.

Adverse events were generally considered comparable between dosing regimens; however, more patients required dose modifications due to adverse events in patients receiving the 10 mg/kg dosing regimen. In an analysis of KN16A versus KN164, a total of 60.7% of patients required temporary interruption of pembrolizumab due to an adverse event in the 10 mg/kg group compared with 21% who received the 200 mg flat dosing regimen. A total of 7.1% of patients in KN16A required discontinuation of pembrolizumab due to an adverse event compared to 3.3% in KN164. Conclusions based on these results are limited, however, because they are derived from cross trial comparisons with differences in overall exposure duration and differences in follow-up between trials.

9. Advisory Committee Meeting

The highly durable response rates across multiple tumor types were considered sufficient to approve this application without discussion in an advisory committee (AC) meeting. Although not discussed during an AC meeting, this application raised unique policy issues that were discussed internally with OHOP/OCE and CDER leadership during OHOP/OCE and CDER Medical Policy Committee meetings, respectively.

10. Pediatrics

Refer to Section 2.5 above.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

The sBLA contained a statement signed by the Executive Director of Global Regulatory Affairs of Merck that certified that Merck did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.2 Financial disclosures

In accordance with 21 CFR 54, the Applicant submitted a list of trial investigators and financial disclosures (FDA Form 3454) for Studies KN164 and KN16. No investigator from either trial held a financial interest or arrangement requiring disclosure per the criteria described on Form 3454.

It is unlikely that financial interests from other studies would have compromised the overall results submitted by Merck in the sBLA. The highest response rates were observed in KN16 which was audited by Merck, inspected by FDA, and confirmed by Independent Radiology Review. Responses from other studies were also confirmed by Independent Radiology Review.

11.3 GCP issues

Merck included a statement in the sBLA that the clinical trials included in this application (KN16, KN12, KN28, KN164, KN158) were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of trials including the archiving of essential documents. Merck also included a statement in the application that 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.

Section 3.1 of the clinical review described inconsistencies between certain data in case report forms (CRFs) and efficacy datasets from KN16. Upon closer inspection, these appeared limited to immune-related response criteria assessments and were in-part based on the design of the case report forms. Review of these inconsistencies found that most had no impact on the patient's overall immune-related response assessment and that there was no systematic bias by the investigators in favor of treatment with pembrolizumab. These inconsistencies were

corrected in the sBLA and other data from this trial submitted to the sBLA appeared accurate and reflective of the CRFs (and source documentation based on the ORA/OSI inspections).

I believe the primary efficacy results of KN16, the study with the highest response rates, to be reliable. To assess the validity of the efficacy data at the Johns Hopkins site, the FDA (ORA/OSI) conducted a site audit and found the data to be reliable. Furthermore, the primary results of KN16 were based on IRC assessment, which were largely consistent with investigator-assessed response determinations (ORR per RECIST was slightly higher in the IRC assessment). Finally, Merck also conducted a complete re-audit of the data from Johns Hopkins due to the minor inconsistencies in the implementation of the irRECIST criteria (which were reconciled following the audit and described in the clinical review).

11.4 Other discipline consults

11.4.1 DMPP

The Division of Medical Policy Programs provided recommendations regarding the proposed Medication Guide. Final agreement regarding labeling is pending as of the completion of this review.

11.4.2 OPDP

OPDP provided advice regarding Section 14 of product labeling. Although OPDP expressed concern regarding the presentation of data in patient subsets based on tumor type, DOP2 believed that inclusion of this data is necessary in order to provide information regarding the tissue agnostic indication. As such, DOP2 does not object to a treatment benefit being inferred in patients with different tumor types.

12. Labeling

This section of the review will focus on high-level issues regarding the labeling submitted by Merck. Numbering below is consistent with the applicable sections in product labeling.

1.5. Indications and Usage: I agree with the recommendation to revise the indication statement to better describe the indication for which accelerated approval will be granted (which requires a meaningful advantage over available therapy). Because few patients achieve durable objective responses to regorafenib or TAS-102, it is appropriate to approve pembrolizumab for patients with mCRC who received prior fluoropyrimidine, oxaliplatin, and irinotecan therapy. For other tumor types, pembrolizumab will be approved for patients who progress following prior treatment and have no satisfactory alternative treatment options. Finally, the Division recommended a limitation of use for children with MSI-H/MMRd (primary) central nervous system tumors based on uncertainty regarding safety in this group of patients who have tumor in an enclosed space (pending further experience with PD-1 inhibition in this group of patients).

2.6. Dosage and Administration: I agree with the recommendation to provide dosing information for children with previously treated, metastatic MSI-H/MMRd cancers as unmet need exists in this group of patients. The appropriate dose of pembrolizumab for children was determined during the review of the classical Hodgkin's lymphoma sBLA.

14. Clinical Studies: I agree with the recommendation to provide additional information regarding the clinical trials pertinent to this application. I also agree with the recommendation to provide results in patients with different tumor types. I acknowledge that this information may not be reliable in the assessment of results in individual tumor types (due to sample size); however, this information provides data regarding the breadth of patients enrolled with different tumor types and the justification to grant the site agnostic indication.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

I recommend (Subpart E) accelerated approval of this supplemental Biologics License Application based on substantial evidence of effectiveness that pembrolizumab can induce durable objective responses in patients with MSI-H/MMRd cancers. This evidence was observed in patients enrolled across multiple clinical trials and responses were confirmed by Independent Radiology Review.

FDA has accepted response rate as an approval endpoint for solid tumor malignancies because such responses are not expected in the absence of anti-tumor therapy (in general, in the absence of therapy, tumors grow or remain stable rather than shrinking). Tumor responses were observed across different MSI-H/MMRd cancers and across multiple clinical trial sites within and outside of the United States.

Importantly, I believe that the scientific and clinical evidence in *this* application supports the site agnostic approval, and FDA's standards for accelerated approval have been met. This should not imply that a site agnostic approach would be appropriate for every drug that targets a specific biomarker that exists across different tumor types. Different resistance mechanisms or other factors that modify treatment effect across tumors will be identified for many biomarkers (e.g., BRAF)[154]; these resistance mechanisms may preclude a sponsor's ability to develop a drug for a site-agnostic indication. Other factors including (but not limited to) treatment context (e.g., the need to administer a drug in combination with other drugs) may also limit a sponsor's ability to develop a drug for a site agnostic indication.

Refer to Section 2.4 above for a more in-depth discussion regarding the Subpart E approval and post-marketing requirements.

13.2 Risk-benefit assessment

Merck submitted this efficacy supplement (Supplement 14, BLA 125514) for pembrolizumab (trade name, Keytruda) which is to be indicated for the treatment of patients with unresectable or metastatic, microsatellite instability-high, or mismatch repair deficient, solid tumors

(b) (4)

I recommend approval of this application under Subpart E (accelerated approval) pending agreement regarding final labeling and agreement regarding post-marketing commitments and requirements. This approval is based on the observation of durable objective responses in patients with MSI-H/MMRd tumors and the strong biological rationale supporting the site agnostic effects of pembrolizumab in patients with MSI-H/MMRd tumors which was described in Section 2.1 of this review.

Unselected (for MSI-H/MMRd) patients with metastatic colorectal cancer who have previously received a fluoropyrimidine, oxaliplatin, and irinotecan clearly have a life-threatening disease and median survival of patients who receive third-line therapy (e.g., with TAS-102 or regorafenib) is expected to be six to seven months. Although there are limitations regarding the data describing the prognosis of patients with MSI-H/MMRd CRC in the *metastatic* setting, data appear to show that prognosis of these patients is not better, and may be worse, than unselected patients.

Prognosis is also expected to be poor for most patients with previously-treated, metastatic, solid tumor malignancies including endometrial cancer, gastric cancer, small intestinal cancer, ampullary cancer, cholangiocarcinoma, and pancreatic cancer. Although data are limited regarding the prognostic effect of MSI-H/MMRd in the metastatic setting (See Section 2.2 above), I believe that most patients with advanced solid tumor malignancies would be expected to die of their underlying cancers and unmet need exists for these patients.

This application is being approved based on durable responses observed in 30 to 40% of patients across the MSI-H/MMRd development program. This reviewer acknowledges that response rate may not capture the full benefit of PD-1 inhibitors. Nevertheless, similar response rates with PD-1 inhibitors have translated into clinical benefit (on either PFS or OS) in other indications. In addition to partial shrinkage of tumors, some patients have experienced complete radiographic disappearance of their cancers. These patients, as long as tumor is undetectable, would no longer be expected to be symptomatic (or become symptomatic) due to tumors affecting nerves or other vital organs.

Ultimately, I would expect PD-1 inhibition to become standard treatment in patients with previously-treated MSI-H/MMRd cancers (with testing of cancers for MSI-H/MMRd to become standard). Studies are ongoing to assess the effects of checkpoint inhibition in earlier line settings (e.g., KN177) in patients with CRC. Additional clinical trials may delineate whether patient-selection factors or combination strategies will play a role in the treatment of patients with MSI-H/MMRd cancers.

The primary risks related to pembrolizumab involve the occurrence of immune-related toxicites. Adverse events in patients with MSI-H/MMRd cancers were largely consistent with

the known toxicity profile of pembrolizumab observed across Merck's development program. Immune-related adverse events including Grade 3 pancreatitis, rash, and pemphigoid were observed. The rate of permanent discontinuation of pembrolizumab due to adverse events (AEs) was 5% in the MSI-H/MMRd safety population, which consisted of 2 subjects each from KN16A and KN164 (n=89).

An additional risk related to the approval of this application involves the possibility that pembrolizumab could be unexpectedly ineffective for a specific tumor type. Based on the strong biological rationale, and the clinical results observed to date, I expect this risk to be low. This risk will be somewhat mitigated because pembrolizumab will receive accelerated approval for patients who have progressed following prior treatment and have no satisfactory alternative treatment options. Therefore, patients should not be forgoing effective therapies to receive pembrolizumab. Ultimately, this risk will be mitigated through the collection of additional data in the post-approval setting.

Overall, the toxicity profile of pembrolizumab is considered acceptable when balancing the anti-tumor effects (e.g., durable responses) across different cancer types in patients with limited treatment options. Although randomized clinical trials investigating the effects of pembrolizumab in patients with MSI-H/MMRd tumors have not been completed, randomized controlled trials of pembrolizumab in other settings with high mutation burden (e.g., melanoma and NSCLC) have been completed and have demonstrated a favorable risk-benefit profile. Physicians and patients will need to individually assess the risk-benefit profile of pembrolizumab to determine if treatment is appropriate for each patient.

Consistent with other drugs intended for the treatment of patients with advanced cancer, risk will be managed through labeling (and a Medication Guide). A Risk Evaluation and Mitigation Strategy (REMS) is not needed to ensure that the benefits of pembrolizumab outweigh its risks. Although pembrolizumab can cause severe or serious toxicities, including serious immunological adverse reactions, pembrolizumab will be prescribed by oncologists who by training understand how to monitor, identify, and manage such toxicities. This approach is standard in the practice of medical oncology.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The review teams did not identify any REMS as necessary prior to a marketing authorization for this supplemental Biologics License Application. Pembrolizumab will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious toxicities caused by anti-neoplastic drugs including immunotherapy. Standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

13.4 Recommendation for other postmarketing requirements and commitments

Refer to Sections 2.4 and 2.5 of this review regarding the Subpart E PMR recommendations; to Section 2.5 for the requirement to further assess safety in children with MSI-H/MMRd primary CNS tumors; and Section 2.3 for the PMCs regarding the development of companion diagnostic tests to identify patients with MSI-H/MMRd cancers.

References

1. Timmermann B, Kerick M, Roehr C, et al. Somatic mutation profiles of MSI and MSS colorectal cancer identified by whole exome next generation sequencing and bioinformatics analysis. PLoS One 2010;5:e15661.
2. Cancer Genome Atlas N. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330-7.
3. Zhao H, Thienpont B, Yesilyurt BT, et al. Mismatch repair deficiency endows tumors with a unique mutation signature and sensitivity to DNA double-strand breaks. Elife 2014;3:e02725.
4. Lin EI, Tseng LH, Gocke CD, et al. Mutational profiling of colorectal cancers with microsatellite instability. Oncotarget 2015;6:42334-44.
5. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-20.
6. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010;138:2073-87 e3.
7. Dudley JC, Lin MT, Le DT, Eshleman JR. Microsatellite Instability as a Biomarker for PD-1 Blockade. Clinical cancer research : an official journal of the American Association for Cancer Research 2016;22:813-20.
8. Ligtenberg MJ, Kuiper RP, Chan TL, et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. Nature genetics 2009;41:112-7.
9. Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513:202-9.
10. Cancer Genome Atlas Research N, Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67-73.
11. Bouffet E, Larouche V, Campbell BB, et al. Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency. J Clin Oncol 2016;34:2206-11.
12. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Jr., Kinzler KW. Cancer genome landscapes. Science 2013;339:1546-58.
13. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.
14. Gubin MM, Zhang X, Schuster H, et al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. Nature 2014;515:577-81.
15. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science 2015;348:69-74.
16. Maletzki C, Schmidt F, Dirks WG, Schmitt M, Linnebacher M. Frameshift-derived neoantigens constitute immunotherapeutic targets for patients with microsatellite-instable haematological malignancies: frameshift peptides for treating MSI+ blood cancers. Eur J Cancer 2013;49:2587-95.
17. Segal NH, Parsons DW, Peggs KS, et al. Epitope landscape in breast and colorectal cancer. Cancer Res 2008;68:889-92.
18. Howitt BE, Shukla SA, Sholl LM, et al. Association of Polymerase e-Mutated and Microsatellite-Instable Endometrial Cancers With Neoantigen Load, Number of Tumor-Infiltrating Lymphocytes, and Expression of PD-1 and PD-L1. JAMA Oncol 2015;1:1319-23.

19. Giannakis M, Mu XJ, Shukla SA, et al. Genomic Correlates of Immune-Cell Infiltrates in Colorectal Carcinoma. Cell Rep 2016;17:1206.
20. Llosa NJ, Cruise M, Tam A, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov 2015;5:43-51.
21. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167-75.
22. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
23. Lipson EJ, Sharfman WH, Drake CG, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clinical cancer research : an official journal of the American Association for Cancer Research 2013;19:462-8.
24. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.
25. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189-99.
26. Van Allen EM, Miao D, Schilling B, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science 2015;350:207-11.
27. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389:67-76.
28. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909-20.
29. Shia J, Ellis NA, Paty PB, et al. Value of histopathology in predicting microsatellite instability in hereditary nonpolyposis colorectal cancer and sporadic colorectal cancer. Am J Surg Pathol 2003;27:1407-17.
30. Shia J, Black D, Hummer AJ, Boyd J, Soslow RA. Routinely assessed morphological features correlate with microsatellite instability status in endometrial cancer. Hum Pathol 2008;39:116-25.
31. Alexander J, Watanabe T, Wu TT, Rashid A, Li S, Hamilton SR. Histopathological identification of colon cancer with microsatellite instability. Am J Pathol 2001;158:527-35.
32. Dolcetti R, Viel A, Doglioni C, et al. High prevalence of activated intraepithelial cytotoxic T lymphocytes and increased neoplastic cell apoptosis in colorectal carcinomas with microsatellite instability. Am J Pathol 1999;154:1805-13.
33. Wang Y, Wang Y, Li J, et al. Lynch syndrome related endometrial cancer: clinical significance beyond the endometrium. J Hematol Oncol 2013;6:22.
34. Nakata B, Wang YQ, Yashiro M, et al. Prognostic value of microsatellite instability in resectable pancreatic cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 2002;8:2536-40.
35. Laghi L, Beghelli S, Spinelli A, et al. Irrelevance of microsatellite instability in the epidemiology of sporadic pancreatic ductal adenocarcinoma. PLoS One 2012;7:e46002.

36. Kim JY, Shin NR, Kim A, et al. Microsatellite instability status in gastric cancer: a reappraisal of its clinical significance and relationship with mucin phenotypes. Korean J Pathol 2013;47:28-35.
37. Grogg KL, Lohse CM, Pankratz VS, Halling KC, Smyrk TC. Lymphocyte-rich gastric cancer: associations with Epstein-Barr virus, microsatellite instability, histology, and survival. Mod Pathol 2003;16:641-51.
38. Agaram NP, Shia J, Tang LH, Klimstra DS. DNA mismatch repair deficiency in ampullary carcinoma: a morphologic and immunohistochemical study of 54 cases. Am J Clin Pathol 2010;133:772-80.
39. Ruemmele P, Dietmaier W, Terracciano L, et al. Histopathologic features and microsatellite instability of cancers of the papilla of vater and their precursor lesions. Am J Surg Pathol 2009;33:691-704.
40. Walsh MD, Buchanan DD, Cummings MC, et al. Lynch syndrome-associated breast cancers: clinicopathologic characteristics of a case series from the colon cancer family registry. Clinical cancer research : an official journal of the American Association for Cancer Research 2010;16:2214-24.
41. Rosty C, Walsh MD, Lindor NM, et al. High prevalence of mismatch repair deficiency in prostate cancers diagnosed in mismatch repair gene mutation carriers from the colon cancer family registry. Fam Cancer 2014;13:573-82.
42. Dellas A, Puhl A, Schraml P, et al. Molecular and clinicopathological analysis of ovarian carcinomas with and without microsatellite instability. Anticancer Res 2004;24:361-9.
43. Boland CR, Lynch HT. The history of Lynch syndrome. Fam Cancer 2013;12:145-57.
44. Seiwert TY, Burtness B, Weiss J, et al. Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+head and neck cancer patients. Journal of Clinical Oncology 2015;33.
45. Ribas A, Robert C, Hodi FS, et al. Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature. Journal of Clinical Oncology 2015;33.
46. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-26.
47. Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clinical cancer research : an official journal of the American Association for Cancer Research 2014;20:5322-30.
48. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol 2010;28:466-74.
49. Cristescu R, Lee J, Nebozhyn M, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med 2015;21:449-56.
50. Basil JB, Goodfellow PJ, Rader JS, Mutch DG, Herzog TJ. Clinical significance of microsatellite instability in endometrial carcinoma. Cancer 2000;89:1758-64.
51. Guastadisegni C, Colafranceschi M, Ottini L, Dogliotti E. Microsatellite instability as a marker of prognosis and response to therapy: a meta-analysis of colorectal cancer survival data. Eur J Cancer 2010;46:2788-98.

52. Sinicrope FA, Foster NR, Thibodeau SN, et al. DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy. J Natl Cancer Inst 2011;103:863-75.
53. Brueckl WM, Moesch C, Brabletz T, et al. Relationship between microsatellite instability, response and survival in palliative patients with colorectal cancer undergoing first-line chemotherapy. Anticancer Res 2003;23:1773-7.
54. Gryfe R, Kim H, Hsieh ET, et al. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. N Engl J Med 2000;342:69-77.
55. Muller CI, Schulmann K, Reinacher-Schick A, et al. Predictive and prognostic value of microsatellite instability in patients with advanced colorectal cancer treated with a fluoropyrimidine and oxaliplatin containing first-line chemotherapy. A report of the AIO Colorectal Study Group. Int J Colorectal Dis 2008;23:1033-9.
56. Koopman M, Kortman GA, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer 2009;100:266-73.
57. Goldstein J, Tran B, Ensor J, et al. Multicenter retrospective analysis of metastatic colorectal cancer (CRC) with high-level microsatellite instability (MSI-H). Ann Oncol 2014;25:1032-8.
58. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol 2012;4:283-301.
59. Jin Z, Sanhueza C, Johnson B, TC; S, DW; L. Outcome of mismatch repair deficient metastatic colorectal cancer (CRC): The Mayo Clinic Experience. J Clin Oncol 2017;35.
60. Marcus L, Lemery SJ, Khasar S, et al. FDA Approval Summary: TAS-102. Clinical cancer research : an official journal of the American Association for Cancer Research 2017.
61. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909-19.
62. Stivarga Prescribing Information. 2016. (Accessed March 7, 2017, 2017, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203085s006lbl.pdf.)
63. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-12.
64. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol 2014;15:569-79.
65. Venook AN, D; Innocenti, F; Fruth, B; Greene, C; O'Neil, BH; Shaw, JE; Atkins, JN, Horvath, LE, Polite, BN; Meyerhardt, JA; O'Reilly, EM; Goldberg, RM; Hochster, HS; Blanke, CD; Schilsky, RL; Mayer, RJ; Bertagnolli, MM; Lenz, H-J. Impact of primary tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol 2016;34.
66. Brule SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer 2015;51:1405-14.

67. Chen KH, Shao YY, Chen HM, et al. Primary tumor site is a useful predictor of cetuximab efficacy in the third-line or salvage treatment of KRAS wild-type (exon 2 non-mutant) metastatic colorectal cancer: a nationwide cohort study. BMC Cancer 2016;16:327.
68. Lee MSA, S.M., Morris, J.; Jiang, Z-Q; Manyam, G.C.; Menter, D; Broom, B.M.; Eng, C; Overman, M.J.; Maru, D.M.; Hamilton S.R.; Kopetz, S. . Association of primary site and molecular features with progression-free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) after anti-epidermal growth factor receptor (EGFR) therapy. J Clin Oncol 2016;34.
69. Moretto R, Cremolini C, Rossini D, et al. Location of Primary Tumor and Benefit From Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies in Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer. Oncologist 2016;21:988-94.
70. National Comprehensive Cancer Network Guidelines Version 1.2017 (colon cancer). 2017.
71. McMeekin DS, Tritchler DL, Cohn DE, et al. Clinicopathologic Significance of Mismatch Repair Defects in Endometrial Cancer: An NRG Oncology/Gynecologic Oncology Group Study. J Clin Oncol 2016;34:3062-8.
72. Kanopiene D, Smailyte G, Vidugiriene J, Bacher J. Impact of microsatellite instability on survival of endometrial cancer patients. Medicina (Kaunas) 2014;50:216-21.
73. Ruiz I, Martin-Arruti M, Lopez-Lopez E, Garcia-Orad A. Lack of association between deficient mismatch repair expression and outcome in endometrial carcinomas of the endometrioid type. Gynecol Oncol 2014;134:20-3.
74. Nelson GS, Pink A, Lee S, et al. MMR deficiency is common in high-grade endometrioid carcinomas and is associated with an unfavorable outcome. Gynecol Oncol 2013;131:309-14.
75. Diaz-Padilla I, Romero N, Amir E, et al. Mismatch repair status and clinical outcome in endometrial cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2013;88:154-67.
76. Moxley KM, McMeekin DS. Endometrial carcinoma: a review of chemotherapy, drug resistance, and the search for new agents. Oncologist 2010;15:1026-33.
77. Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2003;88:277-81.
78. Giampieri R, Maccaroni E, Mandolesi A, et al. Mismatch repair deficiency may affect clinical outcome through immune response activation in metastatic gastric cancer patients receiving first-line chemotherapy. Gastric Cancer 2017;20:156-63.
79. Marrelli D, Polom K, Pascale V, et al. Strong Prognostic Value of Microsatellite Instability in Intestinal Type Non-cardia Gastric Cancer. Ann Surg Oncol 2016;23:943-50.
80. Zhu L, Li Z, Wang Y, Zhang C, Liu Y, Qu X. Microsatellite instability and survival in gastric cancer: A systematic review and meta-analysis. Mol Clin Oncol 2015;3:699-705.
81. Choi YY, Bae JM, An JY, et al. Is microsatellite instability a prognostic marker in gastric cancer? A systematic review with meta-analysis. J Surg Oncol 2014;110:129-35.
82. Kim SY, Choi YY, An JY, et al. The benefit of microsatellite instability is attenuated by chemotherapy in stage II and stage III gastric cancer: Results from a large cohort with subgroup analyses. Int J Cancer 2015;137:819-25.

83. Casak SJ, Fashoyin-Aje I, Lemery SJ, et al. FDA Approval Summary: Ramucirumab for Gastric Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 2015;21:3372-6.
84. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-9.
85. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224-35.
86. Roa JC, Roa I, Correa P, et al. Microsatellite instability in preneoplastic and neoplastic lesions of the gallbladder. J Gastroenterol 2005;40:79-86.
87. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-81.
88. Lamarca A, Hubner RA, Ryder WD, Valle JW. Reply to the letter to the editor 'second-line chemotherapy in advanced biliary cancer: the present now will later be past' by Vivaldi et al. Ann Oncol 2014;25:2444-5.
89. Eatrides JM, Coppola, D., Al Diffalha, S., Kim, R.D., Springett, G.M., Mahipal, A. Microsatellite Instability in Pancreatic Cancer. J Clin Oncol 2016;34.
90. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;387:545-57.
91. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol 2014;32:2423-9.
92. Gu MJ, Bae YK, Kim A, et al. Expression of hMLH1, hMSH2 and hMSH6 in small intestinal carcinomas. Hepatogastroenterology 2012;59:2228-32.
93. Overman MJ. Recent advances in the management of adenocarcinoma of the small intestine. Gastrointest Cancer Res 2009;3:90-6.
94. Balmana J, Castells A, Cervantes A, Group EGW. Familial colorectal cancer risk: ESMO Clinical Practice Guidelines. Ann Oncol 2010;21 Suppl 5:v78-81.
95. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol 2015;33:209-17.
96. Klarskov L, Holck S, Bernstein I, et al. Challenges in the identification of MSH6-associated colorectal cancer: rectal location, less typical histology, and a subset with retained mismatch repair function. Am J Surg Pathol 2011;35:1391-9.
97. Pino MS, Chung DC. Microsatellite instability in the management of colorectal cancer. Expert Rev Gastroenterol Hepatol 2011;5:385-99.
98. Zhang X, Li J. Era of universal testing of microsatellite instability in colorectal cancer. World J Gastrointest Oncol 2013;5:12-9.
99. Bao F, Panarelli NC, Rennert H, Sherr DL, Yantiss RK. Neoadjuvant therapy induces loss of MSH6 expression in colorectal carcinoma. Am J Surg Pathol 2010;34:1798-804.

100. Vilkin A, Leibovici-Weissman Y, Halpern M, et al. Immunohistochemistry staining for mismatch repair proteins: the endoscopic biopsy material provides useful and coherent results. Hum Pathol 2015;46:1705-11.
101. Bartley AN, Luthra R, Saraiya DS, Urbauer DL, Broaddus RR. Identification of cancer patients with Lynch syndrome: clinically significant discordances and problems in tissue-based mismatch repair testing. Cancer Prev Res (Phila) 2012;5:320-7.
102. Samowitz WS. Evaluation of colorectal cancers for Lynch syndrome: practical molecular diagnostics for surgical pathologists. Mod Pathol 2015;28 Suppl 1:S109-13.
103. McConechy MK, Talhouk A, Li-Chang HH, et al. Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. Gynecol Oncol 2015;137:306-10.
104. Billingsley CC, Cohn DE, Mutch DG, Stephens JA, Suarez AA, Goodfellow PJ. Polymerase varepsilon (POLE) mutations in endometrial cancer: clinical outcomes and implications for Lynch syndrome testing. Cancer 2015;121:386-94.
105. Jansen AM, Crobach S, Geurts-Giele WR, et al. Distinct Patterns of Somatic Mosaicism in the APC Gene in Neoplasms From Patients With Unexplained Adenomatous Polyposis. Gastroenterology 2017;152:546-9 e3.
106. Konstantinopoulos PA, Matulonis UA. POLE mutations as an alternative pathway for microsatellite instability in endometrial cancer: implications for Lynch syndrome testing. Cancer 2015;121:331-4.
107. Stelloo E, Jansen AM, Osse EM, et al. Practical guidance for mismatch repair-deficiency testing in endometrial cancer. Ann Oncol 2016.
108. Murphy KM, Zhang S, Geiger T, et al. Comparison of the microsatellite instability analysis system and the Bethesda panel for the determination of microsatellite instability in colorectal cancers. J Mol Diagn 2006;8:305-11.
109. Mead LJ, Jenkins MA, Young J, et al. Microsatellite instability markers for identifying early-onset colorectal cancers caused by germ-line mutations in DNA mismatch repair genes. Clinical cancer research : an official journal of the American Association for Cancer Research 2007;13:2865-9.
110. Xicola RM, Llor X, Pons E, et al. Performance of different microsatellite marker panels for detection of mismatch repair-deficient colorectal tumors. J Natl Cancer Inst 2007;99:244-52.
111. Boyle TA, Bridge JA, Sabatini LM, et al. Summary of microsatellite instability test results from laboratories participating in proficiency surveys: proficiency survey results from 2005 to 2012. Arch Pathol Lab Med 2014;138:363-70.
112. 21 CFR 101.93(g).
113. Hall MJ, Gowen K, Sanford EM, et al. Evaluation of microsatellite instability (MSI) status in gastrointestinal (GI) tumor samples tested with comprehensive genomic profiling (CGP). Journal of Clinical Oncology 2016;34.
114. Huang MN, McPherson JR, Cutcutache I, Teh BT, Tan P, Rozen SG. MSIseq: Software for Assessing Microsatellite Instability from Catalogs of Somatic Mutations. Sci Rep 2015;5:13321.
115. Nowak JA, Yurgelun MB, Bruce JL, et al. Detection of Mismatch Repair Deficiency and Microsatellite Instability in Colorectal Adenocarcinoma by Targeted Next-Generation Sequencing. J Mol Diagn 2017;19:84-91.

116. Salipante SJ, Scroggins SM, Hampel HL, Turner EH, Pritchard CC. Microsatellite instability detection by next generation sequencing. Clin Chem 2014;60:1192-9.
117. Stadler ZK, Battaglin F, Middha S, et al. Reliable Detection of Mismatch Repair Deficiency in Colorectal Cancers Using Mutational Load in Next-Generation Sequencing Panels. J Clin Oncol 2016;34:2141-7.
118. Le Flahec G, Uguen M, Uguen A. Detection of Mismatch Repair Deficiency in Colorectal Cancers: Is It Really Time to Eliminate Immunohistochemistry? J Clin Oncol 2017;35:376-7.
119. Stadler ZK, Saltz LB. Reply to G. Le Flahec et al. J Clin Oncol 2017;35:378.
120. Food and Drug Administration Guidance for Industry, Expedited Programs for Serious Conditions - Drugs and Biologics. 2014.
121. Diaz LA, Le DT, Yoshino T, et al. KEYNOTE-177: First-line, open-label, randomized, phase III study of pembrolizumab (MK-3475) versus investigator-choice chemotherapy for mismatch repair deficient or microsatellite instability-high metastatic colorectal carcinoma. Journal of Clinical Oncology 2016;34.
122. Barone A, Hazarika M, Theoret MR, et al. FDA Approval Summary: Pembrolizumab for the Treatment of Patients with Unresectable or Metastatic Melanoma. Clinical cancer research : an official journal of the American Association for Cancer Research 2017.
123. Beaver JA, Theoret MR, Mushti S, et al. FDA Approval of Nivolumab for the First-Line Treatment of Patients with BRAFV600 Wild-Type Unresectable or Metastatic Melanoma. Clinical cancer research : an official journal of the American Association for Cancer Research 2017.
124. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-26.
125. Ferris RL, Blumenschein G, Jr., Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375:1856-67.
126. Kazandjian D, Khozin S, Blumenthal G, et al. Benefit-Risk Summary of Nivolumab for Patients With Metastatic Squamous Cell Lung Cancer After Platinum-Based Chemotherapy: A Report From the US Food and Drug Administration. JAMA Oncol 2016;2:118-22.
127. Kazandjian D, Suzman DL, Blumenthal G, et al. FDA Approval Summary: Nivolumab for the Treatment of Metastatic Non-Small Cell Lung Cancer With Progression On or After Platinum-Based Chemotherapy. Oncologist 2016;21:634-42.
128. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-13.
129. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
130. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372:2521-32.
131. Sul J, Blumenthal GM, Jiang X, He K, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the Treatment of Patients With Metastatic Non-Small Cell Lung Cancer Whose Tumors Express Programmed Death-Ligand 1. Oncologist 2016;21:643-50.
132. Xu JX, Maher VE, Zhang L, et al. FDA Approval Summary: Nivolumab in Advanced Renal Cell Carcinoma After Anti-Angiogenic Therapy and Exploratory Predictive Biomarker Analysis. Oncologist 2017;22:311-7.

133. Kazandjian D, Blumenthal GM, Luo L, et al. Benefit-Risk Summary of Crizotinib for the Treatment of Patients With ROS1 Alteration-Positive, Metastatic Non-Small Cell Lung Cancer. Oncologist 2016;21:974-80.
134. Blumenthal GM, Pazdur R. Approvals in 2016: the march of the checkpoint inhibitors. Nat Rev Clin Oncol 2017;14:131-2.
135. Blumenthal GM, Goldberg KB, Pazdur R. Drug Development, Trial Design, and Endpoints in Oncology: Adapting to Rapidly Changing Science. Clin Pharmacol Ther 2017.
136. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence - What Is It and What Can It Tell Us? The New England journal of medicine 2016;375:2293-7.
137. Avelumab (BAVENCIO). (Accessed April 11, 2017, 2017, at https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm547965.htm.)
138. Chuk MK, Mulugeta Y, Roth-Cline M, Mehrotra N, Reaman GH. Enrolling Adolescents in Disease/Target-Appropriate Adult Oncology Clinical Trials of Investigational Agents. Clinical cancer research : an official journal of the American Association for Cancer Research 2017;23:9-12.
139. Approval Letter. (Accessed April 11, 2017, 2017, at http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8042d607.)
140. Aronson M, Gallinger S, Cohen Z, et al. Gastrointestinal Findings in the Largest Series of Patients With Hereditary Biallelic Mismatch Repair Deficiency Syndrome: Report from the International Consortium. Am J Gastroenterol 2016;111:275-84.
141. Lavoine N, Colas C, Muleris M, et al. Constitutional mismatch repair deficiency syndrome: clinical description in a French cohort. J Med Genet 2015;52:770-8.
142. Wimmer K, Kratz CP, Vasen HF, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet 2014;51:355-65.
143. Geoerger B, Fox E, Pappo A, et al. Pembrolizumab in Paediatric Patients with Advanced Melanoma or A PD-L1-Positive (PD-L1+) Advanced, Relapsed, or Refractory Solid Tumour or Lymphoma: Phase 1/2 Keynote-051 Study. Pediatric Blood & Cancer 2016;63:S195-S.
144. Geoerger B, Fox E, Pappo A, Yalon M, Marshall V, Heath K. Phase 1/2 study of pembrolizumab (pembro) in children with advanced melanoma or a PD-L1-positive (PD-L1+) advanced, relapsed, or refractory solid tumor or lymphoma (KEYNOTE-051). J Clin Oncol 2016;34:suppl; abstr TPS10585.
145. Zhu X, McDowell MM, Newman WC, Mason GE, Greene S, Tamber MS. Severe cerebral edema following nivolumab treatment for pediatric glioblastoma: case report. J Neurosurg Pediatr 2017;19:249-53.
146. Fuchs CS, Denker AE, Tabernero J, et al. Pembrolizumab (MK-3475) for recurrent or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma: Multicohort phase II KEYNOTE-059 study. Journal of Clinical Oncology 2016;34.
147. Degrassat-Theas A, Paubel P, Parent de Curzon O, Le Pen C, Sinegre M. Temporary authorization for use: does the French patient access programme for unlicensed medicines impact market access after formal licensing? Pharmacoeconomics 2013;31:335-43.
148. Leal A, Paludo J, Finnes H, Grothey A. Response to pembrolizumab in patients with mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC). J Clin Oncol 2017;35:suppl 4S; abstract 714.

149. Cavalieri CC, Swanson E, Whisenant JR, Weis JR, G.W. G. Pembroliuzmab in gastrointestinal (GI) malignancies with defective DNA mismatch repair (dMMR): A single institution experience. J Clin Oncol 2017;35:suppl 4S; abstract 792.
150. Kieler M, Scheithauer W, Zielinski CC, Chott A, Al-Mukhtar A, Prager GW. Case report: impressive response to pembrolizumab in a patient with mismatch-repair deficient metastasized colorectal cancer and bulky disease. ESMO Open 2016;1:e000084.
151. Wu TH, Hsiue HC, Yuan CT, Tseng LH, Lin CC, Yeh KH. Durable response to programmed death-1 (PD-1) blockade in a metastatic gastric cancer patient with mismatch repair deficiency and microsatellite instability. J of Cancer Research and Practice 2016.
152. Bafeta A, Dechartres A, Trinquart L, Yavchitz A, Boutron I, Ravaud P. Impact of single centre status on estimates of intervention effects in trials with continuous outcomes: meta-epidemiological study. BMJ 2012;344:e813.
153. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. Ann Intern Med 2011;155:39-51.
154. Kopetz S, Desai J, Chan E, et al. Phase II Pilot Study of Vemurafenib in Patients With Metastatic BRAF-Mutated Colorectal Cancer. J Clin Oncol 2015;33:4032-8.

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

/s/

STEVEN J LEMERY
05/22/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125514/14
Priority or Standard	Priority, Major Amendment
Submit Date(s)	8 March 2017
Amended PDUFA Date	8 June 2017
Division / Office	DOP2/OHOP
Reviewer Name(s)	Leigh Marcus Steven Lemery, Team Leader
Review Completion Date	26 April 2017
Established Name	Pembrolizumab (MK-3475)
Trade Name	Keytruda
Therapeutic Class	Programmed death 1 (PD-1) receptor blocking antibody
Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	50 mg lyophilized powder in single-use vial for reconstitution 100 mg liquid solution in a single-use vial

Clinical Review
Leigh Marcus
sBLA 125514
Pembrolizumab (Keytruda) [redacted] (b) (4)

Addendum

Dosing Regimen	200mg, intravenous every 3 weeks
Indication(s)	[redacted] (b) (4)
Intended Population(s)	Previously treated patients with MSI-H cancers

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the previously reviewed Supplemental Biologics License Application (sBLA) and the data included in the major amendment to this application, I recommend approval of pembrolizumab (b) (4) at a flat dose of 200mg every 3 weeks.

1.2 Risk Benefit Assessment

The benefit-risk assessment for this BLA was based on data from 5 non-randomized, open-label clinical trials, which in total enrolled 149 patients with advanced microsatellite instability-high (MSI-H), or mismatch repair deficient cancers (dMMR). MSI-H or dMMR were identified using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Additional efficacy data with additional follow-up of the 149 patients with MSI-H cancer described in the major amendment and data from additional patients have demonstrated that 200 mg every 3 weeks is the appropriate dose of pembrolizumab that leads to clinically meaningful benefit over standard therapies in previously treated subjects with MSI-H cancer. The data from the major amendment demonstrate increasing consistency in overall response rates (ORRs) and an overlap in the ORR confidence intervals (CIs) between subjects treated at the 10 mg/kg every 2 weeks dose and those treated at the 200 mg Q3W dose. Progression-free survival (PFS) and overall survival (OS) comparisons by dose indicate overlapping CIs.

There was uncertainty in the appropriate dose for the United States package insert (USPI) based on data from the original sBLA submitted 8 Sept 2016. The ORR and corresponding CIs overlapped between the trials in which pembrolizumab was administered 10mg/kg every 2 weeks versus 200mg every 3 weeks. Additional data including longer follow up duration was requested to facilitate whether dose had the primary effect on the difference in response, and which dose to approve for the USPI. Additionally, there were differences between studies and enrolled populations in the studies which could have also contributed to differences in effects between studies.

Updated data was submitted in a major amendment including longer follow up from subjects on KN158 and KN164, and new data from French Autorisations Temporaires d'Utilisation (ATU), and 7 patients with gastric cancer from KN059.

ORRs in both KN164 and KN158 have continued to increase with longer duration of follow-up. Two patients enrolled on KN164 with stable disease (SD) converted to partial

response (PR), and 1 subject with PR converted to an unconfirmed complete response (uCR). One patient enrolled in KN158 with SD converted into PR while 2 other patients converted from PR to CR. Taken together, in the current dataset which includes 5 trials, ORR increased from 37.6% (95% CI: 29.8-45.9) to 39.6% (95% CI: 31.7-47.9).

1.3 Recommendations for Postmarket Requirements and Commitments

1.3.1 Confirmatory Study

Merck proposes that data from trial KN164 and data from trial KN158, with additional enrollment and extended duration of follow up (minimum follow-up of 12 months), will verify the durable clinical benefit and will constitute the confirmatory study to support regular approval of pembrolizumab, 200 mg every 3 weeks (Q3W), in previously treated subjects with MSI-H or dMMR cancer. KN158 protocol will be amended to enroll additional subjects into the MSI-H/dMMR cohort (Group K). As recommended by FDA, the trial will remain open until 20 subjects with each of the following common primary tumor types have been enrolled: prostate cancer, thyroid cancer, small cell lung cancer, and ovarian cancer. Enrollment of additional subjects with MSI-H biliary cancer, small intestinal cancer, and pancreatic cancer will continue until 20 subjects with each of these tumor types have also been enrolled. The Sponsor estimates that this will result in the enrollment of approximately 200 additional subjects with MSI-H cancer into KN158.

The proposed confirmatory data package will therefore consist of KN158 trial data from approximately 310 (113 + approximately 200) subjects with non-colorectal cancer MSI-H cancer of at least 20 different histologic types and a minimum of 12 months of follow-up, all treated with pembrolizumab 200 mg Q3W. Milestones dates are for finalization of KN158 protocol amendment June, 2017, interim analysis results available November, 2019, study completion date February, 2022, and final study report submission August, 2022.

1.3.2 Pediatric Post Marketing Requirement

The proposed milestone dates are submission of MSI-H/dMMR amendment to Study KN-051 in September, 2017, study completion date January, 2022, and final study report submission June, 2022. The KN-051 trial was previously reviewed under the parent IND and subsequently is enrolling.

According to the recently approved USPI for pembrolizumab for the treatment of Hodgkin's lymphoma, the concentrations of pembrolizumab were comparable in adult and pediatric patients at the same dose level of 2 mg/kg every 3 weeks. The recommended dose of pembrolizumab in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. The dose being administered in the pediatric trial, KN-051, is 2mg/kg every 3 weeks, and the applicant submitted a robust pediatric developmental

program. Based on the mechanism of action of pembrolizumamb, it would not be expected that response would differ in pediatric patients with MSI-H/dMMR tumors; therefore, it is reasonable to extrapolate the effects of pembrolizumab from adults to children. At this time, Merck is planning to enroll pediatric patients with MSI-H/dMMR tumors to confirm this effect. At this time the Division is considering whether to collect this data as a Subpart E PMR versus a PREA PMR (e.g., to collect additional safety data in children).

1.3.3 In-vitro Diagnostic Device Post Marketing Commitment

Merck has begun engagement with potential diagnostic partners to determine the feasibility of assay development and the timing for the submission of a premarket approval (PMA) application to CDRH to satisfy the post-marketing commitment is expected within 24 months after sBLA approval. Merck plans to submit Verification and Validation plans in March 2018 and submission of the PMA in March 2019. Refer to CDRH review for this PMC.

2 Introduction and Regulatory Background

2.1 Summary of Presubmission Regulatory Activity Related to Submission

The sBLA was submitted on 8 Sept 2016 and the major amendment was submitted on 8 March 2017. Refer to the original sBLA clinical review for full details of the regulatory history of this application.

3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

3.1 Clinical Pharmacology

The applicant submitted pharmacologic analyses including data from 8 randomized dose comparison studies of pembrolizumab in multiple tumor types across the clinical program showing a flat pembrolizumab dose-response relationship. Cumulatively, the trials included thousands (2000+) of patients with melanoma and non-small cell lung cancer with similar OS and PFS across doses and intervals.

4 Sources of Clinical Data

The sBLA population consisted of 149 patients with MSI-H/dMMR cancers who were treated with pembrolizumab in studies KN016, KN012, KN028, KN164, and KN158. In the major amendment, the duration of follow-up was extended in KN164 from ≥27 weeks in the Efficacy Update Report (EUR) dated 23-Nov-2016 to ≥54 weeks and in KN158 from ≥18 weeks in the EUR dated 23-Nov-2016 to ≥36 weeks. Updated efficacy information is not provided for Studies KN016, KN012, and KN028, for which sufficient durations of follow-up were presented in the sBLA.

5 Review of Efficacy

Efficacy data in 65 additional subjects with MSI-H cancer administered pembrolizumab at 200mg every 3 weeks: 58 new patients enrolled in KN158 and 7 patients with gastric cancer who received pembrolizumab in the third line (3L)+ setting from KN059, along with 6 patients from a French ATU (expanded access) program.

5.1. Analysis of Primary Endpoint(s)

Since the Efficacy Update Report, in KN164, which administered pembrolizumab at 200 mg every 3 weeks, 2 subjects with stable disease (SD) converted to partial response (PR), which translates to an ORR increase in confirmed response by Independent Review Committee (IRC) from 24.6% to 27.9%. One subject with PR converted to complete response (CR), although CR confirmation is pending.

In KN158, 1 subject with SD converted into PR, which translates to an ORR increase from 31.6% to 36.8%, while 2 (10.5%) other subjects converted from PR to CR. There were a total of 77 patients on KN158, (58 new patients enrolled) all of whom were administered pembrolizumab 200mg every 3 weeks, with ORR 29.9% (37.7% combined confirmed and unconfirmed).

Using these updated data for the 149 subjects with MSI-H cancer presented in the sBLA, a nonrandomized comparison between subjects treated with pembrolizumab at 10 mg/kg every 2 weeks and 200 mg every 3 weeks was performed. The pooled ORRs from studies which administered pembrolizumab at 10 mg/kg every 2 week dose and 200 mg every 3 week dose were 50.7% (95% CI: 38.4-63.0) and 30.0% (95% CI: 20.3-41.3), respectively, and there was an overlap in the 95% CIs. The 2 different doses appear to have similar clinical outcomes as observed in ORR with overlapping CIs.

REVIEWER'S COMMENT: The ORRs in both KN164 and KN158 have continued to increase with longer durations of follow-up. In addition, with longer durations of follow up, responses remain durable and only 1 subject in either study has developed disease progression, and the median durations of response continue to be not reached. Overall,

ORR across 5 trials increased from 37.6% (95% CI: 29.8-45.9) to 39.6% (95% CI: 31.7-47.9).

5.2 Other Endpoints

Specifically in regards to ORR by dose, there were 7 new subjects with MSI-H gastric cancer enrolled on KN059 and identified retrospectively by central PCR-based testing in which subjects who received ≥3 lines of prior therapy were treated with pembrolizumab 200 mg Q3W with ORR 57%; 4 of the 7 subjects developed responses (1 CR, PRs).

In addition, 6 patients with MSI-H/ dMMR cancers were treated in the French ATU program (5 colorectal cancer, 1 duodenal cancer; 2 mg/kg Q3W dose). Two Investigator-assessed unconfirmed responses were reported; ORR was 33% (investigator-assessed).

5.3 Analysis of Clinical Information Relevant to Dosing Recommendations

Potential explanations for the differences in the ORR (and PFS) between studies aside from dose include chance, difference in study populations and sites, and study design (refer to full clinical review). The flat dose of pembrolizumab 200mg every 3 weeks is safe and effective and is supported by data from a larger number of patients. There does not appear to be a compelling rationale at this time that would require labeling with the higher dose, especially noting that the data were collected from non-randomized single arm trials with limited patient numbers [as compared to the randomized reference population (includes patients with melanoma and non-small cell lung cancer)]. Therefore this reviewer recommends treating all patients in the above tissue-agnostic indication with 200mg every 3 weeks.

6 Review of Safety

Please defer to safety analyses documented in the original sBLA clinical review.

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

/s/

LEIGH J MARCUS
04/26/2017

STEVEN J LEMERY
04/26/2017

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125514/14
Priority or Standard	Priority
Submit Date(s)	8 Sept 2016
Received Date(s)	8 Sept 2016
PDUFA Goal Date	8 March 2017
Division / Office	DOP2/OHOP
Reviewer Name(s)	Leigh Marcus Steven Lemery, Team Leader
Review Completion Date	14 Feb 2017
Established Name	Pembrolizumab (MK-3475)
Trade Name	Keytruda
Therapeutic Class	Programmed death 1 (PD-1) receptor blocking antibody
Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	50 mg lyophilized powder in single-use vial for reconstitution 100 mg liquid solution in a single-use vial

Dosing Regimen	200mg, intravenous every 3 weeks
Indication(s)	(b) (4)
Intended Population(s)	Previously treated patients with MSI-H cancers

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

There is currently no microsatellite instability-high (MSI-H)-specific therapy for patients with MSI-H cancers who are managed using Standard of Care therapies. The majority of standard therapies for treating patients with metastatic cancer (including those with a higher prevalence of MSI-H cancer) are associated with poor clinical outcomes, and there is an unmet medical need in patients with advanced MSI-H cancer. The data presented in this application demonstrate a pembrolizumab treatment effect (200 mg every 3 weeks and 10 mg/kg every 2 weeks) that is reasonable likely to predict clinical benefit in patients with MSI-H cancer. Based on the extensive experience of pembrolizumab in other tumors, these effects on durable overall response rate (ORR) is associated with a favorable benefit/risk profile of pembrolizumab in patients with MSI-H cancer who have received previous therapy. Although this effect on durable ORR may be considered clinical benefit in and of itself (based on the unprecedented response duration in patients with previously treated metastatic cancer), residual uncertainty exists in regards to the extent of the effect across different possible tumor types. This residual uncertainty will be addressed through a post-marketing requirement to obtain additional data in patients with MSI-H cancer. Based on the data submitted to this sBLA and my review, I recommend approving pembrolizumab for the treatment of patients with MSI-H/dMMR cancers who have previously received therapy.

REVIEWER'S NOTE: *I recommend approval of this application; however, based on a 13 Feb 2017 meeting with the applicant, additional information regarding dosing will be forthcoming. Therefore, the reader is referred to an addendum for details. Additionally, as a Division, we are further considering edits to the indication statement.*

1.2 Risk Benefit Assessment

The benefit-risk assessment for this BLA was based on data from 5 non-randomized, open-label clinical trials, which in total enrolled 149 patients with advanced microsatellite instability-high (MSI-H), or mismatch repair deficient cancers (dMMR), MSI-H or dMMR were identified using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. The trials enrolled 89 patients with MSI-H/dMMR colorectal cancer (CRC) who progressed on or after at least 2 prior systemic cancer therapy regimens and 60 patients with other MSI-H/dMMR cancers (referred to as nonCRC, 15 different cancer types) who progressed on or after at least one prior systemic cancer therapy regimen. The primary efficacy population consisted of the 149 subjects and the primary endpoint was overall response rate (ORR) assessed by blinded independent review committee (BICR) using RECIST criteria 1.1. Treatment with pembrolizumab occurred until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, or occurred

with a decline in performance status. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year.

KEYNOTE016 was a single arm, activity finding trial in which data from subjects enrolled into 2 cohorts were submitted to the sBLA. KEYNOTE016A consisted of 28 subjects with advanced MSI-H metastatic CRC who had received at least 2 prior therapy regimens, and KEYNOTE016C consisted of 30 subjects with advanced MSI-H nonCRC who had received at least 1 prior regimen. All subjects were identified as MSI-H prospectively and administered pembrolizumab 10 mg/kg every 2 weeks. KEYNOTE012 was a multi-cohort biomarker trial (programmed death ligand 1, [PD-L1]) for subjects with advanced solid tumors that progressed on prior therapy or for which no standard therapy exists. Six subjects with MSI-H tumors were identified retrospectively and the dose of pembrolizumab that was administered was 10 mg/kg every 2 weeks. KEYNOTE028 was also a multicohort biomarker (PD-L1) trial for subjects with advanced solid tumors with the same eligibility criteria as KEYNOTE012, and 5 subjects were retrospectively identified as MSI-H and administered pembrolizumab 10mg/kg every 2 weeks. KEYNOTE158 was also a multicohort trial of rare tumors in which 16 subjects were identified prospectively as MSI-H in cohort K, and 3 subjects were retrospectively identified as MSI-H in cohorts B and D for a total of 19 subjects who were administered pembrolizumab 200mg every 3 weeks. KEYNOTE164 is the prospective trial of subjects with CRC previously treated with fluoropyrimidine and oxaliplatin, fluoropyrimidine and irinotecan, with or without an antiVEGF/EGFR antibody as appropriate. Sixty-one subjects received pembrolizumab 200mg every 3 weeks.

There were 56 responders from the 149 subjects across 5 trials. When assessed for efficacy with all tumor types pooled together, the subjects demonstrated a clinically meaningful ORR (pooled ORR=37.6%, confidence interval [CI] 29.8, 45.9). Fifty-two of the 56 responders were ongoing at the time of submission (range 1.6, 22.7 months), with a median duration of response that was not-reached (15.9 months, NE). The pooled ORR is better than demonstrated in clinical trials investigating treatment of patients with advanced cancers, as is the duration of response, which is improved compared to available therapies. The clinical significance and robustness of the primary ORR analysis were all supported by sensitivity analyses (refer to FDA biostatistical review).

Overall, the safety profile of pembrolizumab appears to be acceptable relative to durable responses observed in patients with advanced, MSI-H or dMMR cancers. The rate of permanent discontinuation of pembrolizumab due to adverse events (AEs) was 5% in the MSI-H safety population, which consisted of 2 subjects each from KEYNOTE016A and KEYNOTE164 (total N=89). This is less than the reference safety population (12%) which consists of 2799+ subjects with melanoma or non-small cell lung cancer (NSCLC) who have received pembrolizumab. The most common adverse drug events including laboratory abnormalities (occurring in ≥20% of patients or clinically significant) in patients with MSI-H cancers treated with pembrolizumab were fatigue, nausea, diarrhea, abdominal pain, vomiting, pyrexia, anemia (19%) arthralgia

(19%), and cough (18%). The incidence of Grades 3-5 events was similar in the MSI-H cancer population (48%) as compared to the reference safety population (45%) as well as the serious adverse events (39% vs. 37%, respectively in data submitted to original sBLA/Not the SUSAR). Adverse reactions occurring in patients with MSI H CRC were generally similar to those occurring in patients with melanoma or NSCLC. In both populations, deaths caused by AEs were similar (3% and 4%) in the MSI-H pooled safety population and reference safety population respectively. The overall safety profile was generally manageable.

The principal strength of the application is the improved ORR and durability of the responses across multiple advanced tumor types that have had historically poor and limited treatment options. Responses were demonstrated in cancers that have previously been unresponsive to checkpoint inhibitors such as pancreas cancer.

Weaknesses in this application include the uncertainty of the consistency of the results across multiple tissue histologies with the commonality that they are MSI-H, referred to as a “tissue agnostic” indication. Nevertheless, the data appear to support improvements in efficacy as measure by ORR in numerous cancer types (N=15) including for example CRC, endometrial, gastric, pancreas.

Previously approved drugs in oncology have had cancer-specific indications such as for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum based therapy, or if there is a target, for example metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. There has not been a drug approved by FDA for which there was no description of a type of cancer specified in the indication statement.

The biologic rationale suggests that MSI-H cancer represents a unique, biomarker-identified disease with a common immunobiology, and that the mechanism of action of pembrolizumab, as a monoclonal antibody inhibitor of PD-L1, has activity across tumor types.

MSI-H determination was made by PCR (polymerase chain reaction for MSI) performed centrally or locally, or IHC (immunohistochemistry for dMMR) performed locally, which the applicant suggest are assays measuring the same biological effect. PCR samples from some patients were tested from Promega to evaluate insertion or deletion of repeating units in the 5 mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21, and NR-24). At least 2 MSI loci were required to demonstrate size shifts for a MSI-H positive result. Subjects were determined to be dMMR when expression of at least 1 of 4 MMR proteins was absent by IHC.

Two distinct doses of pembrolizumab were administered among the 5 trials: 10 mg/kg every 2 weeks and 200mg every 3 weeks. The variability in dosing made it challenging to isolate the effect that different doses had on the efficacy outcome. The trials with pembrolizumab administered at 10 mg/kg every 2 weeks had more responders compared to trials with pembrolizumab administered at 200mg every 3 weeks (ORR

51%, 95% CI [38.4, 63] compared to 26%, 95% CI [17, 37.3]). Subjects from KEYNOTE016 and earlier clinical trials (KEYNOTE012 and KEYNOTE028) were administered the higher and more frequent dose of pembrolizumab. The confidence intervals do not overlap suggesting that the higher dose may be more effective. However, there are small numbers of subjects in the population submitted to the sBLA and uncertainty exists in regards to the dose effect given that the results did not come from randomized studies. Additionally the 10 mg/kg every 2 weeks dose was administered in trials that had longer duration of follow up, so the applicant suggested that the better ORR could be due to this factor (because late responses have been observed in patients with MSI-H tumors treated with pembrolizumab). (b) (4) . At the time of the completion of this review, there was no consensus to whether a PMC regarding dose would be feasible or required (and the applicant will submit new data to support the proposed 200 mg flat dose).

REVIEWER'S NOTE*: An addendum regarding recommendations for the dose will be forthcoming in response to data that will be submitted by applicant as discussed during a 13 Feb 2017 meeting.*

Pembrolizumab was relatively well tolerated in the MSI-H/dMMR subject population and the overall safety profile was largely consistent with the safety profile in the USPI. The totality of the data from the sBLA with 149 subjects across 5 clinical trials study shows a favorable benefit-risk. In conclusion, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed durations of response are clinically meaningful when considering the intended patient population and currently available therapies. The clinical benefits outweigh the risks associated with pembrolizumab administered in the MSI-H/dMMR advanced cancer population identified during the review of this sBLA.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no safety issues identified at this time requiring Risk Evaluation and Mitigations Strategies (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

A clinical post-marketing requirement (PMR) is recommended to further assess efficacy and to support traditional approval. The applicant plans to fully accrue (proposed N=180) Cohort K of KEYNOTE158 with 24 months of follow up. An additional 63 patients have accrued to KEYNOTE164 (Cohort B) with increased duration of follow up (minimum follow up of 24 months). The remainder of the MSI-H/dMMR trials remain open except for KEYNOTE012 and KEYNOTE028.

To note, KEYNOTE177, entitled "A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma", is already underway and as of 21 Dec 2016 has enrolled 76 subjects. The primary endpoint is progression free survival (PFS) and secondary objective is overall survival (OS). Although this study can assess effects of

pembrolizumab in patients with MSI-H/dMMR CRC, it would not be able to assess the effects of pembrolizumab in patients with other tumors.

As of 21 Dec 2016, 416 subjects have enrolled across the MSI-H/dMMR developmental program. The applicant states that based on current enrollment rates, the confirmatory data package (proposed N=304) could be available in 2Q 2019. The applicant (b) (4) will submit their proposed plan for studying the drug in pediatrics shortly.

2 Introduction and Regulatory Background

2.1 Product Information

Pembrolizumab is a humanized monoclonal antibody of the IgG4/kappa (IgG4κ) isotype that binds to programmed death 1 (PD-1) receptor and directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is supplied as a lyophilized powder in single-use vials for reconstitution and as a 100 mg liquid in single-use vials.

2.2 Tables of Currently Available Treatments for Proposed Indications

Colorectal Cancer

According to Surveillance, Epidemiology and End Results (SEER) data accessed on 14 October 2016 (http://seer.cancer.gov/statfacts/html/colorect.html), based on cases and deaths from 2009-13, the annual incidence rate of colorectal cancer (CRC) is, approximately 134,490 new cases of large bowel cancer, of which 95,270 are colon and the remainder rectal cancers. Approximately 49,190 Americans die of CRC each year, accounting for approximately 8 percent of all cancer deaths.[1] CRC is the third highest cause of death due to cancer in the U.S. At least 50% of patients develop metastases, and most patients with metastatic CRC are unresectable.[2]

First- and second-line therapy of advanced or metastatic CRC usually consists of the administration of oxaliplatin or irinotecan in combination with leucovorin and fluorouracil. Monoclonal antibodies are added to these regimens (e.g., an anti-VEFG pathway drug or if RAS wild-type, an anti-EGFR antibody). With the exception of metastatic disease confined to the liver and completely resected, metastatic CRC is generally considered incurable and the aim of therapy is to prolong survival and improve quality of life. The standard of care is to administer chemotherapy in first-line until the disease progresses, recurs, or the toxicity of therapy is deemed intolerable or detrimental to the patient's quality of life. Treatment of metastatic disease is a continuum of care, and if disease progresses during first-line treatment, treatment continues with a different chemotherapy regimen that has not been used before in that particular patient (for example, if a patient received an oxaliplatin-based regimen for first line, an irinotecan-based regimen may be used for the second-line treatment). For patients refractory to these agents, The National Comprehensive Cancer Network (NCCN) guideline version 2.2016 accessed on 14 October 2016

(http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf) recommend regorafenib, lonsurf, BSC, or participation in a clinical trial.

Regorafenib and TAS-102 are approved for the treatment of patients with metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy. However, due to the modest improvement in OS (less than 2 months) and side effect profile of both drugs, it is reasonable for an adequately consented patient to forgo this therapy in lieu of a clinical trial (or best supportive care). In the CORRECT trial, the activity of regorafenib noted a hazard ratio (HR) for OS of 0·77 (95% CI 0·64–0·94; p=0·0052) and a median difference in OS of 1.4 months (6·4 months with regorafenib vs 5·0 months with placebo). Objective responses were noted 1% in CORRECT.[3] In RECOURSE trial for TAS-102, the median OS improved from 5.3 months with placebo to 7.1 months with TAS-102, and the hazard ratio for death in the TAS-102 group versus the placebo group was 0.68 (95% CI, 0.58 to 0.81; P<0.001). Objective response rates of 1.6% with TAS-102 and 0.4% with placebo (P=0.29) were noted.[4]

Microsatellite-instability High Colorectal Cancer

CRC is a heterogeneous disease arising through different pathways including the chromosomal instability (CIN) pathway, the microsatellite instability high (MSI) pathway, and CpG island methylator phenotype (CIMP).[5] MSI is the molecular hallmark of mismatch repair deficiency, which results in high mutational load in MSI tumors and creates tumor specific neo-antigens, and highly activated T-helper-1 (Th1) and cytotoxic T-lymphocyte-rich (CTL) microenvironment within the tumor.[6,7] Microsatellite instability-high colorectal cancer (MSI-H-CRC) comprises approximately 15% of sporadic CRC and 5% of Stage IV CRC, whereas microsatellite stable (MSS) CRC comprises the remainder.[8]

Prognosis of stage II MSI-H CRC appears favorable compared to MSI-S CRC; however, patients with MSI-H CRC (stage II) do not benefit from 5-FU-based adjuvant therapy.[9-11]. Although the prognosis of patients with stage II or III MSI-H CRC may be favorable, the prognosis of MSI-H Stage IV CRC patients appears similar to or may be worse than patients with MSS tumors. In one report, recurrent MSI-H CRC was associated with worse overall survival (when defined as the time between initial diagnosis and death (HR: 1.363) and when defined as the time between recurrence and death (HR: 2.667).[12] The prognosis of patients with metastatic CRC who have progressed on all standard therapies generally is very poor.

MSI-H non Colorectal Cancer

Microsatellites are repetitive sequences distributed throughout the genome that consist of mono-, di-, or higher order nucleotide repeats such as (A)n or (CA)n. These sequences are more frequently copied incorrectly when deoxyribonucleic acid (DNA)

polymerases cannot bind efficiently to repair sequence errors that occur during DNA replication. Mismatch repair (MMR) proteins including MLH1, MSH2, MSH6 and PMS2 are responsible for recognizing and correcting errors in mismatched nucleotides and insertions/deletions that result from DNA polymerase slippage when microsatellites are being replicated. The MSI-H phenotype is associated with defective MMR proteins and can occur as a result of a germline mutation in one of the MMR genes (e.g., Lynch syndrome) or through methylation of an MMR gene promoter. MSI-H cancer may be considered one unique set of cancers that share a common immunobiology characterized by a high mutational burden and tumor-specific neo-antigen load mediated by MSI and common defects in MMR.

MSI-H/dMMR is observed in many types of cancers including CRC, gastric, endometrial, biliary, pancreatic, ovarian, prostate, and small intestinal cancers. According to results of the Moffitt cancer center database (results provided in the sBLA), overall, the prevalence of MSI-H/dMMR cancer is 2% to 5% across tumor histologies; it is more common in colorectal cancer, endometrial cancer, and gastric cancer). There is currently no MSI-H/dMMR-specific therapy for patients with MSI-H/dMMR cancer. Each subject with advanced cancer known to be MSI-H is managed using Standard of Care therapies. There are no approved available therapies for second line biliary, small bowel, or endometrial cancers. The majority of standard therapies for treating advanced cancers are associated with poor clinical outcomes, see Table 1.

Table 1: Efficacy Outcomes in Randomized Trials for advanced cancers that might include MSI-H (common cancers included in this sBLA, modified from submission**)**

	ORR (%)	DoR (months)	PFS (months)	OS (months)
CRC				
2L	11-21	6-7.6	4.5-6.9	11.1-17
3L	0.4-22	3.8-5.4	1.7-4.4	5-10.4
Gastric				
2L	7-28	2.8-4.4	2.3-4.4	3.6-9.6
Biliary				
2L	No randomized studies; no approved standard of care therapy			
Endometrial				
2L	No randomized studies; no approved standard of care therapy			

For CRC, the approved standard of care therapies are described in detail above "colorectal cancer." For gastric cancer, in 2014 FDA approved ramucirumab as a single agent or in combination with paclitaxel, indicated for treatment of advanced gastric or gastro-esophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine-or platinum-containing chemotherapy. There are no randomized studies nor approved therapies for 2L+ biliary or endometrial caners. Note that the trials in the table above do not delineate which subjects were MSI-H/dMMR, if any.

REVIEWER COMMENT: *Treatments administered to patients with certain cancers such as endometrial and biliary cancer in the second-line and later settings are derived*

primarily from small and uncontrolled trials, and clinical evidence from randomized trials is lacking. Therefore it is difficult to accurately measure a historical ORR for comparison. However, outcomes of patients with such tumors are generally poor and as such, unmet medical need exists for such patients.

2.3 Availability of Proposed Active Ingredient in the United States

Pembrolizumab is FDA approved for use for the following indications:

- Treatment of patients with unresectable or metastatic melanoma
- First-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [tumor proportion score (TPS) ≥ 50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations
- Treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations (prior to receiving pembrolizumab)
- (Accelerated approval) Treatment of patients with recurrent head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing therapy

2.4 Important Safety Issues With Consideration to Related Drugs

The safety profile of pembrolizumab is well characterized. Similar to other drugs targeting the PD-1 pathway, such as nivolumab, or drugs such as ipilimumab targeting cytotoxic T-lymphocyte antigen (CTLA-4), which also function as a negative regulator of immune responses, severe or serious immune-mediated adverse reactions have been observed in patients treated with pembrolizumab.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Below is a list of key regulatory history that pertains to this sBLA.

9 May 2013: *Submission of KEYNOTE016: "Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors."*

8 June 2015: Type B meeting minutes *(held 12 May 2015)*
Discussion of KEYNOTE164 "A Phase IIB Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Unresectable Locally Advanced or Metastatic Microsatellite Instability-High Colorectal Adenocarcinoma." FDA recommended that Merck power the study to rule out a higher (e.g., at least 15%) lower bound of the 95% confidence interval of the response rate.

10 June 2015: *Submission of KEYNOTE164: "A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Microsatellite Instability-High Colorectal Carcinoma."*

1 July 2015; 30 Nov 2015 iPSP for MSI-H CRC (submission; FDA agreement for MSI-H CRC).

10 July 2015: *New IND opened for KEYNOTE158.*

29 September 2015: Merck requested FDA's agreement with a proposal to identify patients with **MSI-H-tumors** (b) (4) **KEYNOTE158: "A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors."**

27 October 27 2015, FDA responded by email that the Agency did not agree with the proposal based on (b) (4). FDA stated that an alternative to central testing would be required to ensure the same reagents, protocol, and result reporting are used at all testing sites.

16 February 2016, Merck submitted an amendment containing a proposal stating that MSI-H testing could be performed using IHC or one of two specific PCR assays. Merck stated that the case report forms would collect information about methodology used to identify MSI-H status, including reagents, assay protocols, and results.

29 Oct 2015 Breakthrough Designation Therapy (BTD) granted for MSI-H CRC

22 July 2016 Type B pre-sBLA meeting minutes (meeting 13 July 2016)

FDA requested that a single dataset containing all demographic and tumor response data from all patients be submitted in the sBLA. Additionally, FDA requested that Merck provide clinical pharmacology datasets and population PK and exposure response analyses including results of Study KEYNOTE059 in support of the 200 mg every 3 weeks regimen in patients with MSI-H cancer. FDA requested that Merck provide a discussion regarding the potential reason(s) for the discrepancies in the data between Studies KEYNOTE016 and KEYNOTE164 and whether it is scientifically appropriate to pool the data to provide an estimation of the ORR. The discussion should include whether there were any differences in MSI testing (e.g., was testing in Study KEYNOTE016 more specific), differences in enrolled populations, and any other factors deemed relevant. FDA requested that Merck provide a narrative summary of all patients who developed progression/recurrence limited to the central nervous system. FDA stated that the summary should include whether the patient had CNS imaging at baseline, what treatment the patient received for the CNS metastasis, whether the patient continue to receive pembrolizumab (and for how long), and any other information deemed relevant.

1 Aug 2016 BTD granted for MSI-H cancer

30 Aug 2016 iPSP for MSI-H cancers submission

REVIEWER'S COMMENT: MSI-H nonCRC does not have an agreed upon PSP.

2.6 Other Relevant Background Information

2.6.1 MSI-H testing

In clinical oncology practice, current mismatch-repair/microsatellite-stability instability (MMR/MSI) testing with either an MMR protein immunohistochemical (IHC)-based assay or polymerase chain reaction (PCR)-based MSI loci testing is used mainly in the management of CRC, as recommended by the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology, and American Society of Clinical Oncology. According to NCCN, accessed on 14 October 2016 (https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf), either IHC-based testing or PCR-based testing has been utilized in clinical decision making because patients determined to have defective MMR status are biologically the same population as those with MSI-H status. Some comprehensive cancer centers perform IHC or MSI testing on all newly diagnosed CRC and endometrial cancers to determine which patients should have genetic testing for Lynch syndrome, a cancer predisposition syndrome.

MMR- or MSI status is generally determined by examining either tumor 1) protein expression by immunohistochemistry of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2) or 2) 3-5 tumor microsatellite loci using PCR-based assay, or 3) both. Tumors were reportedly classified as MSI high when at least 2 allelic shifts among the 3-5 analyzed microsatellite markers were detected by PCR or dMMR if there is absence of at least 1 of 4 mismatch repair proteins expression by IHC.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The amended submission was of adequate quality for the clinical review. Data in the datasets were determined to be acceptable for review through an audit of the case report forms (CRFs) versus the datasets in approximately 10% of patients in KN16.

Initially, however, inconsistencies were noted between certain data in the CRFs and SDTM efficacy datasets in KEYNOTE016. Specifically, the inconsistencies were identified in the immune-related Response Criteria (irRC) for the investigator assessed efficacy endpoint at the time that the sBLA was submitted. Based on these inconsistencies, FDA contacted Merck via an information request dated 23 Sep 2016 and held two telephone conferences dated 26 Sep 2016 and 4 Oct 2016.

Based on these FDA observations, Merck amended their BLA on 12 Oct 2016 and 2 Nov 2016. The amended BLA highlighted actions taken to address these inconsistencies.

Merck conducted an investigation, including a review by imaging experts, which included a full review of all available source documentation and CRF data from all 58 subjects in Study KN016. Merck categorized their findings into four groups.

- Incorrect implementation of imaging criteria: One error was related to implementation of RECIST 1.1. This error was in reference to recording a new lesion at week 12 instead of week 20; as such, this error would not have favored pembrolizumab. Additional errors were noted affecting the (immune) response determination of 3 patients at different specific time-points.
- Incorrect dimensions were used in the irRC assessment in two patients. One had no impact on the irRC assessment and one resulted in a patient who was classified as progressive disease at week 20 to have stable disease at this time-point.
- Data entry errors for 11 patients were noted which had no impact on response assessments.
- Case report forms were not optimized for irRC (this potentially created some of the issues related to irRC measurements).

In summary, the audit determined that the inconsistencies (between CRFs and datasets) appeared to be isolated to irRC assessments in KN016 (with one exemption that did not reclassify a patient as a responder). These data errors in the original sBLA did not systematically improve the results for pembrolizumab treatment; therefore, the inconsistencies did not appear to be related to any attempts by the sponsor or investigator to affect the results in the application.

Nevertheless, Merck corrected the patient CRFs and submitted these to the BLA on 2 Nov 2016.

REVIEWER COMMENT: The irRC is for exploratory analysis and does not have clinical significance to the primary efficacy endpoint for KEYNOTE016, which is independent central review using RECIST 1.1. This reviewer could not identify any issue that questioned the integrity of the submission. Other data evaluated from this trial appeared accurate and reflective of the CRFs and the overall assessment based on investigator RECIST 1.1 appeared accurate.

3.2 Compliance with Good Clinical Practices

The clinical trials included in the application (KEYNOTE016, KEYNOTE012, KEYNOTE028, KEYNOTE164, KEYNOTE158) contained a statement that they 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 (module 2, section 2.5 [Clinical Overview], page 15). All trials were conducted following appropriate Good Clinical Practice (GCP) standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.

An Office of Scientific Investigations (OSI) consult was requested for the clinical inspection of one trial site (Johns Hopkins). The site was selected based upon the site-specific efficacy data, and the patient enrollment at the site. This reviewer also used the JMP Clinical (version 6) tool to analyze for possible fraud at sites including searching for excessive patient visits on Saturday/Sundays or holidays, searching for patients with the same birthdates, or with blood pressures ending with the same value. The data was also queried for subjects that discontinued drug or study and frequency of adverse events (AE). No patterns questioning the data were identified in these analyses. Furthermore, OSI found the data from the Johns Hopkins site to be acceptable with a preliminary recommendation of NAI (no action indicated).

3.3 Financial Disclosures

In accordance with 21 CFR 54, the Applicant submitted a list of trial investigators (section 1.3.4, Tables 2 and 3) and financial disclosures (FDA form 3454) for Studies KEYNOTE164 and KEYNOTE016. No investigator from either study held financial interest or arrangements requiring disclosure per the criteria described on Form 2454. There were 2 investigators from KN16 that did not return the financial disclosure form (one Merck form not received and one Johns Hopkins form not received) and another investigator from KN164. The form did not specify investigator versus subinvestigator.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See the FDA Chemistry Review from the original BLA submission. There were no significant safety or efficacy issues identified related to Chemistry, Manufacturing, and Controls (CMC).

4.2 Clinical Microbiology

See the FDA Microbiology Review from the original BLA submission. There were no significant safety or efficacy issues identified related to product quality from a microbiology standpoint.

4.3 Preclinical Pharmacology/Toxicology

See the FDA Pharmacology/Toxicology Review from the original BLA submission for full details.

4.4 Clinical Pharmacology

There were significant review issues regarding dose, specifically, 200mg IV every 3 weeks at a flat dose versus 10 mg/kg IV every 2 weeks. For full details, see the FDA Clinical Pharmacology Review of the current sBLA submission.

4.4.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.[13]

The applicant submitted data on 13 Feb 2017 showing that measures of tumor antigen load/mutation burden and T-cell inflamed microenvironment have low correlation but are independently predictive. Recall that MSI-H and dMMR results in high mutational load in tumors, creating tumor specific neo-antigens, and a highly activated immune microenvironment within the tumor. High mutational load appears to predict responses in pembrolizumab across multiple tumor types.

4.4.2 Pharmacodynamics

See the FDA Clinical Pharmacology Review from the original BLA submission for general PD information.

4.4.3 Pharmacokinetics

See the FDA Clinical Pharmacology Review from the original BLA submission for general PK information. For the current submission, the Applicant proposed a fixed dosing regimen of 200 mg IV every 3 weeks. While pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg every 2 weeks) studied in the first-in-human trial of pembrolizumab, no maximum tolerated dose was identified. The Applicant states that in the pembrolizumab clinical program, flat dose-response and exposure-response relationships for efficacy were found in melanoma and NSCLC patients in the range of doses between 2 mg/kg and 10 mg/kg, and the Applicant suggested that clinical data at 2 mg/kg every 3 weeks is on or near the plateau of the exposure-response curve achieving maximal clinical efficacy.

The dose selected for study in KEYNOTE016 was the highest dose studied, 10 mg/kg every 2 weeks. The Applicant later selected the fixed dose of 200 mg every 3 weeks for KEYNOTE164, KEYNOTE158 and in later phase clinical trials based on simulations performed using the population PK model of pembrolizumab. Per the Applicant, according to this model the fixed dose of 200 mg every 3 weeks will: 1) provide exposures that are optimally consistent with those obtained with the 2 mg/kg every 3 weeks dose, the 3 mg/kg and 10 mg/kg doses as well 2) maintain individual patient exposures in the exposure range established in melanoma as associated with maximal

efficacy response; and 3) maintain individual patient's exposure in the exposure range established in melanoma that are well tolerated and safe.

Based on population PK analysis, the exposure with pembrolizumab 200 mg every 3 weeks is approximately 30% higher than with a 2 mg/kg every 3 weeks dosage regimen. The exposure with the 10 mg/kg every 2 weeks dosage regimen is approximately 4-fold higher than the exposure with the 200 mg every 3 weeks fixed dose. For specific details related to the fixed dosing regimen versus 10 mg/kg IV every 2 weeks, see the FDA Clinical Pharmacology Review of the current sBLA submission.

Also refer to the differences in clinical effects observed in the efficacy section of this review between the two different dosing regimens investigated in the MSI-H/dMMR development program.

REVIEWER'S NOTE: *There was a meeting on 13 Feb 2017 and data regarding recommended dose was discussed. The applicant plans to submit additional data to support the flat dose 200mg IV every 3 weeks. A discussion and recommendation regarding dose will be in an addendum to this review.*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Table of Clinical Trials of subject data submitted to sBLA

Trial	Design/Eligibility	n of N (if applicable)	MSI-H test	Dose	Tumor Types
016 (JHU)	Single arm, activity finding, 6 sites **CRC**: received ≥ 2 prior therapy regimens **nonCRC**: ≥1 prior therapy regimen	28 CRC 30 non CRC	Prosp PCR IHC local	10mg/kg q2w	Endometrial 9 Ampullary/biliary 7 Pancreatic 4 Small bowel 4 Gastric 3, sarcoma Prostate, thyroid
164	**Single arm, multicenter, CRC:** ≥1 prior therapy regimen fluoro+ox, fluoro+irino +/- anti-VEGF/EGFR mAb	61	Prosp PCR IHC local	**200mg q3w**	CRC
012	Multi-Cohort PD-L1 advanced solid tumors failed prior tx, no std tx. Measurable dz.	6 of 297	Retro PCR local	10mg/kg q2w	Gastric 4, breast Bladder

028	Multi-Cohort PD-L1 advanced solid tumors failed prior tx, no std tx, std tx not appropriate. Measurable dz.	5 of 475	Retro PCR local	10mg/kg q2w	Esophageal, Cholangio, breast Endometrial, CRC
158	Multi-Cohort rare tumor basket study advanced cancer. 1st line standard tx has failed. (Prosp: Cohort K; Retro:Cohorts B,D)	19 of 713 (still enrolling at time of submission)	Both PCR IHC local	**200mg q3w**	SCLC, gastric, pancreatic, SB
Total	**5 trials**	**149**	**60 subjects with nonCRC MSI-H tumors**		

Key: Tx=therapy, Prosp=prospectively tested for MSI; Retro=retrospectively tested for MSI, SCLC=small cell lung cancer, std=standard, dz=disease

5.2 Review Strategy

The clinical review is based on the Clinical Study Reports (CSRs) for the pivotal studies, KEYNOTE016 "Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors," and KEYNOTE164, "A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Microsatellite Instability-High Colorectal Carcinoma," outlined in Section 5.1, as well as the Integrated Summary of Safety (ISS), the Integrated Summary of Efficacy (ISE), the updated Summary of Clinical Efficacy (SCE), and the updated Summary of Clinical Safety (SCS) – Safety Update Report which has data from KEYNOTE012, KEYNOTE028, and KEYNOTE158. The data cut-off dates for the initial sBLA submission for KEYNOTE016 and KEYNOTE164 including the CSRs, ISS, ISE, and narratives were 19 Feb 2016 (16A), 13 Apr 2016 (16C), and 3 June 2016 (164). The data cut-off date for the updated safety and efficacy analyses of KEYNOTE158 included in the updated SCE and SCS was 17 Aug 2016, and the data cut-off date for the updated efficacy analysis of KEYNOTE164 was 3 Aug 2016. Among the items reviewed were primary datasets (for baseline characteristics, efficacy, and toxicity) submitted by the Applicant, selected case report forms (CRFs), selected narratives, and a literature review of agents studied for the treatment of recurrent or metastatic CRC and MSI-H/dMMR cancers.

REVIEWER COMMENT: *There was 1 subject on KEYNOTE158 who had response confirmed on 18 Oct 2016, and 3 subjects on KEYNOTE164 who had responses confirmed on 23 Aug 2016, 12 Sept 2016, and 15 Sept 2016. FDA agreed to accept the data for unconfirmed responses from these four patients that were confirmed after the original cut-off date submitted in the sBLA.*

Using the primary patient data from the 5 clinical trials, the statistician confirmed the Applicant's efficacy analyses; supplementary efficacy analyses were also conducted. The clinical reviewer confirmed the Applicant's safety analyses of the pivotal and the supportive studies, conducting analyses of primary data using the MedDRA Adverse

Event Diagnostics (MAED) program. Methods used to perform analyses for specific issues (i.e., detailed assessment of a particular safety issue), are explained in the pertinent section of the review.

The Review of Efficacy in Section 6 is focused primarily on the efficacy results of KEYNOTE016 and KEYNOTE164, and subjects with MSI-H (or dMMR) cancer from KEYNOTE012, KEYNOTE028, and KEYNOTE158.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 KEYNOTE 016

KEYNOTE016 (KN016) is an open label, activity finding, unblinded single arm trial that enrolled patients with MSI-H advanced cancers. Patients enrolled into the trial received pembrolizumab 10mg/kg intravenously every 2 weeks for up to 24 months. Three cohorts of subjects were enrolled to receive pembrolizumab: patients with MSI-H CRC who received at least 2 prior cancer therapy regimens (Cohort A); patients with MSI-H negative CRC and at least 2 prior cancer therapy regimens (Cohort B); and patients with MSI-H solid tumor malignancies other than CRC who received at least 2 prior cancer therapy regimens (Cohort C). The primary objectives were to determine the objective response rate (ORR) at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma, and MSI positive nonCRC adenocarcinoma, treated with pembrolizumab. Statistical considerations are outlined in 9.4.1 KEYNOTE 016.

Evaluable patients were confirmed using the MSI Analysis System from Promega at Johns Hopkins which is a PCR based method used to detect microsatellite instability (MSI). Key inclusion criteria consisted of subjects with measureable disease, and subjects with CRC must have received or refused at least 2 prior cancer therapy regimens. Patients with other cancer types must have received or refused at least 1 prior cancer therapy regimen. Notable for this investigator-initiated trial was that subjects with >50% of liver involvement were excluded from the study initially, but then the study was amended to align with the commercial-sponsored studies. See Appendices Section 9.4.1 KEYNOTE 016 for details on dose adjustments, delays, modifications for toxicity, and stopping rules.

Treatment with pembrolizumab was to continue until confirmed radiologic progressive disease (PD), unacceptable toxicity, or completion of 24 months of study therapy. Protocol-specified reasons for early treatment discontinuation included: patient withdrawal of consent, unacceptable AE, no sign of disease stabilization in 7 months, need for > 2 dose delays due to the same toxicity as per Table 31: Dose Delay Guidelines for Pembrolizumab during KEYNOTE 016, intercurrent illness that prevents further administration of treatment, pregnancy, investigator decision to withdraw the patient, noncompliance with trial treatment or procedure requirements, or patient is lost to follow-up. In addition, discontinuation of treatment could be considered for patients who attained a confirmed complete response (CR), had been treated for at least 24 weeks with pembrolizumab, and had at least two treatments with pembrolizumab

beyond the date when the initial CR was declared. If such a patient then experienced disease progression while off pembrolizumab therapy, that patient could be eligible for up to 1 year of additional treatment with pembrolizumab at the discretion of the investigator.

Tumor imaging was obtained every 8 weeks from the first dose of study therapy and assessed based on Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST 1.1). If imaging was determined to show PD, tumor assessment was to be repeated ≥4 weeks later in order to confirm PD, with the option of continuing treatment for clinically stable patients while awaiting confirmation of PD.

Prestudy assessments were adequate. Physical exams and vital signs, performance status, laboratories, and ECG were performed every 14 days, and radiologic assessment was outlined as above. Study flow charts, abstracted from KEYNOTE016 protocol, outlining the timing of procedures and evaluations were modified and are located in the appendices of this review (9.4.1 KEYNOTE 016), and are sufficient to assess for the clinical effects of pembrolizumab in terms of the effects on ORR and duration of response in this study.

5.3.2 KEYNOTE 164

KEYNOTE164 (KN164) is a multi-center, single-arm, open-label trial with 2 cohorts (A and B) both enrolling subjects with previously treated locally advanced, unresectable or metastatic MSI-H CRC. A total of 61 subjects were enrolled in Cohort A to evaluate the efficacy and safety of pembrolizumab in a subject population who had been previously treated with approved standard therapies. These approved therapies included fluoropyrimidine, oxaliplatin, and irinotecan with adjuvant chemotherapy counting as a line of therapy in amendment 164-01. Cohort B is enrolling subjects with metastatic MSI-High CRC previously treated with at least one line of systemic standard of care therapy: fluoropyrimidine +oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody. Data from Cohort A was submitted to this sBLA to support accelerated approval.

Subjects were to receive single agent pembrolizumab 200 mg IV every 3 weeks. Subjects are required to have at least one measureable lesion by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Subjects were evaluated every 9 weeks (with the first on-study imaging time point performed at 9 weeks and then every 9 weeks, thereafter). ORR per RECIST 1.1, as assessed by the independent radiologist review (IRC) was used as the primary efficacy endpoint. Statistical considerations are outlined in detail in the appendices (9.4.2 KEYNOTE 164).

Key inclusion criteria were that subjects have histologically proven locally advanced unresectable or metastatic CRC (Stage IV) confirmed MSI-H or dMMR by submitting a blood sample and archival or newly obtained tumor tissue for central review by PCR or IHC, and have been previously treated with at least two lines of approved standard therapies, which must have included fluoropyrimidine, oxaliplatin, irinotecan,

bevacizumab and cetuximab or panitumumab (if KRAS wild type), if approved in the respective country. Treatment administered in the adjuvant setting could be counted as one line of therapy. Refer to Section 9.4.2 KEYNOTE 164 (of this review) for details on dose adjustments, delays, modifications for toxicity, and stopping rules

The primary objective was overall response rate (ORR) of pembrolizumab administered as monotherapy, and secondary objectives were assessment of safety and tolerability; ORR per immune-related (irRECIST) by central radiologists' review; Duration of Response (DOR), Disease Control Rate (DCR) and Progression-free Survival (PFS) per RECIST 1.1; and irRECIST assessed by central imaging vendor and Overall Survival (OS). All study subjects were evaluated every 9 weeks following the date of allocation until progression of disease was documented with radiologic imaging (computed tomography or magnetic resonance imaging) based on RECIST 1.1 by blinded central radiologists' review.

Patients were removed from study therapy for disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or the subject received 35 administrations/24 months of pembrolizumab.

After the end of treatment, each subject was followed for 30 days for AE monitoring (SAE and ECI were collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiated new anticancer therapy, whichever was earlier).

Physical exams and vital signs, performance status, laboratories, and ECG were performed every 14 days, and radiologic assessment was outlined as above. Study flow charts, abstracted from 9.4.2 KEYNOTE 164 protocol, outlining the timing of procedures and evaluations, were modified and are located in the appendices of this review (Section 9.4.2 KEYNOTE 164), and are sufficient to assess for the clinical effects of pembrolizumab (in terms of the effects on ORR and safety) in this study.

5.3.3 KEYNOTE 012

KEYNOTE012 (NK012) is an open-label, multi-cohort trial of pembrolizumab monotherapy in subjects with advanced solid tumors expressing PD-L1. This trial enrolled subjects with (A) triple-negative breast cancer; (B/B2) HNSCC; (C) urothelial tract cancer; or (D) cancer of the stomach or gastroesophageal junction. Subjects were required at trial entry to have measurable disease by RECIST 1.1 for response assessment, and to have been previously treated with standard therapies. In Cohorts A, B, C, and D, subjects must have had a PD-L1 positive tumor as determined by IHC at a central laboratory. Subjects with PD-L1 positive and negative tumors were enrolled into Cohort B2, and the clinical activity in both groups of subjects was evaluated. Treatment in Cohorts A, B, C, and D was pembrolizumab 10 mg/kg every 2 weeks, and for Cohort B2 200 mg every 3 weeks. Tumor response was assessed every 8 weeks according to RECIST 1.1 by IRC. The primary efficacy endpoint, ORR, was based on IRC

assessments of response. MSI status was not used for biomarker-selected enrollment but was analyzed retrospectively in available tumor specimens using the PCR-based Promega MSI Analysis System v1.2. Ninety-six of the 297 patients (32%) had tumor tissue available for MSI-H/dMMR testing. The analysis of KEYNOTE012 efficacy data included these 6 subjects with MSI-H/dMMR cancer (four patients with gastric cancer, one patient with triple-negative breast cancer, and one patient with bladder cancer). The data cutoff date was 26-Apr-2016. All analyses were based on the ASaT population, defined as all subjects who received at least 1 dose of trial medication. See Section 9.4.3 KEYNOTE 012 for the trial schema.

5.3.4 KEYNOTE 028

KEYNOTE028 (KN028) is an open-label, non-randomized, multicenter, multi-cohort (20) trial of pembrolizumab monotherapy in subjects with PD-L1 positive advanced solid tumors. Subjects were required at trial entry to have measurable disease as assessed per RECIST 1.1 criteria, and to have a malignancy that is incurable and with any of the following: (a) failed prior standard therapy, (b) no existing standard therapy, or (c) standard therapy was not considered appropriate by the subject and treating physician. Subjects received pembrolizumab 10mg/kg every 2 weeks. Tumor response was assessed every 8 weeks according to RECIST 1.1 for the first 6 months and every 12 weeks thereafter. The primary efficacy endpoint, ORR, is based on IRC assessments of response. MSI status was not used for biomarker-selected enrollment and was analyzed retrospectively in available tumor specimens using the PCR-based Promega MSI Analysis System v1.2. Two hundred sixty-five of the 475 patients enrolled in this trial had tumor tissue available for MSI-H/dMMR testing. The analysis of KEYNOTE028 efficacy data included 5 subjects with MSI-H/dMMR cancer. The data cutoff date was 20-Jun-2016. All analyses were based on the ASaT population, defined as all subjects who received at least 1 dose of trial medication. See Section 9.4.4 KEYNOTE 028 for the trial schema.

5.3.5 KEYNOTE 158

KEYNOTE158 (KN158) is an open-label, non-randomized, multicenter, multi-cohort trial of pembrolizumab monotherapy in subjects with multiple types of advanced (unresectable and/or metastatic) rare cancers. The primary purpose of this trial is to assess the ORR of patients while on treatment with pembrolizumab based on RECIST 1.1, as determined by independent central radiologic review. This trial is also evaluating the efficacy of pembrolizumab in subgroups defined by each of three prespecified primary biomarkers: IHC-based tumor PD-L1 expression, tumor Gene expression profile (GEP) RNA gene signature score, and MSI/dMMR status. Subjects are required at trial entry to have measurable disease as assessed per RECIST 1.1 criteria, and to have progressed on or after prior therapy. Subjects are treated with pembrolizumab 200 mg IV every 3 weeks. Tumor response is assessed every 9 weeks according to RECIST 1.1 by IRC.

MSI-H/dMMR status was required specifically for enrollment into Group K and was prospectively analyzed by local IHC-based or PCR-based testing. For subjects enrolled into Groups A-J, retrospective testing of tumor tissue samples for MSI was performed using the PCR-based Promega MSI Analysis System v1.2. Of the 713 patients enrolled in this trial at the time of sBLA submission, 310 had tumor tissue available for MSI-H/dMMR testing, and 16 patients were prospectively identified as MSI-H/dMMR in Group K. Of the remaining 294 subjects, tumor samples from 54 subjects (Group B and D) were available for retrospective testing of MSI-H/dMMR and 3 subjects were identified at the data cut-off date. The analysis of KEYNOTE158 efficacy data in total included 19 subjects with MSI-H/dMMR cancer. The data cutoff date was 17-Aug-2016. See Section 9.4.5 KEYNOTE 158 for the trial schema.

Table 3: Table of trials with subjects submitted to sBLA

KN	Design/Eligibility/Pop	N	MSI-H	Dose	Prior therapy
016	Single arm, **prospective,** 6 sites, activity finding	28 CRC 30 non CRC	PCR IHC Local	10 mg/kg q2w	**CRC**: received ≥ 2 prior therapy regimens **nonCRC**: ≥1 prior therapy regimen
164	**CRC, prospective** single arm, multi-center Merck trial	61	PCR IHC local	**200mg q3w**	Prior fluoro+ox, fluoro+irino +/- anti-VEGF/EGFR mAb
012	PD-L1 TNBC, gastric, urothelial, H & N. PDL1+. Measurable disease.	6	**Retro** PCR central	10 mg/kg q2w	Previously treated; no standard therapy
028	Multi-disease cohorts PD-L1+. Measurable disease.	5	**Retro** PCR central	10 mg/kg q2w	Previously treated; no standard therapy
158	**Prospective,** MSI-H multi-cohort rare tumor trial: **Cohort K Retrospective: Cohort B, D**	19	PCR IHC local	**200mg q3w**	≥1 prior therapy regimen
Total	5 trials	**149**			

Key: "Retro" (MSI-H) were identified retrospectively, KN=KEYNOTE trial number, PCR=polymerase chain reaction, IHC=immunohistochemistry, q3w=every 3 weeks, q2w=every 2 weeks, fluoro=fluorouracil, irino=irinotecan, ox=oxaliplatin.

REVIEWER COMMENT: *The trials differed with respect to doses administered; MSI-H/dMMR testing; whether testing was prospective or retrospective; and prior therapies. All of the trials were single arm and non-randomized. Also See Table 2*.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Merck proposed the following indication for pembrolizumab in the sBLA submission:

(b) (4)

"

6.1.1 Methods

The primary efficacy population considered for this review consists of 149 pooled patients treated with pembrolizumab across 5 trials: KEYNOTE016, KEYNOTE012, KEYNOTE028, KEYNOTE158, KEYNOTE164 (see 5.3 Discussion of Individual Studies/Clinical Trials). Subjects had either metastatic or locally advanced MSI-H/dMMR CRC or MSI-H/dMMR nonCRC. The results presented here are based on the data cut-off of used for KEYNOTE164 in the updated SCE (3-Aug 2016) and KEYNOTE158 (17-Aug 2016). All data presented for the 5 studies are based on confirmed responses as per IRC assessment using RECIST 1.1, unless otherwise noted. Demographic, tumor characteristics, and prior treatment data for both study populations are presented in Table 4.

6.1.2 Demographics

Demographics and disease characteristics of patients with CRC are described in Table 4. The median age of patients with MSI-H/dMMR CRC (in the safety population, age 52) was lower than the median age of CRC in an unselected patient population with colorectal cancer in the United States (U.S.), age 69 in men and 79 in women, according to the American Cancer Society's colorectal facts and figures from 2014-16.[14] This *may*, in part, be related to the younger age in which patients with Lynch syndrome are diagnosed with CRC. KRAS and BRAF status appeared similar between the two trials. More patients in KEYNOTE016 underwent testing with both PCR and IHC.

All subjects had metastatic or advanced disease in both studies. There were more Asian patients enrolled on KEYNOTE164 (31%) as this study had sites in Asia (Country distribution: U.S. 8, Spain 6, N. Korea 11, Japan 7, Israel 5, Germany 7, France 11, Belgium 4, Australia 2), compared with KEYNOTE16A (4%) which only had sites in the

U.S. (Portland, Oregon; Stanford, California; Pittsburgh, Pennsylvania, National Cancer Institute: Bethesda, Maryland; Baltimore, Maryland, Columbus, Ohio). KEYNOTE16A also enrolled more patients with ECOG PS1 (ECOG 1: 82% vs ECOG 0: 18%) compared to KEYNOTE164 ECOG 1:0 (52%:48%). There was one subject enrolled who received no prior treatment for CRC in the metastatic setting on KEYNOTE016A. However, this subject received 5-FU plus oxaliplatin as a neo-adjuvant therapy and 5-FU plus irinotecan plus bevacizumab as an adjuvant therapy. However, the subject experienced disease progression within 1 month after the last dose of the adjuvant therapy.

Table 4: Demographic and Baseline Characteristics of CRC population

Demographic Baseline Characteristics		KEYNOTE 016 Cohort A		KEYNOTE 164	
		N=28		N=61	
Age	Mean (range)	51 (24-75)		54 (21-84)	
	Median	49		53	
		Count	%	Count	%
Age Group	≥ 65 years	8	29	19	31
	< 65 years	20	71	42	69
	65 <= Age <75	7	25	15	25
	≥ 75 years	1	4	4	7
Sex	F	13	47	25	41
	M	15	54	36	59
Race	Asian	1	4	19	31
	Black	2	7	0	0
	White	23	82	42	69
	Other	1	4	0	0
Ethnicity	Hispanic Or Latino	1	4	1	2
	Not Hispanic Or Latino	27	96	54	89
	Not Reported	0	0	3	5
ECOG PS	0	5	18	29	48
	1	23	82	32	52
Prior therapy	None	1	4	0	0
	1st line	7	25	6	10
	2nd line	8	29	28	46
	3rd line	7	25	13	21
	4th line	4	14	5	8
	≥ 5th line	1	4	9	15
KRAS^	Mutant	11	39	16	26
	Wild Type	17	61	38	62

Demographic Baseline Characteristics		KEYNOTE 016 Cohort A		KEYNOTE 164	
		N=28		N=61	
NRAS[$]	Mutant	NA		3	5
	Wild Type			25	41
B Raf	Mutant	3	11	9	15
	Wild type	16	57	28	46
	Undetermined	9	32	24	39
MSI-H	PCR	21	75	39	64
	IHC	19*	68	38	62
	Both tests	12*	43	16	26
	MSI-H total (either test)	28	100	60[#]	98
Metastatic disease	Stage 4	28	100	61	100

ADSL datasets for KEYNOTE Cohort 16A and KEYNOTE 164 were assessed using JMP.
^KRAS only was assessed in KEYNOTE016A; Both KRAS^ and NRAS[$] were assessed in KEYNOTE164.
*For KEYNOTE 016A: IHC was tested in 21 subjects and positive (High) in 19; Therefore both MSI tests were performed in 14 subjects but only high in 12 subjects.
[#]One subject had “Negative” MSI in ADSL dataset, however “Positive” PCR.

In study KEYNOTE164, one patient had a history of metastatic CRC and a known PMS2 germline mutation N335S. Upon recognition that the presence of a germline mutation in PMS2 gene alone did not satisfy the biomarker requirement for the study, the site performed IHC of the 4 MMR enzymes on an archived paraffin tumor sample. The results showed nuclear expression for MLH1, weak; MSH2, MSH6, and PMS2 positive. There was no evidence for MSI-H per the institutional pathologist. During the same period of time, the subject’s first on-study radiographic assessment demonstrated progressive disease after Cycle 3. The subject was discontinued from study treatment due to malignant neoplasm progression.

Per protocol, the MSI status was to be determined by examining either protein expression by IHC of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2) or 3-5 tumor microsatellite loci using PCR-based assay, respectively, and tumors were classified as MSI high when at least 2 allelic shifts among the 3-5 analyzed microsatellite markers were detected by PCR or absence of at least 1 of 4 mismatch repair proteins expression was detected by IHC.

Seventy-five percent (75%) of subjects enrolled on KEYNOTE016A had MSI-H tested by PCR and 43% had MSI-H identified by both PCR and IHC while only 26% utilized both tests and was MSI-H on KEYNOTE164. See Table 5 for details.

Table 5: Demographics of pooled MSI-H population vs. reference safety population

	MSI-H N=89; n (%)	Reference safety N=2799; n (%)

Gender - Male - Female	 51 (57) 38 (43)	 1659 (59) 1140 (41)
Age - Median (range) - ≥ 65 y.o.	 52 (21-84) 27 (30)	 62 (15-94) 1212 (43)
Race - White - Asian - African American - Other	 65 (73) 20 (22) 2 (2) 2 (2)	 2474 (88) 233 (8) 48 (2) 44 (2)
ECOG - 0 - 1	 34 (38) 55 (62)	 1446 (52) 1347 (48)
Geographic region - U.S. - Ex- U.S.	 36 (40) 53 (60)	 1250 (45) 1549 (55)

Subjects were younger in the MSI-H/dMMR population (median 52 years of age) as compared to the reference safety population (median 62 years of age), and there were a few sites open in Asia, which explains why the Asian population is of higher frequency in the MSI-H/dMMR population.

REVIEWER COMMENT: Demographic data was reviewed and was consistent with the sBLA. Note that the applicant assessed MSI status by test performed (PCR vs IHC or both) for the safety population with 13-14% of subjects having both PCR and IHC performed.

6.1.3 Subject Disposition

Subjects were followed for an adequate amount of time, for example, in KEYNOTE016A, median follow-up at the data cut-off date of 19 Feb 2016 was 10 months (range, 0.7 to 26.3 months).The disposition of subjects in the 5 trials are described in the summary table below based on data submitted to the sBLA (Table 6).

Table 6: Subject disposition across 5 trials in MSI-H cancers

KEYNOTE Trial	**016A* N=28 (%)**	**016C N=30 (%)**	**012 N=6 (%)**	**028 N=5 (%)**	**164 N=61 (%)**	**158 N=19 (%)**
Study discontinuation and cut off date	19 Feb 2016	13 Apr 2016	26 Apr 2016	20 Jun 2016	3 Aug 2016	17 Aug 2016
Death					9 (15)	2 (11)
Lost to follow-up					1 (2)	-
Treatment discontinuation						
Patients who discontinued treatment	8 (29)	12* (40)	4 (67)	2 (40)	27 (44)	8 (42)
Administrative decision	-	-	-	-	3 (5)	-
Adverse event	1 (4)	-	-	-	4 (7)	4 (21)
Death	1 (4)	-	-	-	-	-

KEYNOTE Trial	016A* N=28 (%)	016C N=30 (%)	012 N=6 (%)	028 N=5 (%)	164 N=61 (%)	158 N=19 (%)
Disease progression (clinical and radiological progression)	5 (18)	10 (33)	3 (50)	1 (20)	18 (30)	4 (21)
Consent withdrawal	1 (4)	1 (3)	1 (17)	1 (20)	2 (3)	-
Continuation/Completion						
Continue	18 (64)	17 (57)	-	3 (60)	34 (56)	11 (58)
Complete	2 (7)	1 (3)	2 (33)	-		

*One subject on KEYNOTE16C discontinued treatment for "clinical response" that was a CR.

Protocol deviations were identified in 1 subject (4%) on KEYNOTE16A due to a thyroid panel not completed per protocol, but this subject was not excluded from the analysis. In KEYNOTE164, 32 major protocol deviations were identified in 61 subjects. Only one major deviation was considered clinically relevant per the applicant in whom MSI-H was not confirmed per protocol in 1 subject (see details in 6.1.2 Demographics).

For KEYNOTE164, a major protocol deviation was defined as any protocol deviation that significantly/adversely impacted the completeness, accuracy and/or reliability of the trial data or that significantly/adversely affected a subject's rights, safety or well-being. Major deviations were defined based on subject protections described in the protocol and included protocol specific deviations based on the trial design, critical procedures, trial data, and the planned analyses of trial data. Minor protocol deviations, which were considered unlikely to impact the subject's safety/rights or negatively affect the quality of their trial data, were not included in the CSR.

Informed consent violations were identified for 13 subjects; however, all signed an informed consent (1 signed an incorrect version of the informed consent, 11 did not sign an updated informed consent version in a timely manner, 1 signed but did not date the informed consent). Thirteen subjects did not satisfy all inclusion/exclusion criteria (10 had screening labs not performed and/or performed outside required window, 1 did not have MSI-H status confirmed as described above, 1 had prior chemotherapy within 14 days prior to pembrolizumab initiation, and 1 received steroid within 7 days of pembrolizumab initiation); 5 subjects had a serious adverse event (SAE) or event of clinical interest (ECI) not reported in a timely manner within 24 hours; and 1 subject took disallowed concomitant medication.

Most of the discontinuations were due to disease progression. Taken together, there were 9 AEs attributable to treatment discontinuation across all patients (note that this does not include KEYNOTE16C as no data was submitted in the sBLA).

REVIEWER COMMENT: Duration of follow-up (median >8 months) was adequate. The protocol violations do not appear to affect the overall integrity of the trials.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for the clinical review of this application is the confirmed ORR by RECIST 1.1 as assessed by independent central radiology review in the ASaT population of 149 patients treated with pembrolizumab across 5 clinical trials (KEYNOTE012, KEYNOTE016, KEYNOTE028, KEYNOTE158, KEYNOTE164) with MSI-H/dMMR metastatic, locally advanced CRC and nonCRC.

There were 56 patients with responses per RECIST 1.1, resulting in an ORR of 37.6% (95% CI: 29.8, 45.9). This included 9 CR (6%) and 47 PR (31.5%). See Table 7 for details.

Table 7: ORR Analysis Results (*with permission from FDA biostatistical review***)**

	N (%)	95 % CI
Patients in Efficacy Analysis	149 (100)	
CR+PR (%)	56 (37.6)	(29.8, 45.9)
CR	9 (6.0)	
PR	47 (31.5)	
SD	36 (24.2)	
PD	47 (24.5)	
NE	7 (4.7)	
Non-CR/Non-PD	1 (0.7)	
Missing	2 (1.3)	

Responses were demonstrated in patients with almost all types of MSI-H/dMMR cancer (N=15) enrolled across the 5 trials except 4: thyroid, kidney, bladder, sarcoma; although only single subjects had been enrolled in these 4 cohorts. See table below.

Table 8: ORR by Tumor type across all trials

	N	Response (ORR)	95% of ORR	DOR
GI Tumor				
BILIARY	11	3 (27%)	(6.0%, 61.0%)	(11.6, 19.6)
COLORECTAL	90	30 (33%)	(23.7%, 44.1%)	(1.6, 22.7)
GASTRIC	8	4 (50%)	(15.7%, 84.3%)	(2.0, 22.1)
PANCREATIC	6	5 (83%)	(35.9%, 99.6%)	(2.0, 9.1)
SMALL INTESTINAL	8	3 (38%)	(8.5%, 75.5%)	(1.9, 6.2)
ESOPHAGEAL	1	PR		18.2, on-going
GE JUNCTION	1	PD		
Non-GI Tumor				
ENDOMETRIAL	14	5 (36%)	(12.8%, 64.9%)	(1.9, 17.3)
BREAST	2	PR, PR		7.6, 15.9, on-going
PROSTATE	2	PR, SD		9.8, on-going
BLADDER	1	Missing		
SARCOMA	1	PD		
THYROID	1	NE		
RETROPERITONEAL	1	PR		2.1, on-going

SMALL CELL LUNG	1	PR		2.2, on-going
RENAL CELL	1	PD		

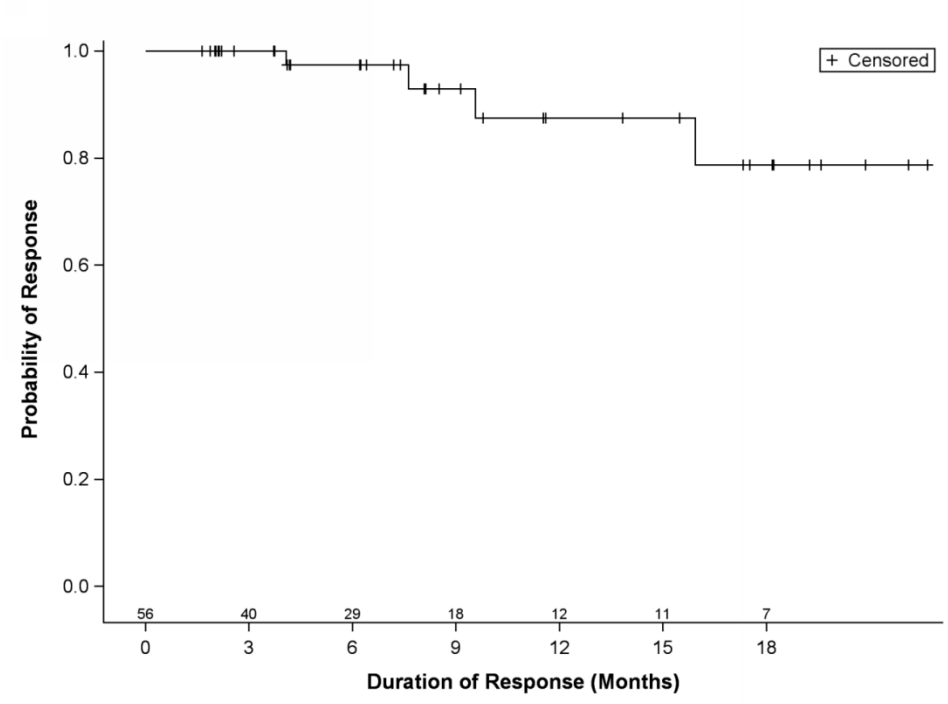
Key: GE=Gastroesophageal tumor, PR=partial response; PD=progressive disease; NE=non-evaluable

REVIEWER COMMENT: *Responses were demonstrated in cancers that have previously been unresponsive to checkpoint inhibitors such as pancreas cancer. Some of the tumors are only represented by 1 or 2 patients; therefore and the results may not be representative of that particular tumor type.*

6.1.5 Analysis of Secondary Endpoints(s)

Duration of response (DoR) is considered a key secondary endpoint for this clinical review. The median time to response was 2.7 months (range 1.7 to 8.4 months). The median of the duration of responses was not reached and ranged from 1.6 to 22.7 months. For these 56 subjects, 52 (93%) responses were ongoing. DOR longer than 6 months was reported in 29 subjects, 51.8% of 56 subjects who responded based on observed data (some patients had not yet had their response followed for six months). Two subjects had completed the pre-specified treatment duration of 2 years and were being followed without further pembrolizumab treatment.

Figure 1: Kaplan Meier curve of Duration of Response



6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

A sensitivity analysis was performed to identify the influence of patient characteristics, study conduct, and drug exposure on the objective response rate (ORR), PFS and OS across Studies KEYNOTE016, KEYNOTE012, KEYNOTE028, KEYNOTE158, KEYNOTE164.

Table 9: ORR Subgroup Analyses

Subgroup	N	Response (ORR)	95% CI of ORR	DOR Range
< 65	96	37 (39%)	(28.8%, 49.0%)	(1.6, 22.7)
>= 65	53	19 (36%)	(23.1%, 50.2%)	(1.9, 19.3)
Female	66	27 (41%)	(29.0%, 53.7%)	(1.9, 19.6)
Male	83	29 (35%)	(24.8%, 46.2%)	(1.6, 22.7)
Non-White	34	15 (44%)	(27.2%, 62.1%)	(1.6, 22.1)
White	115	41 (36%)	(26.9%, 45.1%)	(1.9, 22.7)
Asia	23	7 (30%)	(13.2%, 52.9%)	(1.9, 22.1)
USA	73	36 (49%)	(37.4%, 61.3%)	(1.6, 22.7)
Western	53	13 (25%)	(13.8%, 38.3%)	(2.0, 15.9)

REVIEWER COMMENT: At first glance, the analyses show that younger patients (<65 years of age) had a higher response rate, male and female patients have comparable response rates, non-white patients had a higher response rate as well as patients from the U.S. However, the population had limited subjects numbers (N=149) compared to the reference (N=2799) enrolled across 5 non-randomized trials.

Clinically, there is no evidence to indicate an influence of patient characteristics, study conduct, or drug exposure on the efficacy of pembrolizumab in patients with MSI-H/dMMR cancer.

ORR was also evaluated by study, and presented in the table below:

Table 10: ORR Subgroup Analysis by Study

Subgroup	N	Response (ORR)	95% CI of ORR	DOR Range
KN012	6	3 (50%)	(11.8%, 88.2%)	(7.6, 22.1)
KN016-A	28	14 (50%)	(30.6%, 69.4%)	(1.6, 20.9)
KN016-C	30	14 (47%)	(28.3%, 65.7%)	(1.9, 19.6)
KN028	5	4 (80%)	(28.4%, 99.5%)	(15.9, 22.7)
KN158	19	6 (32%)	(12.6%, 56.6%)	(1.9, 2.2)
KN164	61	15 (25%)	(14.5%, 37.3%)	(2.0, 8.1)

Consistent anti-cancer activity was observed between subjects with GI (CRC, small bowel, gastro-esophageal junction, pancreas) and non-GI MSI-H cancer (see Table 8). For subjects with MSI-H GI and MSI-H non-GI cancer, the ORRs based on assessment by IRC using RECIST 1.1 were 36.8% and 41.7%, respectively, see Table 11.

Table 11: ORR in GI and non-GI tumors *(modified from submission)*

Response Evaluation	GI Tumors (N=125)		Non-GI Tumors (N=24)		Total (N=149)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Complete Response (CR)	6 (4.8)	(1.8, 10.2)	3 (12.5)	(2.7, 32.4)	9 (6.0)	(2.8, 11.2)
Partial Response (PR)	40 (32.0)	(23.9, 40.9)	7 (29.2)	(12.6, 51.1)	47 (31.5)	(24.2, 39.7)
Objective Response (CR+PR)	**46 (36.8)**	**(28.4, 45.9)**	**10 (41.7)**	**(22.1, 63.4)**	**56 (37.6)**	**(29.8, 45.9)**

Note: Based on confirmed response per IRC except for KN164 and KN158 (based on confirmed and unconfirmed response per IRC). 7 subjects with non-evaluable assessments: 2 subjects in KN016-A, 3 subjects in KN016-C, and 2 subjects in KN164 without a post-baseline assessment. There are 2 subjects with no assessment: 1 subject in KN012 and 1 subject in KN158 who discontinued the trial prior to the first post-baseline assessment.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Sixty-nine subjects were administered pembrolizumab 10mg/kg every 2 weeks in this sBLA (*6 from KN012, 5 from KN028, 28 from KN016A, 30 from KN016C)* while eighty subjects were administered 200 mg every 3 weeks (*19 from KN158, 61 from KN164)*. Taken together, there were 51% responders for subjects administered pembrolizumab at 10mg/kg every 2 weeks and there were 26% responders with administration of pembrolizumab 200 mg every 3 weeks. The CI for the response rates do not overlap (see Table 12).

Table 12: ORR by Dose for sBLA

Dose	10 mg/kg every 2 weeks	200 mg every 3 weeks
	N=69	N=80
Responders (%)	35 (51%)	21 (26%)
95% CI of ORR	(38.4%, 63.0%)	(17.0%, 37.3%)
DOR	(1.6, 22.7)	(1.9, 8.1)

REVIEWER COMMENT: The CIs of the ORR do not overlap between the different doses (10 mg/kg every 2 weeks versus 200mg every 3 weeks). As such, a difference in treatment effect may exist between the two doses. Nevertheless, uncertainty exists given that patients were enrolled at different sites and there may have been differences among patients enrolled. Although uncertainty exists, the Johns Hopkins study (10

mg/kg) appeared to have consistently high response rates across the study sites. Additionally, inspection of the Johns Hopkins site appeared to confirm the efficacy findings at the site. Finally, the response rate among the patients enrolled in KN012 and KN028 were consistent with the results in KN016 (although the patients in KN012 and KN028 were retrospectively identified).

Whether or not a higher dose leading to a better ORR applies to the general population is discussed elsewhere (refer to risk:benefit). Furthermore, even if the difference in ORR was true, uncertainty would remain as to whether this difference would translate into differences in other clinical outcomes. A meeting was held 13 Feb 2017 and the applicant will submit further data supporting the flat dose of 200mg IV every 3 weeks. See addendum to this review for details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

A discussion of tolerance effects is not applicable to this review.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For a discussion of the review strategy for this sBLA, see Section 5.2 Review Strategy. This reviewer confirmed the Applicant's safety analyses of KEYNOTE016A and KEYNOTE164, conducting analyses of per patient incidence rates of AEs from primary data using the MAED program. Patient narratives were reviewed for KEYNOTE012, KEYNOTE028, and KEYNOTE158. Note that for KEYNOTE164 and KEYNOTE158, the datasets used for the safety review were the initial datasets submitted to the sBLA, and not the SCS – Safety Update Report. Safety data was briefly reviewed in the SCS and appeared to be in line with pooled data from previous studies, so safety assessments for this study are based on the CSR and datasets with a cut-off date of 19 Feb 2016 for KEYNOTE016A and 3 June 2016 for KEYNOTE164.

In this review, major safety results (Section 7.3 Major Safety Results) are presented for KEYNOTE016A and KEYNOTE164, unless otherwise noted. Pooled safety data, as reported by the Applicant, from 2799 clinical trial patients with NSCLC (treated in KEYNOTE001 and 010) or melanoma (treated in KEYNOTE001, 002, and 006), referred to as "pooled melanoma and NSCLC population" is considered to represent the known safety profile of pembrolizumab and is used for purposes of comparison in this review.

REVIEWER COMMENT: *As agreed upon in the pre-sBLA meeting, patient narratives were submitted but not granular subject level safety data from KEYNOTE016C, KEYNOTE012, KEYNOTE028, or KEYNOTE158. Note that the data from KEYNOTE158 is relatively immature and KEYNOTE012 and 028 would have provided data from only a limited number of patients. Based on the vast safety experience of pembrolizumab in other uses, it is not expected that safety datasets from these limited numbers of patients would have contributed substantive new information, especially after reviewing summary safety information in the submission.*

7.1.2 Categorization of Adverse Events

The severity of adverse events was documented using Common Terminology Criteria for Adverse Event, NCI-CTCAE version 4.0. The MedDRA 19.0 dictionary was used to code adverse event data. Listings provided by the Applicant included all AEs occurring from Day 1 through 30 days after the last dose of pembrolizumab, serious AEs (SAEs) occurring from Day 1 through 90 days after the last dose of pembrolizumab, and AEs resulting in death.

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

As discussed with Merck during the pre-sBLA meeting held 22 July 2016, FDA and Merck agreed that safety analyses from KEYNOTE016 cohort A and KEYNOTE164 compared to the combined reference safety information from studies KN001, KN002, KN006, and KN010, would enable the safety evaluation of the proposed sBLA. In this submission (see Section 7.3 Major Safety Results) safety datasets for studies KEYNOTE016A and KEYNOTE164 were analyzed. The studies used for the reference safety database have been previously analyzed by FDA and the comparative tables will use the pooled reference data as provided in the submission.

7.2 Adequacy of Safety Assessments

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

For KEYNOTE016A (10 mg/kg), the mean number of weeks on therapy was 44.18 (range 2-103.1; median 38.5), and the mean number of doses administered was 20.1 (range 2-49; median 18.5). The majority of patients (75%) were exposed for ≥ 6 months (18 patients were still on treatment at the time of data cut-off).

For KEYNOTE164 (200mg flat dose), according to the applicant after an updated summary of safety was submitted for KEYNOTE164 with an additional 9 week follow-up (cut off 3-August 2016), the median number of days on therapy was 160.11 ± 78.69

days (range: 1 day to 283 days), with 32 subjects (52.5%) receiving pembrolizumab for greater than 6 months.

Extensive safety information is available related to the use of pembrolizumab at similar or higher doses for other indications, including the approved melanoma, NSCLC, and HNSCC indications.

7.2.2 Explorations for Dose Response

The exposure with the 10 mg/kg every 2 weeks dosage regimen is approximately 5-fold higher than the exposure with the 200 mg every 3 weeks fixed dose (see Section 4.4.3 Pharmacokinetics of this review). The ORRs observed using the two dosage regimens are different with confidence intervals that do not overlap (although this reviewer acknowledges that uncertainty exists in regards to dose effect given that the results did not come from randomized studies). Also see the FDA Clinical Pharmacology review and Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations of this review. *A meeting was held 13 Feb 2017 and the applicant will submit further data supporting the flat dose of 200mg IV every 3 weeks. See addendum to this review for details.*

7.2.3 Special Animal and/or In Vitro Testing

See the FDA Pharmacology/Toxicology Review from the original BLA submission.

7.2.4 Routine Clinical Testing

The tests conducted as part of routine clinical testing and the frequency of such testing are detailed in the Study Flow Charts included in Sections 9.4 Supplemental information of this review. The safety assessment methods and time points described in the protocols appear adequate for the population, disease, and indication being investigated.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the FDA Clinical Pharmacology review for details.

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

Similar to other drugs targeting the PD-1 pathway, such as nivolumab, immune mediated adverse reactions have been observed in patients treated with pembrolizumab. The safety information submitted by the Applicant includes evaluating of adverse events of special interested (AEOSI), which includes immune-mediated AEs (irAEs) and infusion reactions. These are discussed in Section 7.3.5 **Submission Specific Primary Safety Concerns**

7.3 Major Safety Results

The safety analyses were performed for all treated patients enrolled in KEYNOTE016 Cohort A with a data cutoff date of 19 Feb 2016, and KEYNOTE164 with a data cutoff date of 3 Jun 2016. The primary safety data for pembrolizumab in subjects with MSI-H/dMMR cancer provided in this application are from 89 pooled subjects enrolled in KN016 (cohort A) and KN164 (cohort A). The safety data in MSI-H/dMMR subjects were evaluated relative to safety data from a pooled population of 2799 patients with NSCLC or melanoma from the All Subjects as Treated populations of KN001, KN002, KN006, and KN010 named the "reference" safety population.

For KEYNOTE016A, the safety population included 28 patients. All patients received pembrolizumab 10 mg/kg IV every 2 weeks. AEs were reported in all patients. The applicant states that due to limitations in data base conversion (the study was an investigator-initiated study not initially intended for marketing that was conducted and the data managed by the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins School of Medicine), analyses involving laboratory tests, vital signs, and other physical observations were not reported. Table 13 summarizes the major safety results.

Table 13: KEYNOTE 16A: Summary of Major Safety Results

	N=28 (%)
Subjects who experienced an AE	28 (100)
Subjects who experienced a Grade 1-2 AE	27 (96)
Subjects who experienced a Grade 3-4 AE	13 (46)
Subjects who experienced an SAE	14 (50)
Deaths reported as an AE	4 (14)

For KEYNOTE164, the safety population included 61 patients. All patients received pembrolizumab 200 mg IV every 2 weeks. AEs were reported in 60 patients. Table 14 summarizes the major safety results.

Table 14: KEYNOTE164 Summary of Major Safety Results

	N=61 (%)
Subjects who experienced an AE	60 (98)
Subjects who experienced a Grade 1-2 AE	57 (93)
Subjects who experienced a Grade 3-4* AE	28 (46)
Subjects who experienced an SAE	23 (38)
Deaths related to an AE	2 (3)

As summarizes in Table 15, there are no significant differences between the MSI-H/dMMR safety population and the reference safety populations in terms of the overall major safety results.

Table 15: Comparison of major safety results, MSI-H pooled safety data and Pembrolizumab reference safety population

	MSI-H N=89; n (%)	Reference safety* N=2799; n (%)
Incidence AEs	88 (99)	2727 (98)
Grade 3-5 AEs	43 (48)	1272 (45)
SAEs	35 (39)	1041 (37)

	MSI-H N=89; n (%)	Reference safety* N=2799; n (%)
Deaths related to AE	3 (3)	110 (4)
Dose modification due to AE	33 (37)	884 (32)
Dose discontinued due to AE	4 (4)	334 (12)

*Reference safety population consists of subjects with melanoma and non-small cell lung cancer (NSCLC) who have been treated with pembrolizumab

REVIEWER COMMENT: The overall incidence rates of AEs and the type of toxicities were similar to the published incidence rates of pembrolizumab and were previously reviewed by FDA in separate efficacy supplements. There was an updated summary of safety for KEYNOTE164 with data cut-off 3 Aug 2016 that did not differ significantly from the safety assessments listed here.

7.3.1 Deaths

For KEYNOTE016A, of the four deaths reported in the safety dataset, one patient died of Trousseau syndrome (Day 277 on study), one patient died due to malnutrition (Day 249 on study), and one patient died due to aspiration pneumonia (Day 21 on study), all considered to be due to the patient's underlying disease condition. The fourth patient had disease progression, which should have not been reported as an AE.

For KEYNOTE164, there were two deaths reported as an AE: a 32 year old patient who died of disease progression and a 49 year old patient who died because of aspiration (Day 6 of treatment) while experiencing vomiting. The applicant states that there was a suspicion of ruptured tumor involving the abdominal wall at baseline. A total of 8 deaths are reported in the study; 6 patients had progressive disease, and one subject opted for euthanasia (after withdrawal of consent).

In summary, in the pooled MSI-H/dMMR population, there were 3 deaths related to an AE (3%) and in the reference safety database, there were 110 (4%).

REVIEWER COMMENT: The incidence of death due to AEs in the MSI-H/dMMR cancer population (3%) is similar to the reference safety population (4%). Review of the details of these deaths does not raise any new safety concerns relative to the safety profile of pembrolizumab reflected in the current USPI (see additional reviewer comments in this section).

7.3.2 Nonfatal Serious Adverse Events

For KEYNOTE16A, there were 33 serious adverse events (SAEs) in 14 patients. Grade 1-2 SAEs (one of each) were abdominal pain, acute kidney injury, arthritis, cerebrovascular accident, device malfunction, drug withdrawal syndrome, dyspnea, malnutrition, pleuritic pain, pyrexia, skin disorder, and stent malfunction. None of these were life-threatening and all patients recovered; there is no data for the need of hospitalization.

Grade 3 SAEs (one of each) were acute kidney injury, anemia, brain tumor operation, delirium, disease progression, intestinal obstruction, acute pancreatitis, pulmonary embolism, spinal cord compression, and syncope. Grade 4 SAEs were hydronephrosis, pulmonary embolism, sepsis, and urinary tract obstructions. Grade 5/fatal SAEs were death due to disease progression, aspiration, and Trousseau syndrome.

These SAEs are generally consistent with the baseline disease (disease progression, which should not be considered an AE, abdominal pain, intestinal obstruction, urinary tract obstruction and hydronephrosis, etc.) and the known safety profile of pembrolizumab. In addition, they may be reflective of institutional practices as patients may have been hospitalized for monitoring or symptomatic management.

For KEYNOTE164, 23 patients (38%) experienced an SAE. See Table 16 for details of the PT for each SAE.

Table 16: KEYNOTE164 Serious Adverse Events

Preferred Term	Grade 2	Grade 3	Grade 5
Abdominal pain	0	3	0
Pulmonary embolism	0	2	0
Acute myocardial infarction	0	1	0
Blood bilirubin increased	0	1	0
Cholecystitis acute	0	1	0
Dehydration	0	1	0
Duodenal ulcer	0	1	0
Female genital tract fistula	0	1	0
Flank pain	0	1	0
Ileus	0	1	0
Incisional hernia	0	1	0
Influenza	0	1	0
Muscle swelling	0	1	0
Pyrexia	1	1	0
Sinus bradycardia	0	1	0
Small intestinal obstruction	0	1	0
Squamous cell carcinoma	0	1	0
Tumor pain	0	1	0
Upper gastrointestinal hemorrhage	0	1	0
Urinary tract infection	0	1	0
Urinary tract obstruction	0	1	0
Aspiration	0	0	1
Headache	1	0	0
Nausea	1	0	0
Vaginal hemorrhage	1	0	0

With the exception of a vaginal bleeding event, all other Grade 2 SAEs (headache, nausea, fever) were considered serious because the patient required hospitalization. This listing of SAEs is consistent with the known safety profile of pembrolizumab and the baseline disease.

7.3.3 Dropouts and/or Discontinuations

For KEYNOTE016A, there were 3 treatment discontinuations which occurred in patients who died: due to Trousseau syndrome, aspiration pneumonia, and disease progression. However, none of the discontinuations were considered to be drug-related as all were associated with underlying malignancies.

The narratives these events indicated that the etiology of Trousseau syndrome was thought to be possibly related to the subject's prior history of this syndrome in the context of worsening clot burden. The subject had a known history of thromboembolic disease and progressed previously through treatment with heparin, levofloxacin, and fondaparinux. The subject with aspiration pneumonia had aspirated during a hospitalization for abdominal pain, requiring intubation, and then died due to asystole.

Treatment was temporarily held in 17 patients (61%) in KEYNOTE016A, and 8 subject's treatment interruptions were noted to be attributed to study drug. Grade 1-2 adverse events associated with treatment temporary interruptions were (one of each) acute kidney injury, AST increase, alkaline phosphatase increase, device malfunction, diarrhea, drug withdrawal syndrome, dyspnea, hematuria, pancreatitis, pleuritic pain, pyrexia, skin disorder, thrombocytopenia, thyroiditis, upper respiratory tract infection, and decreased weight. Grade 3 adverse events associated with treatment temporary interruptions were (one of each, with the exception of 3 patients with anemia) AST increased, intestinal obstruction, leukopenia, lymphopenia, pancreatitis, acute pancreatitis, pemphigoid, pulmonary embolism, rash pruritic, and syncope. Grade 4 adverse events associated with treatment temporary interruptions were (one of each, except two patients with thrombocytopenia) were hydronephrosis, pulmonary embolism, sepsis, and urinary tract obstruction. Most of these events appeared likely to be unrelated to pembrolizumab; however, some may have represented immune-related events (e.g., thyroiditis, pemphigoid, rash, and possibly pancreatitis).

For KEYNOTE164 as of the initial sBLA submission, 2 subjects discontinued treatment because of AEs that were considered not drug-related (data cutoff 3-Jun 2016): a patient who died on Day 6 (aspiration) and a patient with decreased appetite and ileus. By the updated summary of clinical safety (data cutoff 3-Aug 2016) 2 additional subjects discontinued due to AEs due autoimmune arthritis and pneumonitis, both known AEs related to pembrolizumab.

For KEYNOTE164, treatment was temporarily held in 13 patients (21%). AEs described as related to study drug were known AEs as listed in the pembrolizumab USPI such as pancreatitis, pneumonitis, and ALT/AST elevations. Note there was a subject with PT "increased bilirubin" captured as related to study drug, however, this was in the setting of other increased liver enzymes in a subject with metastatic CRC so it may have been related to the underlying disease. Causes for treatment interruption are summarized on Table 17 (some patients had more than one dose interruption or concomitant conditions).

Table 17: KEYNOTE164 Treatment interruptions

Preferred Term	N
AST increased	3
ALT increased	2
Blood alkaline phosphatase increased	2
Blood bilirubin increased	2
Pulmonary embolism	2
Abdominal pain	1
Amylase increased	1
Anemia	1
Blood creatinine increased	1
Cough	1
Influenza like illness	1
Inspiratory capacity decreased	1
Lipase increased	1
Pancreatitis	1
Pneumonitis	1
Pyrexia	1
Tooth infection	1
Upper gastrointestinal hemorrhage	1
Urinary tract obstruction	1

Of these treatment discontinuations, all were Grade 3 with the exception of ALT increased (2 patients), cough, influenza like illness, inspiratory capacity decreased, pneumonitis, fever, and tooth infection (1 patient each).

Taken together for the pooled safety of CRC in KEYNOTE016A and KEYNOTE164, treatment interruptions due to AEs were reported in 34% of subjects in the MSI-H/dMMR cancer population versus 22% in the reference population. The most frequently reported AEs leading to treatment interruption in the MSI-H/dMMR cancer population were anemia, aspartate aminotransferase increased, and pulmonary embolism (4.5% each). Treatment was withdrawn for 8% of subjects compared to 12% in the reference population. The most common reasons for treatment discontinuation were related to underlying disease or to known immune-related AEs.

In summary, patients in KEYNOTE016A had a higher rate of drug modifications due to toxicity. Although the frequency of all-grades AEs that led to drug interruption (temporarily held) was numerically higher in KN016A compared with those of KN164 and the reference safety population, the frequency of AEs that led to treatment discontinuation in KN016A and KN164 was lower than or consistent with that of the reference safety population. In the MSI-H/dMMR safety population, the frequency of deaths was lower than or consistent with that of the reference safety population (Table 18).

Table 18: Disposition of Safety Population and Reference Safety Population

As of Cut Off Data Date	KN016A (N=28)			KN164 (N=61)			Reference Safety Population (N=2799)		
	All Grades N (%)	Grade 3/4/5 Drug Modify <6 Months N (%)	Grade 3/4/5 Drug Modify ≥6 Months N (%)	All Grades N (%)	Grade 3/4/5 Drug Modify <6 Months N (%)	Grade 3/4/5 Drug Modify ≥6 Months N (%)	All Grades N (%)	Grade 3/4/5 Drug Modify <6 Months N (%)	Grade 3/4/5 Drug Modify ≥6 Months N (%)
Deaths	2 (7.1%)	1 (3.6%)	1 (3.6%)	1 (1.6%)	1 (1.6%)	0	110 (3.9%)	92 (3.3%)	18 (0.6%)
Discontinuation due to AE	2 (7.1%)	1 (3.6%)	1 (3.6%)	2 (3.3%)	1 (1.6%)	0	334 (11.9%)	208 (7.4%)	52 (1.9%)
Temporarily held due to AE [Interruptions]	17 (60.7%)	7 (25.0%)	4 (14.3%)	13 (21.3%)	9 (14.8%)	0	622 (22.2%)	219 (7.8%)	98 (3.5%)

REVIEWER COMMENT: KEYNOTE016A had a higher rate of drug modifications due to toxicity, but it is unclear whether this was from a longer duration of follow-up or a higher dose, or due the small sample size of each study. Patients in the safety reference database had a higher rate of treatment discontinuation associated with AEs, likely related to the larger numbers of patients treated and stage of development of pembrolizumab (as this population includes patients in the first clinical studies).

7.3.4 Significant Adverse Events (Grade 3-5)

AEs that occurred at toxicity Grade 3 or higher in the 89 patients in KEYNOTE016A and KEYNOTE164 are listed by system organ class (SOC) in Table 19 and Table 20.

Table 19: KEYNOTE016A: AEs by System Organ Class (SOC)

System Organ Class	Grade 3-4 N (%)	All Grades N (%)
Gastrointestinal disorders	5 (18)	24 (86)
General disorders and administration site conditions	1 (4)	21 (75)
Respiratory, thoracic and mediastinal disorders	2 (7)	17 (61)
Infections and infestations	2 (7)	16 (57)
Musculoskeletal and connective tissue disorders	0	16 (57)
Skin and subcutaneous tissue disorders	1 (4)	16 (57)
Nervous system disorders	2 (7)	15 (54)
Metabolism and nutrition disorders	4 (14)	14 (50)
Blood and lymphatic system disorders	10 (36)	13 (46)
Investigations	5 (18)	13 (46)
Psychiatric disorders	1 (4)	10 (36)
Injury, poisoning and procedural complications	1 (4)	9 (32)
Vascular disorders	1 (4)	9 (32)
Renal and urinary disorders	2 (7)	7 (25)
Cardiac disorders	0	6 (21)
Endocrine disorders	0	6 (21)
Ear and labyrinth disorders	0	5 (18)
Eye disorders	0	5 (18)
Reproductive system and breast disorders	0	5 (18)
Hepatobiliary disorders	0	2 (7)
Surgical and medical procedures	1 (4)	2 (7)
Congenital, familial and genetic disorders	0	1 (4)
Immune system disorders	0	1 (4)
Neoplasms benign, malignant and unspecified	0	1 (4)
Product issues*	0	1 (4)

*This is not a recognized MedDRA term. Investigators used the term “product issues” to describe 4 events of drain malfunction and stent malfunction in a single patient.

Table 20: KEYNOTE164 AEs by SOC

System Organ Class	Grade 3-4 N (%)	Total N (%)
Gastrointestinal disorders	5 (8)	44 (72)
General disorders	7 (11)	37 (61)
Musculoskeletal and connective tissue disorders	2 (3)	24 (39)
Infections and infestations	3 (5)	23 (38)
Respiratory, thoracic and mediastinal	4 (7)	22 (36)

System Organ Class	Grade 3-4 N (%)	Total N (%)
disorders		
Investigations	8 (13)	18 (30)
Skin and subcutaneous tissue disorders	0	17 (28)
Metabolism and nutrition disorders	3 (5)	16 (26)
Nervous system disorders	0	15 (25)
Blood and lymphatic system disorders	2 (3)	12 (20)
Vascular disorders	1 (2)	8 (13)
Neoplasms benign, malignant and unspecified	5 (8)	7 (11)
Renal and urinary disorders	1 (2)	7 (11)
Endocrine disorders	0	5 (8)
Eye disorders	0	5 (8)
Ear and labyrinth disorders	0	4 (7)
Hepatobiliary disorders	1 (2)	4 (7)
Psychiatric disorders	0	4 (7)
Cardiac disorders	2 (3)	3 (5)
Injury, poisoning and procedural complications	1 (2)	3 (5)
Reproductive system and breast disorders	1 (2)	3 (5)

Grade 3-4 AEs for PT and HLT are listed in Section 7.4.1 Common Adverse Events. Details for Grade 5 AEs from both studies are provided in Section 7.3.1 Deaths of this review.

REVIEWER COMMENT: There was an increased frequency of blood and lymphatic system disorders in the sBLA safety population compared to the reference safety population, specifically anemia (see Sections 7.4.1 Common Adverse Events*,* 7.4.2 Laboratory Findings*). Gastrointestinal events were also in greater frequency (11.2% in the sBLA safety population compared to 8.3% in the reference safety population), possible due to higher frequency of abdominal pain, diarrhea, and pancreatitis (see Section* 7.4.1 Common Adverse Events*) which can be attributed to underlying disease (CRC) or from noted AEs in the pembrolizumab USPI (pancreatitis). Investigation-related AEs were also higher in the submission, mostly liver enzymes, which may be reflective of the underlying disease etiology (metastatic CRC) see Section* 7.4.2 Laboratory Findings*). However, overall incidence of Grades 3-5 adverse events was similar between the two safety populations.*

7.3.5 Submission Specific Primary Safety Concerns

Immune-mediated AEs

Below are data on AEOSI for the 89 patients with MSI-H/dMMR cancers which represent the CRC safety population (KEYNOTE016A and KEYNOTE164).

In KEYNOTE016A, four AEOSI categories with reported events were hypothyroidism, pancreatitis, skin disorders, and thyroiditis. The AEOSI were presented in the CSR regardless of investigator-assessed causality and generally included all AE grades (with the exception of severe skin reactions). A total of 9 subjects (32.1%) had one or more AEOSIs. A total of 8 subjects (28.6%) reported a drug-related AEOSI. The most

commonly reported AEOSI was thyroiditis, at an incidence of 14.3% (n=4) and highest Grade 2, followed by pancreatitis at 10.7% (n=3). One patient experienced Grade 2 pancreatitis (asymptomatic), one patient experienced Grade 3 (symptomatic) pancreatitis, one patient experienced Grade 4 pancreatitis (in the context of a biliary tract stent malfunction). One patient experienced Grade 3 pruritic rash and pemphigoid. Of the 9 subjects, 2 required concomitant corticosteroid use; however there are not full details regarding the need of corticosteroids for the treatment of these irAEs per the applicant due to issues with the Johns Hopkins University (JHU) database.

In KEYNOTE164, there were 12 events identified in 10 subjects with an incidence of 16.4%: (incidence; number as follows): hypothyroidism (6.6%; n = 4), hyperthyroidism (4.9%; n = 3), pancreatitis (4.9%; n = 3), colitis (1.6%; n = 1), and pneumonitis (1.6%; n = 1). The majority of these events (10 of 12) were Grade 1 or Grade 2 AEOSI. Two patients (both with pancreatitis) had Grade 3 events. None of these events resulted in treatment discontinuation. Four of these patients were treated with corticosteroids (all pancreatitis AEs and one patient with pneumonitis).

Pancreatitis

Seven subjects in the MSI-H/dMMR CRC cancer population developed pancreatitis [Grade 2 (n=2); Grade 3 (n=4); and Grade 4 (n=1)]. Pancreatitis was considered to be drug-related for 6 of 7 subjects and only one of the drug related events was considered serious although dose modifications and steroid treatment were required for 4 of the subjects. Median time to onset was 79.0 days (range: 7 to 135 days) and the median duration was 33 days (range 2 to 126 days).

For KEYNOTE164, one of the 2 patients with Grade 3 pancreatitis had chemical pancreatitis (diagnosed by lipase/amylase) without clinical symptoms. Both events resolved within 5 weeks. One subject resumed pembrolizumab without recurrence of pancreatitis, while the other did not resume pembrolizumab as the last dose of study treatment was administered 29 days prior to the onset of pancreatitis.

The majority (4 of 7) of subjects with pancreatitis were biochemically diagnosed with lipase/amylase laboratories without associated clinical symptoms typically observed with pancreatitis. Of these 4 subjects, 1 was diagnosed in the context of a malfunctioning percutaneous biliary drain placed 16 days prior to the event due to obstructing carcinomatosis. Two of these 4 subjects had no radiographic change to indicate inflammatory changes usually observed with pancreatitis, both before or after the reported event, and the 4th subject had a 27-year history of alcohol consumption, which can lead to pancreatitis. Pancreatitis is an identified safety risk for the pembrolizumab program. Given that only 1 of the 7 subjects had pancreatitis that was considered serious, none resulted in study treatment discontinuation, and most (6 of 7) had already resolved at data cutoff, it is reasonable to conclude that pancreatitis does not change the overall safety profile of pembrolizumab. Furthermore, given the relatively small number of subjects in the MSI-H/dMMR cancer population, it is difficult to determine if the difference is a true difference (e.g. increased rate) versus a chance finding.

Thyroiditis

There were 4 reports of thyroiditis: all were reported from KEYNOTE016. One was Grade 1, and 3 were Grade 2. All incidents were considered to be drug-related. The thyroid laboratory panel results for these cases suggest that they were consistent with hypothyroidism and hyperthyroidism (1 subject each) and subclinical hyperthyroidism (2 subjects). Both subjects with subclinical hyperthyroidism eventually became hypothyroid. For KEYNOTE164, thyroid dysfunction events (by HLT) were infrequently observed, although follow-up was limited: increased TSH was observed in one patient, hyperthyroidism (Grade 1-2) in 3 patients, and hypothyroidism (Grade 1-2) in 4 patients, starting on Cycle 2 and up to Cycle 10.

REVIEWER COMMENT: Pancreatitis and thyroid disorders are known and uncommon identified risks of pembrolizumab therapy. The applicant submitted summary data on pancreatitis and thyroiditis across all 5 clinical trials which was reviewed. Of the 60 subjects with MSI-H/dMMR non-CRC, pancreatitis (Grade 3, serious) was reported in only 1 subject with biliary cancer. There were no thyroiditis events reported in KEYNOTE016C, KEYNOTE164, KEYNOTE012, KEYNOTE028, and KEYNOTE158, and the applicant attributed the reports in KEYNOTE016A to a function of terminology. This reviewer agrees that the risk of pancreatitis and thyroiditis in MSI-H/dMMR cancer are consistent with those described in the label.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, the incidence rates of adverse events were similar to the published incidence rates and were previously reviewed by FDA in separate efficacy supplements. The following tables summarize the AEs (irrespective of whether caused by pembrolizumab) by SOC, HLT and PT.

KEYNOTE016A

The safety of pembrolizumab in patients with MSI-H CRC was assessed in 28 patients. All patients experienced AEs. As in prior studies with pembrolizumab, the most frequently observed AEs in KEYNOTE016A were in the gastrointestinal (GI) system (mostly Grade 1-2 nausea, diarrhea, vomiting, and abdominal pain) and general disorders and administration site conditions (mostly Grade 1 fatigue). The most frequently reported AEs were fatigue/asthenia (54%), nausea/vomiting (46%), anemia (32%), arthralgia (32%), rash (32%), and diarrhea (32%). Most of these toxicities were Grade 1-2; Grade 3-4 events were reported in 46% patients. Grade 3-4 events that occurred in 3 or more patients were anemia, lymphopenia, hypocalcemia, and hypoalbuminemia. It appears that hematologic findings were more frequent in this population, as the incidence of anemia was 32% (including 25% Grade 3 anemia).

As described in Table 21, when combined as a high level term (HLT), the incidence of fatigue/asthenia is 54%, nausea/vomiting is 46%, diarrhea is 32%, and rashes is 32%.

Table 21: KEYNOTE016A: Adverse Events (AEs) by High Level Term (HLT) incidence > 4 subjects

High Level Term	N subjects	%
Asthenic conditions	15	54
Nausea and vomiting symptoms	13	46
Musculoskeletal and connective tissue pain and discomfort	11	39
Anemias	9	32
Diarrhea	9	32
Joint related signs and symptoms	9	32
Pruritus	9	32
Rashes, eruptions and exanthems	9	32
Gastrointestinal and abdominal pains	8	29
Upper respiratory tract infections	8	29
Upper respiratory tract signs and symptoms	8	29
Anxiety symptoms	7	25
Coughing and associated symptoms	7	25
Febrile disorders	7	25
Feelings and sensations	7	25
Headaches	7	25
Physical examination procedures and organ system status	7	25
Dermal and epidermal conditions	6	21
White blood cell analyses	6	21
Appetite disorders	5	18
Breathing abnormalities	5	18
Liver function analyses	5	18
Nasal congestion and inflammations	5	18
Edema	5	18
Acute and chronic pancreatitis	4	14
Acute and chronic thyroiditis	4	14
Apocrine and eccrine gland disorders	4	14
Flatulence, bloating and distension	4	14
Gastrointestinal atonic and hypomotility disorders	4	14
Muscle related signs and symptoms	4	14
Neurological signs and symptoms	4	14
Oral dryness and saliva altered	4	14
Peripheral vascular disorders	4	14
Protein metabolism disorders	4	14
Sodium imbalance	4	14
Supraventricular arrhythmias	4	14
Thrombocytopenias	4	14
Tissue enzyme analyses	4	14

Fatigue, nausea, anemia, diarrhea, arthralgia, rash, vomiting, abdominal pain, and fever were the most frequently observed AEs (irrespective of attribution). Grade 3-4 AEs observed in ≥ 2 patients were anemia (7 patients, incidence 25%), lymphopenia (5

patients, incidence 18%), hypocalcemia and hypoalbuminemia (3 patients each, incidence 11%), thrombocytopenia, sepsis, pulmonary embolism, pancreatitis, hyponatremia, diarrhea, and AST increased (2 patients each, incidence 7%). See Table 22 for the full listing of incidence of AEs by PT for at least 4 subjects. There was one patient who experienced a Grade 4 event of each of the following: hydronephrosis, lymphopenia, pancreatitis, pulmonary embolism, sepsis, and urinary tract infection; there were two patients with Grade 4 thrombocytopenia.

Table 22: KEYNOTE016A: AEs by Preferred Term (PT) incidence > 4 patients

Preferred Term	Gr 3-4	Gr 3-4%	Total	Total %
Fatigue	0	0	15	54
Nausea	0	0	11	39
Anemia	7	25	9	32
Diarrhea	2	7	9	32
Arthralgia	0	0	9	32
Rash	0	0	9	32
Vomiting	0	0	8	29
Abdominal pain	0	0	7	25
Headache	0	0	7	25
Pyrexia	0	0	7	25
Anxiety	0	0	6	21
Back pain	0	0	6	21
Cough	0	0	6	21
Dry skin	0	0	6	21
Lymphocyte count decreased	5	18	5	18
AST increased	2	7	5	18
Weight decreased	1	4	5	18
Decreased appetite	0	0	5	18
Nasal congestion	0	0	5	18
Oropharyngeal pain	0	0	5	18
Pruritus	0	0	5	18
Upper respiratory tract infection	0	0	5	18

The incidence rates in the CRC safety population appeared similar to the rates described in labeling for the pembrolizumab monotherapy studies with the exception of anemia. It is possible that due to GI bleeding, anemia may be more likely in patients with CRC. In summary, the overall number, type, and frequency of AEs reported in this study are consistent with the safety profile previously described for pembrolizumab at this higher dose (with many of the events expected in patient population with advanced CRC). As this is a small study population, incidences should be taken cautiously. No new safety concerns were identified in this study.

KEYNOTE164

The safety of pembrolizumab in patients with MSI-H/dMMR CRC was assessed in 61 patients. All but 1 patient experienced AEs (98%). The most frequently reported AEs are fatigue/asthenia, nausea/vomiting, abdominal pain, and diarrhea.

As described in Table 23, when combined as a HLT, the incidence of fatigue/asthenia is 46%, nausea/vomiting 38%, diarrhea 25%, and rashes 13%.

Table 23: KEYNOTE164: AEs by HLT (all Grades, incidence > 4 patients)

HLT	N (all grades)	%
Asthenic conditions	28	46
Nausea and vomiting symptoms	23	38
Gastrointestinal and abdominal pains	19	32
Diarrhea	15	25
Coughing and associated symptoms	14	23
Febrile disorders	13	22
Musculoskeletal and connective tissue pain and discomfort	13	22
Anemias	9	15
Appetite disorders	9	15
Liver function analyses	9	15
Edema	9	15
Joint related signs and symptoms	8	13
Rashes, eruptions and exanthems	8	13
Gastrointestinal atonic and hypomotility disorders	7	11
Pruritus	7	11
Headaches	6	10
Physical examination	6	10
Tissue enzyme analyses	6	10
Upper respiratory tract infections	6	10
General signs and symptoms	5	8
Pain and discomfort	5	8

Thyroid dysfunction events were infrequently observed: increased TSH was observed in one patient, hyperthyroidism (Grade 1-2) in 3 patients, and hypothyroidism (Grade 1-2) in 4 patients, starting on Cycle 2 and up to Cycle 10.

Table 24: KN164: AEs by PT (incidence > 4 patients)

Preferred Term	Gr 3-4	Gr 3-4%	Total	Total %
Fatigue	2	3	17	28
Abdominal pain	3	5	16	26
Nausea	0	0	16	26
Diarrhea	0	0	15	25
Vomiting	0	0	14	23
Pyrexia	1	2	13	21
Asthenia	2	3	10	16
Cough	0	0	10	16
Peripheral edema	1	2	9	15
Anemia	2	3	8	13
Arthralgia	0	0	8	13
Decreased appetite	0	0	8	13
ALT increased	3	5	6	10
Headache	0	0	6	10
Pruritus	0	0	6	10
Rash	0	0	6	10
Blood alkaline phosphatase increased	2	3	5	8

Preferred Term	Gr 3-4	Gr 3-4%	Total	Total %
Constipation	0	0	5	8
Weight decreased	0	0	5	8

Most of these toxicities were Grade 1-2; Grade 3 events (there was only one Grade 4 event which was increased bilirubin during long-term follow up) were reported in 46% patients and there was no Grade 3 event with an incidence higher than 5%. Grade 3 events with incidence rates between 3-5% were abdominal pain, ALT/AST increased, anemia, asthenia and fatigue, increased alkaline phosphatase, increased bilirubin, increased lipase, pancreatitis, ileus, and pulmonary embolism. The incidence rates appeared similar to the rates described in labeling for the pembrolizumab monotherapy studies.

Pooled CRC Safety Population

The type and incidence of AEs in the MSI-H/dMMR mCRC population were similar to the reference safety population (N=2799) with the exception of those events that are likely also related to advanced CRC, such as abdominal pain, which had an incidence in the pooled CRC population of 26% versus 10% in the reference population, and vomiting, which was 25% in the pooled population versus 14% in the reference population. The following were the AEs with the highest incidence in the pooled population (N=89; incidence; number): fatigue (36%;32), nausea (30%;27), diarrhea (27%;24), abdominal pain (26%;23), vomiting (25%;22), fever (22%;20), and anemia (19%;17). Again, anemia had a higher incidence in the pooled CRC population compared to the reference population (12%) possibly due to GI bleeding from the underlying cancer.

Grade 3-5 AEs in the MSI-H/dMMR CRC population occurred in 14 patients (16%); however, the only events observed in 2 or more patients were pancreatitis (3 patients) and fatigue (2 patients). Therefore, no conclusions can be made in regards to comparisons with the reference safety population (incidence of Grade 3-5 AEs 14%).

In conclusion, tolerance to treatment with pembrolizumab in subjects with MSI-H/dMMR mCRC treated in studies KEYNOTE016A and KEYNOTE164 was similar to other pembrolizumab studies as described in FDA's reviews and product labeling. The overall AE profile for the MSI-H/dMMR cancer population is representative of underlying AEs that occur in patients with CRC and consistent with that of the reference population safety data from subjects with melanoma and NSCLC. There were no new safety issues identified.

It is unlikely that data from Study KEYNOTE016 cohort C (subjects with MSI-H non-colorectal solid tumors), KEYNOTE012, KEYNOTE028, or KEYNOTE158 will substantively differ from the data analyzed in this review. In addition to the reviewed pooled data, Merck also submitted pooled data from an ongoing study in patients with head and neck carcinoma, consistent with the overall safety profile of pembrolizumab. This reviewer agrees that data from KEYNOTE016A and KEYNOTE164 is sufficient for the determination of the risk of pembrolizumab for the proposed indication.

7.4.2 Laboratory Findings

The applicant stated that due to factors related to data collection, changes in laboratory parameters from baseline could not be analyzed for KEYNOTE016A. The analyses are based on the worst toxicities observed. As expected and previously described, liver function abnormalities were frequently observed, as summarized in Table 25.

Table 25: KEYNOTE016A Liver Function Laboratory Assessment

Laboratory category	N (%)
ALT	
Grade 2 (> 3 – 5 x ULN)	3 (11)
Grade 3-4 (> 5 x ULN)	0
AST	
Grade 2 (> 3 – 5 x ULN)	3 (11)
Grade 3 (> 5 – 20 x ULN)	1 (4)
Bilirubin	
≥ 2 x ULN	4 (14)
Alkaline phosphatase	
≥ 1.5 x ULN	11 (41)
Transaminase AND bilirubin	
AT ≥ 3 x ULN and BI ≥ 1.5 x ULN	1 (4)
AT ≥ 3 x ULN and BI ≥ 2 x ULN	1 (4)

Other laboratory abnormalities observed, irrespective of causality (patient incidence in parentheses), were Grade 1-2 hypoalbuminemia (43%), Grade 3 hypoalbuminemia (4%), Grade 1-2 increased amylase (11%), Grade 3 amylase (7%), Grade 1-2 hypocalcemia (25%), Grade 3-4 hypocalcemia (7%), Grade 3 hypercalcemia (4%), Grade 1-2 increased creatinine (18%), Grade 4 hypoglycemia (4%), Grade 1-2 hyperglycemia (79%), and hematologic abnormalities. Most of these lab abnormalities were also reported as adverse events or were concurrent with clinical events for which they are expected (i.e., pancreatitis and elevated amylase).

For KEYNOTE164, the most significant laboratory changes (from Grade 1-2 at baseline to ≥ Grade 3 or from normal at baseline to Grade 2) included increased alkaline phosphatase (7%), increased AST increased (5%), increased aPTT (3%), increased ALT (3%), increased amylase (3%), increased bilirubin (3%), hemoglobin (3%), and increased creatinine (2%). One subject (1.6%) had a shift to Grade 4 in bilirubin. All these changes are reflected in the AEs dataset when there were clinical manifestations (i.e., pancreatitis, liver toxicity, etc.). As expected and previously described, liver function abnormalities were frequently observed, as summarized in Table 26 (summary based on 59 patients who had normal liver function at baseline).

Table 26: KN164 liver function laboratory assessment

Laboratory category	N (%)
ALT	
Grade 2 (> 3 – 5 x ULN)	4 (7)
Grade 3 (> 5 – 20 x ULN)	3 (5)
Grade 4 (>20 x ULN)	0
AST	

Grade 2 (> 3 – 5 x ULN)	6 (10)
Grade 3 (> 5 – 20 x ULN)	3 (5)
Grade 4 (>20 x ULN)	0
Bilirubin	
≥ 2 x ULN	4 (7)
Alkaline phosphatase	
≥ 1.5 x ULN	19 (32)
Transaminase AND bilirubin	
AT ≥ 3 x ULN and BI ≥ 1.5 x ULN	4 (7)
AT ≥ 3 x ULN and BI ≥ 2 x ULN	4 (7)

REVIEWER COMMENT: Aside from the laboratories associated with pancreatitis (elevated amylase/lipase), there were no appreciable differences in laboratory values between the safety population and the reference population.

7.4.3 Vital Signs

Vital signs, weight, physical examinations, ECOG performance status, laboratory safety tests were obtained and assessed at designated intervals throughout the study for the pembrolizumab and chemotherapy treatment arms. Refer to the Study Flow Charts 9.4 Supplemental information in for timing of assessments.

Due to JHU data availability, the mean change in vital signs and other physical observations for the subjects in the as treated population could not be provided for KEYNOTE016A.

No clinically meaningful vital sign changes were observed in the KEYNOTE164 population based on mean change in vital sign measurements from baseline over time.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained as part of routine clinical testing.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies/clinical trials conducted with pembrolizumab.

7.4.6 Immunogenicity

An integrated immunogenicity evaluation was performed across data from studies KEYNOTE001, KEYNOTE002, KEYNOTE006, KEYNOTE010, KEYNOTE012, P024, KEYNOTE052, P055 and KEYNOTE164. The total of 3048 subjects were included in the immunogenicity assessment (1535 melanoma subjects, 1237 NSCLC subjects, 101 head and neck squamous cell cancer subjects, 121 urothelial cancer [UC] subjects and 54 MSI-H subjects), and 1437 subjects were evaluable. The observed incidence of treatment-emergent anti-drug antibodies (ADAs) in evaluable subjects based on the pooled population is 1.9% (28 out of 1437), based on 28 subjects with confirmed

treatment-emergent positive status, relative to 1437 evaluable subjects (of 1437 subjects, 28 subjects had treatment-emergent positive, 14 subjects had non-treatment-emergent positive and 1395 subjects had negative immunogenicity status). These data indicate pembrolizumab has a low potential for eliciting the formation of ADAs.

In the subgroup of MSI-H/dMMR subjects, 1 of 54 evaluable subjects (51 negative, 2 non-treatment emergent positive, and 1 treatment emergent) had treatment emergent ADA yielding an incidence rate for treatment emergent antibodies of 1.9%.

None of the subjects had any AEs associated with ADAs, such as hypersensitivity events (e.g., anaphylaxis, urticaria, angioedema) or injection site reactions. No clinically significant impact on efficacy (i.e., tumor size change) was established.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The sBLA has data submitted from subjects on 5 trials who were administered 2 different doses of pembrolizumab: 10 mg/kg every 2 weeks or 200 mg every 3 weeks.

Table 27: Dose by trial

Study	N (MSI-H)	Dose
012	6 non CRC	**10mg/kg every 2 weeks**
016	30 non CRC 28 CRC	
028	5 non CRC	
164	61 CRC	**200mg every 3 weeks**
158	19 non CRC	

Below is a reviewer table of summary AEs by trial, which also shows the difference in dose for each trial:

Table 28: Summary AEs per trial and dose

	KN016A 10mg/kg 2 weeks	KN164 200mg 3 weeks	Pooled MSI-H
	N=28 (%)	N=61 (%)	N=89; n(%)
Subjects who experienced an AE	28 (100)	60 (98)	88 (99)
Subjects who experienced a Grade 1-2 AE	27 (96)	57 (93)	84 (94)
Subjects who experienced a Grade 3-4 AE	13 (46)	28 (46)	41 (46)
Subjects who experienced an SAE	14 (50)	23 (38)	35 (39)
Deaths reported as an AE	4 (14)	2 (3)	3 (3)*

*In review of the death data from the MSI-H/dMMR safety population, 3 deaths appeared to be at least partly caused by AE and not completely by the underlying etiology.

There were no obvious differences in AEs by dose. Although three deaths associated with adverse events were reported in KEYNOTE016A, all appeared to be related to underlying disease progression.

REVIEWER COMMENT: Due to the small numbers of subjects in this safety cohort compared to the reference safety pool (N=2799), and due to the different doses administered in each study (KEYNOTE016A was 10 mg/kg every 2 weeks vs KEYNOTE164 at 200mg every 3 weeks) it is difficult to determine the clinical significance of dose dependency for AEs. There are no new safety signals identified thus far.

7.5.2 Time Dependency for Adverse Events

REVIEWER COMMENT: Due to the small numbers of subjects in this safety cohort compared to the reference safety pool (N=2799), it is difficult to determine the clinical significance for time dependency for AEs.

7.5.3 Drug-Demographic Interactions

Below is the table for key demographics and baseline characteristics for the safety population (KEYNOTE016A and KEYNOTE164) for this sBLA:

Table 29: Demographic and Baseline Characteristics for Safety Population

Demographic Baseline Characteristics		KEYNOTE 016 Cohort A		KEYNOTE 164	
		N=28		N=61	
Age	Mean (range)	49 (24-75)		54 (21-84)	
		Count	%	Count	%
Age Group	≥ 65 years	8	29	19	31
	< 65 years	20	71	42	69
	65 <= Age <75	7	25	15	25
	≥ 75 years	1	4	4	7
Sex	F	13	47	25	41
	M	15	54	36	59
Prior therapy	None	1	4	0	0
	1st line	7	25	6	10
	2nd line	8	29	28	46
	3rd line	7	25	13	21
	4th line	4	14	5	8
	≥ 5th line	1	4	9	15
KRAS	Mutant	11	39	16	26
	Wild Type	17	61	38	62

Demographic Baseline Characteristics		KEYNOTE 016 Cohort A		KEYNOTE 164	
		N=28		N=61	
MSI-H	PCR	21	75	39	64
	IHC	19	68	38	62
	Both tests	12	43	16	26
	MSI-H total (either test)	28	100	60	98
Metastatic disease	Stage 4	28	100	61	100

The applicant performed a sensitivity analysis for the influence of patient characteristics and drug exposure on efficacy (see 6.1.7 Subpopulations) and they concluded that there was no influence.

REVIEWER COMMENT: The applicant's analysis of subgroups in regards to AE was reviewed for age, gender, ECOG, and region. Demographic characteristics did not appear to have an impact on the safety of pembrolizumab in the MSI-H/dMMR population; however, as noted earlier, the population had limited numbers (N=89) compared to the reference (N=2799).

7.5.4 Drug-Disease Interactions

Data from subjects with 15 tumor histologies (see Table 30) was submitted to the sBLA. Based on the limited numbers of patients with different tumor-types, it would be difficult to assess whether safety would be different in patients with different tumor types; however, based on the underlying mechanism of action of pembrolizumab, it would not be expected that large differences in safety would exist.

Table 30: Enrollment by tumor type over 5 trials for MSI-H/dMMR cancers

Cancer type	(n)
Colorectal	90
Esophageal	1
Gastric	9
Ampullary / Biliary	11
Pancreatic	6
Small Intestine	8
Breast	2
Endometrial	14
Thyroid	1

Cancer type	(n)
SCLC	1
Bladder	1
Kidney	1
Prostate	2
Sarcoma	1
Retroperitoneal	1

7.5.5 Drug-Drug Interactions

No formal PK drug interaction studies have been conducted with pembrolizumab. Pembrolizumab belongs to the class of immunoglobulin G (IgG) antibodies, which are administered parentally and cleared by catabolism, and consequently extrinsic factors, including food and drug-drug interactions, are not anticipated to influence the exposure of pembrolizumab. See the FDA Clinical Pharmacology review for details.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No studies have been performed to test the potential of pembrolizumab for carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Females of reproductive potential are advised to use effective contraception during treatment with pembrolizumab and for at least 4 months following the final dose. For additional details, see the FDA Pharmacology/Toxicology Review from the original BLA submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness of pembrolizumab have not been established in pediatric patients. However, based on the expected comparability in PKs between adolescents and adults, and based on the expectation that pembrolizumab is reasonably likely to predict benefit across MSI-H/dMMR tumors, I agree that pembrolizumab can be indicated for the treatment of adolescent patients (e.g., 12 years of age and older) with MSI-H/dMMR tumors. There are reports of Lynch Syndrome-associated cancers in older adolescents. Merck is conducting an ongoing pediatric study of pembrolizumab

and during the 13 Feb 2017 meeting, agreed to obtain data in pediatric patients with MSI-H/dMMR tumors.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No experience with overdose with pembrolizumab is available. On the basis of its pharmacological properties, there are no concerns regarding the potential for abuse, withdrawal, or rebound with pembrolizumab.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Pembrolizumab received accelerated approval for the treatment of patients with unresectable or metastatic melanoma in September 2014, for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 in October 2015, and for the treatment of recurrent or metastatic HNSCC in August 2016. It is currently under review for Hodgkin's lymphoma. The safety profile has largely been consistent in clinical trials following the initial approval.

9 Appendices

9.1 Literature Review/References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66:7.

2. Ohhara Y, Fukuda N, Takeuchi S, Honma R, Shimizu Y, Kinoshita I, Dosaka-Akita H. Role of targeted therapy in metastatic colorectal cancer. World J Gastrointest Oncol. 2016 Sep 15;8(9):642-55.

3. Grothey A., Van Cutsem E., Sobrero A., Siena S., Falcone A., et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. The Lancet 2013 Jan; 381 (9863):303-12.

4. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. RECOURSE Study Group. 303-12. N Engl J Med. 2015 May 14;372(20):1909-19.

5. Setaffy L, Langner C.Microsatellite instability in colorectal cancer: clinicopathological significance. Pol J Pathol. 2015 Sep;66(3):203-18

6. Gubin MM, Zhang X2, Schuster H, Caron E, Ward JP, Noguchi T, Ivanova Y, Hundal J, Arthur CD, Krebber WJ, Mulder GE, Toebes M, Vesely MD, Lam SS, Korman AJ, Allison JP, Freeman GJ, Sharpe AH, Pearce EL, Schumacher TN, Aebersold R, Rammensee HG, Melief CJ, Mardis ER, Gillanders WE, Artyomov MN, Schreiber RD. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. Nature. 2014 Nov 27;515(7528):577-81.

7. Llosa NJ, Cruise M2, Tam A, Wicks EC, Hechenbleikner EM, Taube JM, Blosser RL, Fan H, Wang H, Luber BS, Zhang M, Papadopoulos N, Kinzler KW, Vogelstein B, Sears CL, Anders RA, Pardoll DM, Housseau F. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov. 2015 Jan;5(1):43-51. Epub 2014 Oct 30.

8. Kawakami H, Zaanan A, Sinicrope FA. Implications of mismatch repair-deficient status on management of early stage colorectal cancer. J Gastrointest Oncol. 2015 Dec;6(6):676-84.

9. Müller CI, Schulmann K, Reinacher-Schick A, Andre N, Arnold D, Tannapfel A, Arkenau H, Hahn SA, Schmoll SH, Porschen R, Schmiegel W, Graeven U; AIO Colorectal Study Group. Predictive and prognostic value of microsatellite instability in patients with advanced colorectal cancer treated with a fluoropyrimidine and oxaliplatin

containing first-line chemotherapy. A report of the AIO Colorectal Study Group. Int J Colorectal Dis. 2008 Nov;23(11):1033-9.

10. Microsatellite instability and colorectal cancer prognosis. Benatti P, Gafà R, Barana D, Marino M, Scarselli A, Pedroni M, Maestri I, Guerzoni L, Roncucci L, Menigatti M, Roncari B, Maffei S, Rossi G, Ponti G, Santini A, Losi L, Di Gregorio C, Oliani C, Ponz de Leon M, Lanza G.Clin Cancer Res. 2005 Dec 1;11(23):8332-40. Erratum in: Clin Cancer Res. 2006 Jun 15;12(12):3868-9.NCCN states that there is data to suggest that MSI-H tumors have a decreased likelihood to metastasize

11. Oh BY, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, Lee WY, Chun HK. Prognostic factors in sporadic colon cancer with high-level microsatellite instability. Surgery. 2016 May;159(5):1372-81.

12. Chang Gon Kim, Joong Bae Ahn, Minkyu Jung, Seung Hoon Beom, Chan Kim, Joo Hoon Kim,Su Jin Heo, Hyung Soon Park, Jee Hung Kim, Nam Kyu Kim, Byung Soh Min, Hoguen Kim, Woong Sub Koom and Sang Joon Shin. Effects of microsatellite instability on recurrence patterns and outcomes in colorectal cancers. British Journal of Cancer (2016) 115, 25–33.

13. USPI Label (revision date 10/24/2016). Available at: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

14. American Cancer Society accessed on 25 Jan 2017 https://www.cancer.org/research/cancer-facts-statistics/colorectal-cancer-facts-figures.html

9.2 Labeling Recommendations

The label was not sent back to the applicant for review before the time of my submission.

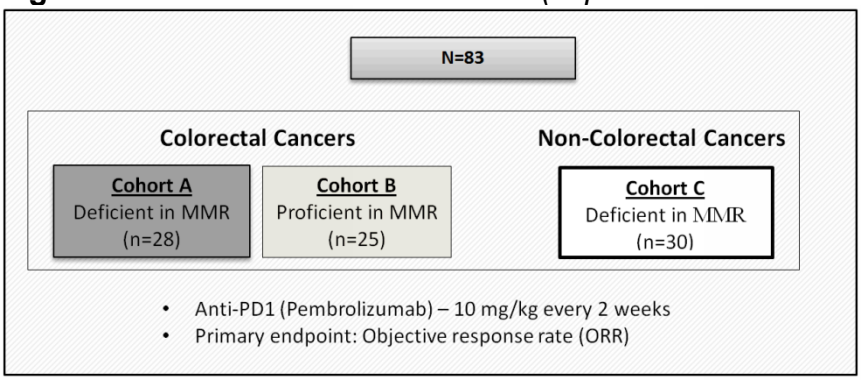
9.3 Advisory Committee Meeting

There was no advisory committee meeting for this application because the safety profile of pembrolizumab is acceptable for the treatment of patients with recurrent or metastatic MSI-H cancers, the application did not raise significant public health questions regarding the role of pembrolizumab for this indication, and outside expertise was not necessary as there were no controversial issues that could benefit from an Advisory Committee discussion.

9.4 Supplemental information

9.4.1 KEYNOTE 016

Figure 2: Schema of KEYNOTE 016 *(copied from sBLA submission)*



Evaluable patients were confirmed using the MSI Analysis System from Promega at Johns Hopkins (see description below). This test determined MSI status through the insertion or deletion of repeating units in the five nearly monomorphic mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21 and NR-24). At least 2 MSI loci were required to be evaluable in Cohorts A and C. Patients were assigned to a new cohort and/or replaced based on the Promega test results.

The MSI Analysis System (Promega), Version 1.2, is a fluorescent multiplex PCR based method used to detect microsatellite instability (MSI). This instability is due to insertion or deletion of repeating units during DNA replication and failure of the mismatch repair system (MMR) to correct these errors. MSI analysis typically involves comparing allelic profiles of microsatellite markers generated by amplification from matching pairs of test samples, which may be MMR-deficient, and normal tissue samples. New alleles in the abnormal sample not found in the corresponding normal sample indicate the presence of MSI. The MSI Analysis System, Version 1.2, includes fluorescently labeled primers (marker panel) for co-amplification of seven markers for analysis of the MSI-high (MSI-H) phenotype, including five nearly monomorphic mononucleotide repeat markers (BAT-25, BAT-26, MON0-27, NR-21 and NR-24) and two highly polymorphic pentanucleotide repeat markers (Penta C and Penta D). Amplified fragments are detected using an ABI PRISM® 310, 3100, 3100-Avant, 3130 or 3130xl Genetic Analyzer after spectral calibration. GeneMapper® 4.0 software was used for data analysis and assignment of genotype.

Key Inclusion Criteria

- Subjects with measureable disease
- Patients with locally advanced unresectable or metastatic CRC must have received or refused at least 2 prior cancer therapy regimens.

    - include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS wild type)
- Patients with other cancer types must have received or refused at least 1 prior cancer therapy regimen.
- MSI testing: performed locally by CLIA certified immunohistochemistry (IHC) or PCR based tests (see Section 2.6.1 MSI-H testing)
- Age > 18 years
- ECOG performance status 0-1
- Adequate organ function, defined as:
    - Absolute neutrophil count (ANC) ≥1500/mcL
    - Platelets ≥100,000/uL
    - Hemoglobin ≥9.0 g/dL
    - Serum creatinine ≤1.5 x upper limit normal (ULN)
    - Total bilirubin ≤1.5 x ULN
    - Albumin ≥2.5mg/dL
    - Coagulation parameters ≤1.5 x ULN
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN

Key Exclusion Criteria

- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- Patient who has had chemotherapy, radiation, or biological cancer therapy within 14 days prior to the first dose of study drug; investigational agent or using an investigational device within 28 days of the first dose of study drug; surgery within 4 weeks; Patients who have received any of the following concomitant therapy: IL-2, interferon or other non-study immunotherapy regimens; immunosuppressive agents; other investigational therapies; or chronic use of systemic corticosteroids (used in the management of cancer or non-cancer-related illnesses) within 1 week; patients who have received any non-oncology vaccine therapy used for prevention of infectious diseases including live seasonal vaccinations for up to 30 days prior to dosing of study drug; growth factors within 14 days
- History of any autoimmune disease, HIV, hepatitis B or C
- Interstitial lung disease

Treatment Plan

Pembrolizumab was administered as monotherapy 10mg/kg intravenously every 14 days as a 30 minute infusion, for up to 24 months. No prophylactic pre-medication was given.

Dose adjustments/modifications

Dose adjustments were not permitted in individual patients. Pembrolizumab was withheld for drug-related Grade 4 hematologic toxicities, nonhematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 31 below. Supportive care guidelines, including use of corticosteroids, were included in the protocol and also provided to investigators in a separate document, the Events of Clinical Interest Guidance Document. The protocol also included supportive care treatment guidelines for infusion reactions (see Section 9.4 Supplemental information).

Table 31: Dose Delay Guidelines for Pembrolizumab during KEYNOTE 016

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion
Non-hematological toxicity	1	No	N/A	N/A	N/A
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	4	Yes	Toxicity resolved to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
Severe or life-threatening AEs	Any	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Subject should be discontinued if toxicity does not resolve within 12 weeks of last infusion

If toxicity did not resolve to Grade 0-1 within 12 weeks after the last infusion, the trial treatment was discontinued after consultation with the Applicant. Subjects with a laboratory adverse event still at Grade 2 after 12 weeks continued treatment in the trial only if asymptomatic and controlled.

Permanent discontinuation of pembrolizumab was considered for any of the following immune-related adverse reactions (irAEs):

- 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, and gastrointestinal perforation
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal
- 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
- Any grade Guillain-Barré syndrome, or myasthenia gravis or other neurologic symptoms that impact activity of daily living
- Severe immune-mediated reactions 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

Statistical Analysis Plan

• The primary efficacy endpoint was ORR per RECIST 1.1. The point estimate and 95% confidence interval were provided using the exact binomial method. The subjects without response, in the primary analysis population (ASaT) data, were counted as non-responders.

• For DCR (per RECIST 1.1), the point estimate, 95% confidence interval was provided using the exact binomial method. The subjects without response data, in the analysis population (ASaT), were considered as having the disease not under control.

• For DOR (per RECIST 1.1), Kaplan-Meier (KM) curves and median estimates from the KM curves were provided as appropriate.

• For PFS (per RECIST 1.1) and OS endpoints, Kaplan-Meier (KM) curves and median estimates from the KM curves were provided as appropriate.

Protocol Amendments

Key changes are described for the following protocol amendments relevant to this application:

- *Amendment 1 (12 July 2013): Updated protocol to allow for testing of MSI status in subjects with non-CRC tumors. Eligibility criteria for bilirubin were updated to include patients with diagnosed Gilbert's Syndrome.*
- *Amendment 2 (19 Sept 2013): Clarified the evaluable population. MSI-H tumors will be defined by using standard clinical criteria and require at least two affected loci.*
- *Amendment 3 (13 Jan 2014): Updated eligibility criteria for subjects with CRC and non-CRC tumors. Removed Promega testing must take place at Johns Hopkins.*
- *Amendment 4 (18 March 2014): Subjects with thyroid disease were allowed but subjects with a history of any autoimmune disease were to be excluded.*
- *Amendment 5 (5 May 2014): Updated the definition and eligibility rules for Cohort C. The requirement for ECG monitoring while on study has been removed to reflect the guideline of the commercial sponsor for this product.*
- *Amendment 6 (19 Nov 2014): Updated exclusion criteria regarding administration of live vaccines.*
- *Amendment 7 (4 March 2015): Expanded Cohorts A and C to include up to an additional 50 subjects in each cohort. Changes in the eligibility criteria pertaining to the acceptable ranges for AST/ALT, and revision of criteria for dosing delays to make consistent with the commercial sponsor were amended.*
- *Amendment 8 (1 May 2016): Clarification that serious adverse events were to be monitored for 90 days after the last infusion of study drug. Revisions to exclusion criteria to conform to the commercial sponsor's development program. Clarifications regarding follow-up and re-treatment procedures following 24 months on study drug.*

Schedule of Key Events (modified from sBLA submission)

Trial Period	Screening Phase	Treatment Cycles						End of Treatment		Post-Treatment	
Treatment Cycle	Screening	1	2	3	4	5	Cycle 6 and beyond	Last Dose	Safety Follow-up	Follow Up Visits	Survival Follow up
								At time of tx discon	30 d post dose	Q 9 wks post last dose	Q 8 weeks
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Clinical Procedures/Assessments											
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG (Local)	X										
Full or directed Phys. Exam; ECOG	X	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status									X	X	X
Survival Status											X
Trial Treatment Administration											
Pembrolizumab		X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory											
PT/INR and aPTT; UA	X										
CBC with Differential and Chem Panel	X		X	X	X	X	X*	X	X		
T3(or Free T3), FT4 and TSH	X		X		X		X*		X		
Serum tumor markers: CEA	X	X	X	X	X	X	X	X			
Efficacy Measurements											
Tumor Imaging	X			X			X	X		X	
Tumor Tissue Collection											
Archival and/or Newly Obtained Tissue Collection	X										

* not on Cycle 7

9.4.2 KEYNOTE 164

Key Inclusion Criteria

- Cohort A enrolled subjects who have experienced documented objective radiographic or clinical disease progression previously treated with standard of care therapies (including fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab [if KRAS wild type])
- Locally advanced unresectable or metastatic pathologically; MMR deficient or MSI-H CRC
  - MSI status in tumor samples was determined locally at each participating center using an IHC- or PCR-based test.
- Measurable disease by RECIST 1.1
- ECOG Performance Status 0 or 1
- Adequate renal, hepatic, and hematologic function defined as follows: serum creatinine ≤1.5 mg/dL, total serum bilirubin ≤ 1.5 x upper limit of normal (ULN), serum AST (SGOT) and/or ALT (SGPT) ≤ 2.5 x ULN (or ≤ 5.0 x ULN if considered due to tumor), albumin ≥ 2.5 mg/dL, INR or PT or aPTT ≤ 1.5 x ULN (unless patient on anticoagulation therapy), ANC ≥ 1500/mm^3, platelets ≥100,000/mm^3 and hemoglobin ≥ 9g/dL

Key Exclusion Criteria

- Investigational agent or investigational device within 4 weeks of the first dose of trial treatment
- Active autoimmune disease that has required systemic treatment in past 2 years (with use of disease modifying agents, corticosteroids or immunosuppressive drugs)
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or immunosuppressive therapy within 7 days prior to the first dose of trial drug
- Has had a prior anti-cancer monoclonal antibody, chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study or who has not recovered to ≤ Grade 1 or at baseline
- Other active malignancy
- Patients with brain metastasis that are not stable
- Infection requiring systemic therapy
- Known positive serology for HIV, active Hepatitis B, and/or active Hepatitis C infection

- Patients who have had a major surgery and not recovered from side effects of such procedure
- History of, or any evidence of interstitial lung disease or active, noninfectious pneumonitis
- Has received a live vaccine within 30 days of planned start of study therapy

Treatment

Pembrolizumab 200mg fixed dose was administered as an intravenous 30 minute infusion q 3 weeks.

Dose modifications

Pembrolizumab will be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 32.

Table 32: Pembrolizumab dose adjustments for toxicities

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Dose modifications and treatment guidelines for infusional reaction treatment were provided as were suggested supportive care measures for the management of adverse events with potential immunologic etiology.

Prohibited medications

Aside from live vaccines and systemic glucocorticoids, all treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Radiation therapy for tumor control was prohibited.

Statistical Analysis Plan

There was one planned interim analysis for futility. For the primary efficacy endpoint of ORR per RECIST 1.1 assessed by central imaging vendor, the point estimate and 95% confidence interval were provided using exact binomial method by Clopper and Pearson. Subjects in the ASaT population without response assessments were counted as non-responders.

Protocol Amendments

Key changes are described for the following protocol amendments relevant to this application:

- *Amendment 1 (8 July 2015): Indication statement updated to mismatched repair deficient or microsatellite instability High CRC. Baseline imaging assessment was changed from within 14 days prior to allocation to within 28 days prior to allocation. Overall survival follow up changed from every 8 weeks to every 9 weeks.*
- *Amendment 2 (19 Oct 2015): Modification of inclusion criterion to define previous lines of therapy, "Subjects who have been previously treated with approved standard therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan." ORR, DOR, and PFS per RECIST 1.1 assessed by Investigator were added to "other objectives."*
- *Amendment 3 (24 March 2016): Addition of a new cohort B consisting of subjects with locally advanced unresectable or metastatic MMR deficient or MSI high CRC*

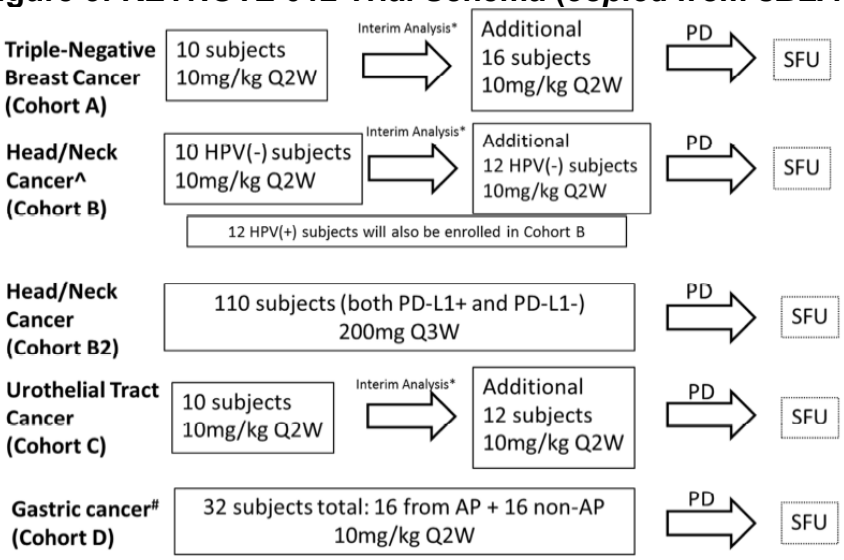
and who have been previously treated with at least one line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody, N=60) to the protocol. A second cohort of 60 subjects was added to evaluate pembrolizumab 200 mg 3QW in subjects with colorectal cancer (CRC) who have undergone 1 line of systemic treatment (fluoropyrimidine +oxaliplatin or fluoropyrimidine +irinotecan +/- anti-VEGF/EGFR monoclonal antibody). The first cohort will be designated Cohort A, the second, Cohort B. A requirement was added for required tumor tissue sampling in Cohort B. Newly obtained tissue from primary tumor is encouraged if it is accessible and not a contraindication due to subject safety concerns; otherwise, archival tumor tissue from primary tumor is accepted. Statistics were amended for new sample size.

Table 33: KEYNOTE 164 Schedule of Events *(modified from sBLA submission)*

Trial Period	**Screening Phase**	**Treatment Cycles**						**End of Treatment**		**Post-Treatment**	
Treatment Cycle	Screening	1	2	3	4	5	Cycle 6 and beyond	Last Dose	Safety Follow-up	Follow Up Visits	Survival Follow up
								At time of tx discon	30 d post dose	Q 9 wks post last dose	Q 8 weeks
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Clinical Procedures/Assessments											
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	
ePROs (HRQoL Measures)		X	X	X	X	X		X	X		
12-Lead ECG (Local)	X										
Full or directed Phys. Exam; ECOG	X	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status										X	X
Survival Status											X
Trial Treatment Administration											
Pembrolizumab		X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory											
Pregnancy Test Serum or Urine	X	X	X	X	X	X	X		X		
PT/INR and aPTT; UA	X										
CBC with Differential and Chem Panel	X		X	X	X	X	X	X	X		
T3(or Free T3), FT4 and TSH	X		X		X		X		X		
Serum carcinoembryonic antigen (CEA) and CA19-9	X			X		X	X				
Efficacy Measurements											
Tumor Imaging	X			X			X	X		X	
Tumor Tissue Collection											
Archival and/or Newly Obtained Tissue Collection	X							X			

9.4.3 KEYNOTE 012

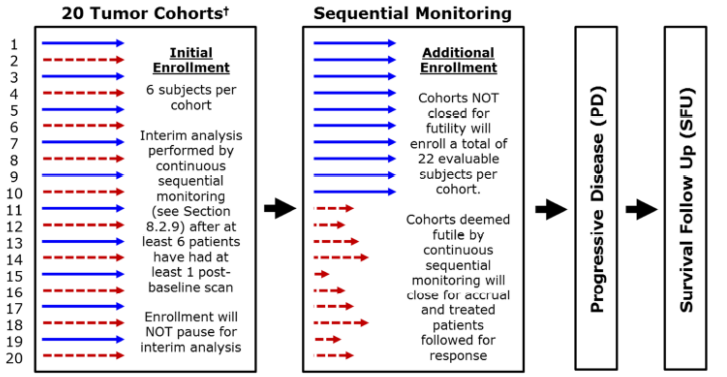
Figure 3: KEYNOTE 012 Trial Schema (*copied from sBLA submission*)



*An interim analysis for each cohort may be performed depending on the rate of enrollment or other factors determined during the course of the trial. This interim analysis would only be performed when ≥ 10 patients in the respective cohort have had at least two post-baseline scans.
^A total of 34 subjects with head/neck cancer will be enrolled in Cohort B of the study
# The gastric cancer cohort will be stratified to enroll 16 patients in Asia Pacific (AP) and 16 patients ex-AP. No interim analysis will be performed in this cohort.
PD = Progressive Disease
SFU = Survival Follow-up

9.4.4 KEYNOTE 028

Figure 4: KEYNOTE 028 Trial Schema (*copied from sBLA submission)*



† List of 20 Advanced Solid Tumor Indication for which No Curative Therapy Exists:

A1 Colon or Rectal Adenocarcinoma
A2 Anal Canal Squamous Cell Carcinoma
A3 Pancreas Adenocarcinoma
A4 Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction)
A5 Biliary Tract Adenocarcinoma (Gallbladder and Biliary Tree but excluding Ampulla of Vater Cancers)
A6 Carcinoid Tumors
A7 Neuroendocrine Carcinomas (Well or moderately differentiated Pancreatic Neuroendocrine Tumor)

B1 ER Positive HER2 Negative Breast Cancer
B2 Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma
B3 Endometrial Carcinoma
B4 Cervical Squamous Cell Cancer
B5 Vulvar Squamous Cell Carcinoma

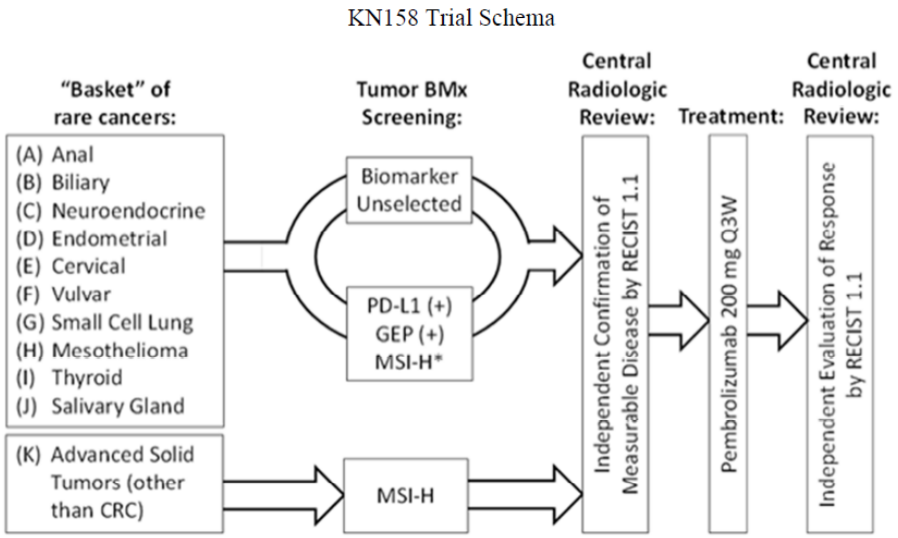
C1 Small Cell Lung Cancer
C2 Mesothelioma (Malignant Pleural Mesothelioma)

D1 Thyroid Cancer (Papillary or Follicular Subtype)
D2 Salivary Gland Carcinoma
D3 Nasopharyngeal Carcinoma

E1 Glioblastoma Multiforme
E2 Leiomyosarcoma
E3 Prostate Adenocarcinoma

9.4.5 KEYNOTE 158

Figure 5: KEYNOTE 158 Trial Schema (*copied from sBLA submission)*



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

/s/

LEIGH J MARCUS
02/15/2017

STEVEN J LEMERY
02/15/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

CHEMISTRY REVIEW(S)

Memorandum of Review

(Environmental Assessment)

Date: February 14, 2017
To: File for STN: 125514 SUPPL-14 (SD#775)

From: Mark Paciga, Ph.D., Product Quality Reviewer, DBRR1/OBP

Through: Sarah Kennett, Ph.D., Review Chief, DBRR1/OBP

Subject: 125514/SUPPL-14 Environmental assessment and acceptability of drug product used in the clinical study

Applicant: Merck Sharp & Dohme Corp.

Product: Keytruda® (pembrolizumab)

Indication: (b) (4)

Received: September 8, 2016
Action Due Date: March 8, 2017

Review Recommendation: The claim of categorical exclusion from the environmental assessment is accepted. Appropriate pembrolizumab drug product supplies were used in these studies.

1. FDA Regional Information
1.12. Other Correspondence
1.12.14. Environmental Analysis

Merck requests a categorical exclusion from the preparation of an environmental assessment pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, as provided in 21 CFR 25.31(c) for an action on a supplemental Biologics License Application. Under this regulation, exclusion is provided if the substance comprises naturally occurring elements but has a sequence different from that of a naturally occurring substance, and when approval of the application does not significantly alter the concentration or distribution of the substance, its metabolites or degradation products in the environment.

Reviewer comment: *There is no information in this supplement indicating that any additional environmental information is needed, and the claim of categorical exemption is accepted.*

Clinical Supplies Dispensed to Patients
In the Phase 2 trial in patients with microsatellite unstable (MSI) tumors (Protocol Number MK-3475-

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

016V09) the clinical material used was supplied as 50 mg/vial lyophilized MK-3475. In the Phase 2 trial in patients with previously treated locally advanced unresectable or metastatic (Stage IV) mismatched repair deficient or microsatellite instability-high colorectal carcinoma (Protocol Number MK-3475-164) the clinical material used was (b) (4) MK-3475, 100 mg/vial ((b) (4) DS).

Reviewer comment: *The drug substance (DS) manufactured at (b) (4) is not approved for commercial release. Merck has presented data from release testing, extended characterization studies, forced degradation studies and stability studies to demonstrate that this material is comparable to the licensed product (IND 110,080 SD# 1095), and it was determined that the drug product manufactured from the (b) (4) DS is sufficiently representative of the commercial material for use in pivotal clinical studies. From the information available in this supplement, it is not clear whether the DS used to manufacture the DP in the MK-3475 50 mg/vial was manufactured at clinical (b) (4) or licensed sites. However, given that the pembrolizumab drug product manufactured from (b) (4) DS is sufficiently representative of the commercial material, the use of these products in these clinical trials is acceptable.*

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

/s/

MARK PACIGA
02/17/2017

SARAH B KENNETT
02/17/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA Serial Number:	125514/ 14
Drug Name:	Keytruda (Pembrolizumab/MK-3475)
Indication(s):	Microsatellite instability-high (MSI-H) cancer
Applicant:	Merck
Submission Date:	09/08/2016
PDUFA Date:	03/08/2017
Review Priority:	Priority
Biometrics Division:	V
Statistical Reviewer:	Weishi Yuan
Concurring Reviewers:	Lisa Rodriguez, Team Leader Rajeshwari Sridhara, Division Director
Medical Division:	Oncology Products 2
Clinical Team:	Leigh Marcus, Clinical Reviewer Steven Lemery, Team Leader Patricia Keegan, Division Director
Project Manager:	Sharon Sickafuse
Keywords:	Objective Response Rate, Microsatellite Instability-High (MSI-H) Cancer, Exact Method

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

The applicant submitted data and analysis of pooled data from 5 single arm studies to support approval of pembrolizumab (MK-3475) as [redacted] (b) (4) Pembrolizumab had previously received approval for unresectable or metastatic melanoma; metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy, and accelerated approval for recurrent head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing therapy.

This application was based on pooled data analysis from 5 single arm studies listed below. The primary endpoint was objective response rate (ORR) per the RECIST 1.1 criteria.

- KN016:
  - Cohort A included patients with MSI-H colorectal cancer (CRC) who had been previously treated with at least 2 lines of systemic therapies (must have included fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab [if KRAS wild type]).
  - Cohort C included patients with MSI-H non-CRC solid tumors (including gastric, small intestine, ampullary/biliary, pancreatic, endometrial, prostate, and thyroid cancers plus sarcoma) who had been previously treated with more than 1 prior therapies.
- KN012: included patients with PD-L1-positive advanced solid tumors in Cohorts A (triple-negative breast cancer), C (urothelial tract cancer), and D (gastric cancer), who were previously treated with standard of care (SOC) chemotherapies. The MSI analysis was not used for biomarker selected enrollment and 6 patients were identified as MSI-H upon retrospective analysis.
- KN028: included patients with PD-L1-positive advanced solid tumors (including CRC, biliary, esophageal, breast, and endometrial cancers), who were previously treated with SOC chemotherapies. The MSI analysis was not used for biomarker selected enrollment, and 5 patients were identified as MSI-H upon retrospective analysis in this cohort.
- KN164: included patients with MSI-H CRC who were previously treated with approved standard therapies (must have included fluoropyrimidine, oxaliplatin, and irinotecan).
- KN158: included prospectively enrolled patients with MSI-H non-CRC (including gastric, biliary, pancreatic, endometrial, kidney, prostate, retroperitoneal adenocarcinoma, small cell lung cancer and small intestine cancers) and patients with endometrial cancer identified as MSI-H upon retrospective analysis, all of whom were previously treated with SOC therapies.

A total of 149 patients were included in the final analysis for MSI-H. The ORR assessed by independent review was 35.6% (95% CI: 27.9, 43.8). The median duration of response

was not reached, and duration ranged from 1.6 to 27.7 months. A total of 26 (46%) patients had a response of 6.0 months or longer.

Based on the data and analyses, the results showed 35.6% ORR in pembrolizumab treated patients. Whether the data and analyses provided in this submission indicate a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

According to the meeting with the applicant on 02/13/2017, a major amendment will be submitted to support the flat dose of 200 mg every 3 weeks. A review addendum may be filed after the additional data are submitted.

2. INTRODUCTION

The applicant submitted data and final study report of pooled analysis from 5 single arm studies to seek accelerated approval for a new indication for pembrolizumab. This application was based on data from the Studies K016, KN012, KN028, KN164, and KN1598, in patients with advanced MSI-H cancers.

2.1 Overview

2.1.1. Class and Indication

Pembrolizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to block the interaction between programmed cell death 1 (PD-1) and its ligands, PD-L1 and (programmed cell death ligand 2 (PD-L2).

Microsatellites are repetitive sequences, distributed throughout the genome. Microsatellite instability (MSI) is the phenotype associated with defective dismatch repair (dMMR) proteins and can occur due to a germline mutation in one of the mismatch repair (MMR) genes or through methylation of an MMR gene promoter. High MSI is indicative of a high mutational load and a highly immunogenic molecular phenotype. MSI-H cancer represents a unique set of cancers with a common defect in MMR) and immunobiology. The overall MSI-H cancer prevalence is 2% to 5% across tumor histologies. MSI-H cancer represents an area of high unmet medical need, with up to 26,000 patients per year in the US alone.

The applicant is seeking an indication as a (b) (4)

2.1.2. Regulatory History

Pembrolizumab had previously received approval as

- treatment for unresectable or metastatic melanoma;
- first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [tumor proportion score (TPS) ≥ 50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations;
- treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations (prior to receiving pembrolizumab); and
- (accelerated approval) treatment of patients with recurrent head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing therapy.

The sBLA was submitted on September 8, 2016. FDA held a meeting with the applicant on 02/13/2017, and the applicant stated that a major amendment will be submitted to support the flat dose of 200 mg every 3 weeks.

2.1.3. Studies Reviewed

KN016 is an ongoing, 2-stage, multi-cohort, single arm trial in previously treated patients to evaluate the clinical activity of pembrolizumab monotherapy. The 3 cohorts includes: patients with metastatic or locally advanced MSI-H CRC with at least 2 prior regimens (Cohort A); patients with metastatic or locally advanced non-MSI-H CRC (Cohort B); and patients with metastatic or locally advanced MSI-H non-CRC with at least 1 prior regimen (Cohort C). Only results from Cohort A and Cohort C are presented to support this application. The analysis of KN016 efficacy data included 58 patients with MSI-H cancer, with 28 from Cohort A and 30 from Cohort C.

KN164 is an ongoing Phase 2, single arm trial of pembrolizumab in previously treated patients with MSI-H CRC. All patients receive pembrolizumab 200 mg Q3W. Patients are required to have been previously treated with the standard therapies fluoropyrimidine, oxaliplatin, and irinotecan. The analysis of KN164 efficacy data included 5 patients with MSI-H cancer.

KN158 is an ongoing Phase 2, multi-cohort trial of pembrolizumab monotherapy in patients with advanced solid tumors evaluated for predictive biomarkers. Patients are required at trial entry to have measurable disease as assessed per RECIST 1.1 criteria, and to have failed prior therapy. Patients are treated with pembrolizumab 200 mg Q3W. The analysis of KN158 efficacy data included 19 patients with MSI-H cancer.

KN012 was a multi-cohort trial of pembrolizumab in patients with advanced solid tumors. Patients were enrolled into Cohort A for triple negative breast cancer (TNBC), Cohort B as the initial HNSCC cancer cohort, Cohort B2 as the HNSCC cancer expansion cohort, Cohort C for urothelial tract cancer, or Cohort D for gastric cancer. Only patients with PD-L1 positive tumors were enrolled in cohorts A, B, C and D. Treatment in Cohorts A, B, C, and D was pembrolizumab 10 mg/kg Q2W, and for Cohort B2 200 mg Q3W. In Cohorts A, B, C, and D, patients must have had a PD-L1 positive tumor as determined by IHC at a central laboratory. Patients with PD-L1 positive and negative tumors were enrolled into Cohort B2. MSI status was not used for biomarker-selected enrollment but was analyzed retrospectively. Tumor response was assessed every 8 weeks according to RECIST 1.1 by IRC. The analysis of KN012 efficacy data included 6 patients with MSI-H cancer.

KN028 is an ongoing Phase 1b open-label, multi-cohort trial of pembrolizumab monotherapy in patients with PD-L1 positive advanced solid tumors. Patients received pembrolizumab 10mg/kg every 2 weeks (Q2W). MSI status was not used for biomarker-selected enrollment but was analyzed retrospectively. Tumor response was assessed every 8 weeks according to RECIST 1.1 for the first 6 months and every 12 weeks thereafter. The analysis of KN028 efficacy data included 5 patients with MSI-H cancer.

The primary efficacy endpoint was ORR based on Independent Radiology Review (IRC) assessment of confirmed response for KN012, KN016 and KN028. For KN164, patients who had an unconfirmed response first documented at the last disease assessment prior to the database cutoff date are included as responders. For KN158, confirmed and unconfirmed responses per Investigator (INV) assessment were utilized due to the short duration of follow-up, and no IRC data were available as of the database cutoff date.

A total 149 patients with MSI-H CRC were included in the final efficacy analysis from the 5 studies.

2.2 Data Sources

Data used for review is from the electronic submission received on February 9, 2016 and April 27, 2016. The network paths are

- \\CDSESUB1\evsprod\BLA125514\0267
- \\CDSESUB1\evsprod\BLA125514\0308

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data for the 5 studies as well as the related SAS programs for analysis.

The reviewer was able to perform most of the analyses using the submitted data.

3.2 Evaluation of Efficacy

3.2.1. Study Design and Endpoints

KN016 is an ongoing, investigator-initiated, multi-center, open label, 2-stage, Phase 2 trial in previously treated patients to evaluate the clinical activity of pembrolizumab monotherapy. The following 3 cohorts are being enrolled to receive pembrolizumab 10 mg/kg Q2W: patients with MSI-H CRC (Cohort A); patients with non-MSI-H CRC (Cohort B); and patients with MSI-H non-CRC (Cohort C). Only results from Cohort A and Cohort C are presented to support this application. Patients in Cohort A were required to have received at least 2 prior cancer therapy regimens. Patients in Cohort C were required to have received at least 1 prior cancer therapy regimen. Disease assessments based on RECIST 1.1 criteria are conducted at Week 12 and every 8 weeks thereafter. The analysis of KN016 efficacy data included 58 patients with MSI-H cancer, with 28 from Cohort A and 30 from Cohort C. The data cut-off for Cohort A was 2/19/2016, and for Cohort C was 4/13/2016.

KN164 is an ongoing Phase 2, single arm, open-label, multicenter trial of pembrolizumab in previously treated patients with MSI-H CRC. All patients receive pembrolizumab 200 mg Q3W. Patients are required to have been previously treated with the standard therapies fluoropyrimidine, oxaliplatin, and irinotecan. MSI status in tumor samples is determined locally at each participating center using an IHC- or PCR-based test. Disease assessments based on RECIST 1.1 criteria are conducted every 9 weeks. The analysis of KN164 efficacy data included 5 patients with MSI-H cancer. The data cur-off was 08/03/2016.

KN158 is an ongoing Phase 2, open-label, non-randomized, multicenter, multi-cohort trial of pembrolizumab monotherapy in patients with advanced solid tumors evaluated for predictive biomarkers. Patients are required at trial entry to have measurable disease as assessed per RECIST 1.1 criteria, and to have failed prior therapy. Patients are treated with pembrolizumab 200 mg Q3W. MSI-H status is required specifically for enrollment into Group K and was prospectively analyzed by local IHC-based or PCR-based testing. For patients enrolled into Groups A-J, retrospective testing of tumor tissue samples for MSI is performed. Tumor response is assessed every 9 weeks according to RECIST 1.1 by IRC. The analysis of KN158 efficacy data included 19 patients with MSI-H cancer. The data cut-off was 08/17/2016.

KN012 was a multicenter, nonrandomized, multi-cohort trial of pembrolizumab in patients with advanced solid tumors. Patients were enrolled into Cohort A for triple negative breast cancer (TNBC), Cohort B as the initial HNSCC cancer cohort, Cohort B2 as the HNSCC cancer expansion cohort, Cohort C for urothelial tract cancer, or Cohort D for gastric cancer. Only patients with PD-L1 positive tumors were enrolled in cohorts A, B, C and D. Treatment in Cohorts A, B, C, and D was pembrolizumab 10 mg/kg Q2W, and for Cohort B2 200 mg Q3W. In Cohorts A, B, C, and D, patients must have had a PD-L1 positive tumor as determined by IHC at a central laboratory. Patients with PD-L1 positive and negative tumors were enrolled into Cohort B2. MSI status was not used for biomarker-selected enrollment but was analyzed. Tumor response was assessed every 8 weeks according to RECIST 1.1 by IRC. The analysis of KN012 efficacy data included 6 patients with MSI-H cancer. The data cut-off was 04/26/2016.

KN028 is an ongoing Phase 1b open-label, non-randomized, multicenter, multi-cohort trial of pembrolizumab monotherapy in patients with PD-L1 positive advanced solid tumors. Patients were required at trial entry to have measurable disease as assessed per RECIST 1.1 criteria, and to have a malignancy that is incurable with any of the following: (a) failed prior standard therapy, (b) no existing standard therapy, or (c) standard therapy is not considered appropriate by the patient and treating physician. Patients received pembrolizumab 10mg/kg every 2 weeks (Q2W). MSI status was not used for biomarker-selected enrollment and was analyzed retrospectively. Tumor response was assessed every 8 weeks according to RECIST 1.1 for the first 6 months and every 12 weeks thereafter. The analysis of KN028 efficacy data included 5 patients with MSI-H cancer. The data cut-off was 06/20/2016.

The primary endpoint of these studies was objective response rate (ORR) per RECIST1.1 criteria by the independent central radiology review for KN012, KN016 and KN028. For KN164, patients who had an unconfirmed response first documented at the last disease assessment prior to the database cutoff date are included as responders. For KN158, confirmed and unconfirmed responses per Investigator (INV) assessment were utilized due to the short duration of follow-up, and no IRC data were available as of the database cutoff date.

The following is a table that summarizes the studies involved in this submission. A total 149 patients were included in the final efficacy analysis.

Table 1. Summary of Studies

	Cohort	N/Total	MSI Status	Dosage
KN012	4 Indications	6 /165	Retrostpective	10mg/kg Q2W
KN016-A	mCRC	28 /28	Prospective	10mg/kg Q2W
KN016-C	non-CRC	30 / 30	Prospective	10mg/kg Q2W
KN028	20 Indications	5 / 450	Retrostpective	10mg/kg Q2W
KN158	10 Indications + non-CRC MSI-H	61 /61	Retrostpective/Prospective	200 mg Q3W
KN164	MSI-H mCRC	19 /on-going enrollment	Prospective	200 mg Q3W

Reviewer's Comment:

The original sBLA submission included report and data for Study KN 164 and KN158 with a cut-off date of June 3, 2016. The applicant submitted an updated report, based on data with cut-off August 3, 2016 which had additional 9 weeks of follow-up. This review used the updated data.

3.2.2. Efficacy Measures

The primary endpoint ORR was defined as the percentage of patients who have a complete response [CR] or partial response [PR] defined by RECIST 1.1. The confidence interval of the ORR was calculated using the exact method.

3.2.3. Sample Size Consideration

The studies did not include sample size justification included in the protocols. All of the studies are still on-going.

Reviewer's Comments:

In a single arm study, the point estimate and its 95% confidence interval will be used in decision making, instead of formal testing with a selected null hypothesis.

3.2.4. Statistical Methodologies

The efficacy analysis dataset pooled patients across the 5 studies regardless of dosage and tumor types. Patients were analyzed as treated.

The ORR was calculated as the percentage of patients who have a CR or PR defined by RECIST 1.1 by independent central review. Patients without response data were treated as non-responders. A 95% confidence interval (CI) was derived for the ORR using the exact Clopper-Pearson method.

Reviewer's Comments:

The efficacy analysis pooled data from 5 different trials, which included two distinct doses administered and 16 different tumor types. The rationale for pooling from different studies with different doses was based on the consistency of demographic and baseline disease characteristics of the trial populations, and consistent improvement in ORR and durability of the response across trials.

3.2.5. Patient Disposition, Demographic and Baseline Characteristics

This trial was conducted at 49 centers, of which 18 were in the United States; 5 were in France; 4 each were in Israel, Japan, Korea and Spain; 3 were in Germany; 2 each were

in Belgium, and Russia; 1 each was in Canada, Australia and Taiwan. A total of 149 patients from 5 studies were combined to form the efficacy analyses set. The disposition of the patients is presented in Table 2.

Table 2. Patient Disposition

Dispotion	**N (%)**						
Study	**KN016A**	**KN016C**	**KN164**	**KN158**	**KN012**	**KN028**	**Pooled**
No. of Patients	28 (100)	30 (100)	61 (100)	19 (100)	6 (100)	5 (100)	**149 (100)**
Completed Treatment	2 (7.1)	1 (3.3)			2 (33.3)		**5 (3.4)**
Discontinued Treatment	8 (28.6)	12 (40)	27 (44.3)	8 (42.1)	4 (67.7)	2 (40)	**61 (40.9)**
Adverse Event	1 (3.6)		4 (6.6)	4 (21.1)			**9 (6.0)**
Physician Decision			3 (4.9)				**3 (2.0)**
Death	1 (3.6)						**1 (0.7)**
Progression	5 (17.9)	10 (33.3)	18 (29.5)	4 (21.1)	3 (50)	1 (20)	**41 (27.5)**
Patient Withdrawn	1 (3.6)	1 (3.3)	2 (3.3)		1 (16.7)	1 (20)	**6 (4.0)**
Ongoing Treatment	18 (64.3)	17 (56.7)	34 (55.7)	11 (57.9)		3 (60)	**83 (55.7)**

Demographic data at baseline are summarized in the Table 3.

Table 3. Patients Demographics

Demographics	**N (%)**
Patients in Efficacy Analysis	149 (100)
Age	
< 65	96 (64.4)
≥ 65	53 (35.6)
Sex	
Male	83 (55.7)
Female	66 (44.3)
Race	
White	115 (77.2)
Other	34 (22.8)
Region	
USA	73 (49.0)
Western	53 (35.6)
Asia	23 (15.4)

Disease characteristics at baseline are summarized in Table 4.

Table 4. Patients Baseline Characteristics

Baseline Characteristics	N (%)
Patients in Efficacy Analysis	149 (100)
ECOG Status	
0	53 (35.6)
1	96 (64.3)
Prior Lines of Therapy	
Missing	1 (0.7)
None	6 (4.0)
1st Line	35 (23.5)
2nd Line	51 (34.2)
3rd Line	26 (17.5)
4th Line	18 (12.1)
5th Line or Greater	12 (8.1)
KRAS Status	
Mutant	31 (20.8)
Wild Type	65 (43.6)
Undetermined	25 (16.8)
Data Unavailable	28 (18.8)
Brain Metastases	
Yes	1 (0.7)
No	90 (60.4)
Missing	58 (38.9)

Reviewer's comments:

The percentage for patients discontinued treatment due to adverse event was higher in KN158 than other trials. However, the sample size was relatively small.

The demographic and baseline characteristics are from the 149 patients in the efficacy analysis population. More patients were Caucasians. More patients were younger than 65 years old. About 44% of the patients were females. About half of the patients were enrolled in the USA. Most patients had metastatic disease. Most patients had prior lines of therapies.

All 6 patients from KN012 and 19 patients from KN158 did not have data available for KRAS status. Only 1 patient in Study KN012 had brain metastasis. All 58 patients in KN016A and KN016C did not have brain metastases data available.

3.2.6. Results and Conclusions

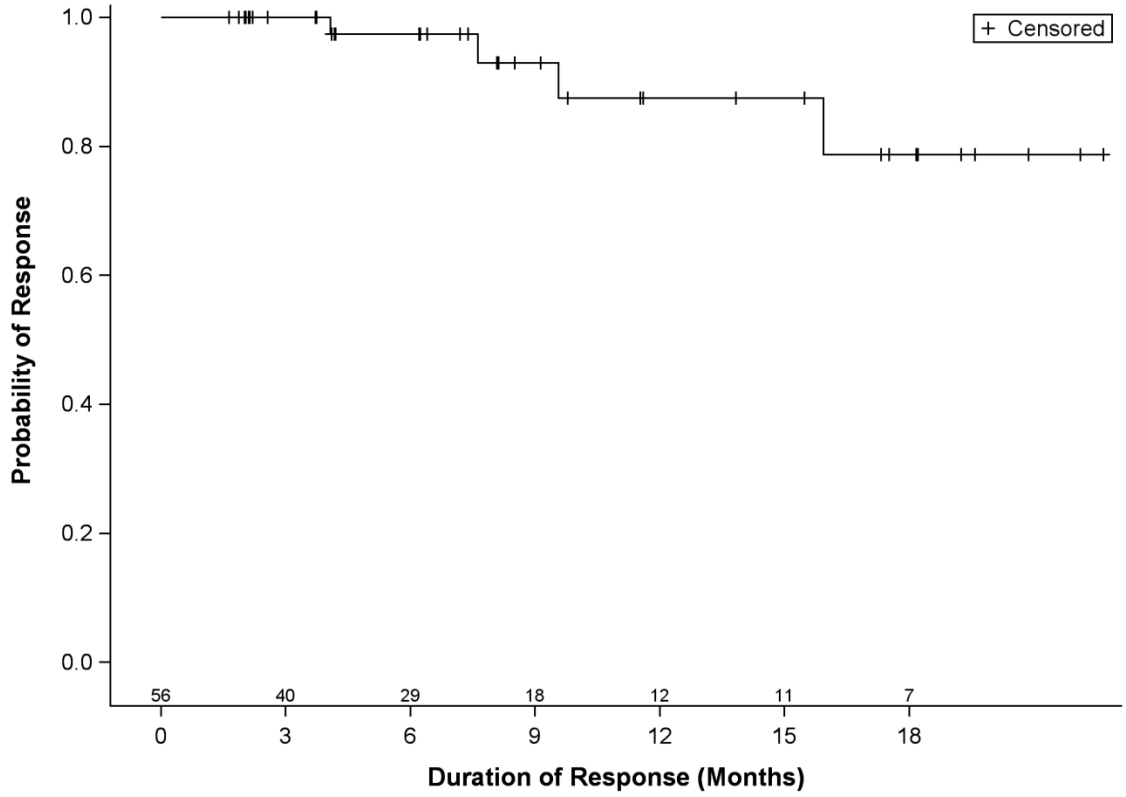
Based on the 149 patients in the efficacy analysis population, there were a total of 56 responders. The primary efficacy endpoint was ORR based on Independent Radiology Review (IRC) assessment of confirmed response for KN012, KN016 and KN028. The following table summarizes the ORR results based on independent central radiology review.

Table 5. ORR Analysis Results

	N (%)	95 % CI
Patients in Efficacy Analysis	149 (100)	
CR+PR (%)	56 (37.6)	(29.8, 45.9)
CR	9 (6.0)	
PR	47 (31.5)	
SD	36 (24.2)	
PD	47 (24.5)	
NE	7 (4.7)	
Non-CR/Non-PD	1 (0.7)	
Missing	2 (1.3)	

The median of the duration of responses was not reached. The duration ranged from 1.6 to 22.7 months. There were 52 patients with responses that were on-going at time of data cut-off. There were 26 patients who had 6 months or longer duration of response. The following is a Kaplan-Meier curve of DoR.

Figure 1. K-M Curve of Duration of Response



Reviewer's Comments

The ORR results pooled data from 5 trials which involved two dosages, and 16 tumor types. Please see additional analysis by subgroup in Section 4.2.

The protocols of the 5 trials did not provide sample size justification. All trials are still ongoing and KN164 is still enrolling patients.

The rationale for pooling the data for efficacy analysis was based on the consistency of the patients population, and the consistency of the ORR results and duration of response.

3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The following table summarizes the subgroup analysis of ORR.

Table 6. ORR Subgroup Analyses

Subgroup	N	Response (ORR)	95% CI of ORR	DOR Range (Months)
< 65	96	37 (39%)	(28.8%, 49.0%)	(1.6, 22.7)
>= 65	53	19 (36%)	(23.1%, 50.2%)	(1.9, 19.3)
Female	66	27 (41%)	(29.0%, 53.7%)	(1.9, 19.6)
Male	83	29 (35%)	(24.8%, 46.2%)	(1.6, 22.7)
Non-White	34	15 (44%)	(27.2%, 62.1%)	(1.6, 22.1)
White	115	41 (36%)	(26.9%, 45.1%)	(1.9, 22.7)
Asia	23	7 (30%)	(13.2%, 52.9%)	(1.9, 22.1)
USA	73	36 (49%)	(37.4%, 61.3%)	(1.6, 22.7)
Western	53	13 (25%)	(13.8%, 38.3%)	(2.0, 15.9)

Reviewer's comments:

There were no outlier subgroup with respect to response rate among the subgroups analyzed.

4.2 Other Subgroup Analysis

The following tables summarize the subgroup analyses of ORR by dosage, study, and tumor types.

Table 7. ORR Subgroup Analyses by Dose

Dose	10 mg/kg Q2W	200 mg Q3W
	N=69	N=80
Responders (%)	35 (51%)	21 (26%)
95% CI of ORR	(38.4%, 63.0%)	(17.0%, 37.3%)
DOR Range	(1.6, 22.7)	(1.9, 8.1)
Studies	6 from KN012, 5 from KN028, 28 from KN016A, 30 from KN016C	19 from KN158, 61 from KN164

Table 8. ORR Subgroup Analyses by Study

Subgroup	N	Resp (ORR)	95% CI of ORR	DOR Range (Months)
KN012	6	3 (50%)	(11.8%, 88.2%)	(7.6, 22.1)
KN016-A	28	14 (50%)	(30.6%, 69.4%)	(1.6, 20.9)
KN016-C	30	14 (47%)	(28.3%, 65.7%)	(1.9, 19.6)
KN028	5	4 (80%)	(28.4%, 99.5%)	(15.9, 22.7)
KN158	19	6 (32%)	(12.6%, 56.6%)	(1.9, 2.2)
KN164	61	15 (25%)	(14.5%, 37.3%)	(2.0, 8.1)

Table 9. ORR Subgroup by Tumor Type

	N	Response (ORR)	95% CI of ORR	DOR Range (Months)
GI Tumor				
BILIARY CANCER	11	3 (27%)	(6.0%, 61.0%)	(11.6, 19.6)
COLORECTAL CANCER	90	30 (33%)	(23.7%, 44.1%)	(1.6, 22.7)
GASTRIC CANCER	8	4 (50%)	(15.7%, 84.3%)	(2.0, 22.1)
PANCREATIC CANCER	6	5 (83%)	(35.9%, 99.6%)	(2.0, 9.1)
SMALL INTESTINAL CANCER	8	3 (38%)	(8.5%, 75.5%)	(1.9, 6.2)
ESOPHAGEAL CANCER	1	PR		18.2, On-going
GE JUNCTION CANCER	1	PD		
Non-GI Tumor				
ENDOMETRIAL CANCER	14	5 (36%)	(12.8%, 64.9%)	(1.9, 17.3)
BREAST CANCER	2	PR, PR		7.6, 15.9, ended
PROSTATE CANCER	2	PR, SD		9.8, on-going
BLADDER CANCER	1	Missing		
SARCOMA	1	PD		
THYROID CANCER	1	NE		
RETROPERITONEAL ADENOCARCINOMA	1	PR		2.1, on-going
SMALL CELL LUNG CANCER	1	PR		2.2, on-going
RENAL CELL CANCER	1	PD		

Reviewer's comments:
The results were based on pooled data from 5 studies.

1. The ORR was higher in the 10mg/kg Q2W patients group than the 200 mg Q3W patient group. The 95% CIs of ORR do not overlap between the different doses. This may indicate that the response may be different among the patients with these two different doses. The application will file a major amendment to justify for the flat dose of 200 mg Q3W.
2. Patients in KN028 reported a higher response rate, which may be a spurious result due to the small sample size of 5. The studies KN158 and KN164 reported a lower response rate than the other studies.

3. There were a total of 16 different tumor types presented in the analysis dataset. Some of the tumors are only represented by 1 or 2 patients; therefore whether the results apply to all disease types with MSI-H status is uncertain.
4. Some of the MSI-H samples were retrospectively identified, which included 6 from KN012, 5 from KN028, and 3 from KN158. Therefore the samples are not prospectively selected and bias may have been introduced into the selection.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This application is based on pooling of selected patients from 5 independently conducted studies. The pooling of data was not pre-specified in any of the study protocols. The dosing regimen varied among the studies. There were 16 different tumor types included in the data, and the sample size for each tumor type varies from 1 to 90. The clinical team opined that defining the MSI-H over multiple disease sites can be considered as a single disease.

A total of 149 patients were included in the final analysis for MSI-H. The ORR assessed by the independent review was 35.6% (95% CI: 27.9, 43.8). The median duration of response was not reached, and duration ranged from 1.6 to 27.7 months. A total of 26 (46%) patients had response of 6.0 months or longer.

5.2 Conclusions and Recommendations

Based on the data and analyses, the results showed 35.6% ORR in pembrolizumab treated patients. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

5.3 Labeling Recommendations

1. The ORR results combined by data from 5 studies by independent review should be included in the label as the primary efficacy results.
2. The subgroup analysis by tumor type provides current available information of clinical benefit for each tumor type, and should be included in the label.

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

/s/

WEISHI YUAN
02/14/2017

LISA R RODRIGUEZ
02/14/2017

RAJESHWARI SRIDHARA
02/14/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review Addendum	
BLA (supplement)	125514 (S-14)
Submission Date:	September 8th, 2016
Amendment Submission Date	March 8th, 2017
Brand Name:	Keytruda ®
Generic Name:	Pembrolizumab (MK-3475)
Sponsor:	Merck
Submission Type; Code:	Efficacy Supplement; Major amendment
Dosing regimen:	200 mg once every 3 weeks (Q3W) and 10 mg/kg once every two weeks (Q2W) as a 30 minute intravenous (IV) infusion
Proposed Indication:	(b) (4)
Pharmacometrics Reviewer:	Hongshan Li, Ph.D.
PBPK Lead**:**	Ping Zhao, Ph.D.
Pharmacometrics Team Leader:	Jiang Liu, Ph.D.
OCP Reviewer:	Brian D. Furmanski, Ph.D.
OCP Team Leader:	Hong Zhao, Ph.D.
OCP Divisions:	Division of Clinical Pharmacology V Division of Pharmacometrics
ORM Division:	Division of Oncology Products 2 (DOP2)

Table of Contents

1. Executive summary

Merck submitted BLA125514 Supplement 14 (S14) in support of the proposed indication of pembrolizumab for the [redacted] (b) (4) on Sept 8th, 2016. The sBLA population consisted of 149 patients with MSI-H/dMMR cancers who were treated with pembrolizumab in Trials KN016, KN012, KN028, KN164, and KN158. The clinical pharmacology review of S14 was finalized on Feb 17th, 2017, recommending pembrolizumab 10 mg/kg Q2W as the starting dose for patients with MSI-H. The proposed dose can be reduced to 200 mg Q3W as needed by tolerability and safety. The recommendation was based on the totality of evidence that pembrolizumab 10 mg/kg Q2W showed a consistent trend towards better response rate than 200 mg Q3W in patients with MSI-H while the safety profile was comparable among the two dose levels. In addition the review included the results of the trials for melanoma and NSCLC indications where 10 mg/kg Q2W or Q3W dose demonstrated a trend towards increased overall survival compared to the 200 mg Q3W or 2 mg/kg Q3W.

On February 13, 2017, Merck discussed with the FDA on the outstanding review issues for S14, and subsequently submitted a major amendment to support pembrolizumab 200 mg Q3W dose for MSI-H on March 8, 2017. In the major amendment, no updated information is provided for Trials KN016, KN012, and KN028 that demonstrated the efficacy of 10 mg/kg Q2W dose. The duration of follow-up was extended to ≥54 weeks (from ≥27 weeks in the original S14 submission) and ≥36 weeks (from ≥18 weeks in the original S14 submission) in KN164 and KN158. The trials KN164 and KN158 supported the effectiveness of 200 mg Q3W dose. The efficacy data in 65 additional MSI-H cancer patients were also submitted as supportive evidence, which included an additional 58 patients enrolled in KN158 and 7 patients with gastric cancer who received pembrolizumab in the third line (3L)+ setting enrolled in KN059. Results of 6 patients from French ATU program as well as a physiologically based pharmacokinetic (PBPK) analysis of pembrolizumab PD-1 engagement across multiple tumor types were also submitted.

For the 149 patients presented in the sBLA, 2 patients in trial KN164 with stable disease (SD) converted to partial response (PR) with longer follow-up duration, which increases the ORR from 24.6% to 27.9% and 1 patient with PR converted to unconfirmed complete response (uCR). In KN158, 1 patient with SD converted into PR, which increases the ORR from 31.6% to 36.8%, while 2 (10.5%) other patients converted from PR to CR (**Table 1**).

Overall, for the 149 patients in the sBLA the updated ORR of 30.0% (95% CI: 20.3, 41.3) at 200 mg/kg Q3W dose remains lower than the mean of 50.7% (95% CI: 38.4, 63.0) at the 10 mg/kg Q2W dose (**Table 1**) with 2.9% overlap of confidence intervals. In addition, the complete response rate was 13% (9/69) with the 10 mg/kg Q2W dose versus 2.5% (2/80) with 200 mg Q3W dose. Merck's PBPK analysis is exploratory and the model remains to be verified with regard to its ability to represent heterogeneity in PD-1 expression and tumor heterogeneity.

Both doses of 10 mg/kg Q2W and 200 mg Q3W have demonstrated significant tumor response in the MSI-H refractory population. Although potential factors such as cross-trial comparison may limit a definitive comparison, accumulated clinical data have demonstrated that pembrolizumab 10 mg/kg Q2W or Q3W showed better efficacy than the 200 mg Q3W or 2 mg/kg Q3W dose in indications including melanoma, NSCLC, and MSI-H without compromising the safety profile. Therefore, consistent with our original review, the updated data did not change the overall risk/benefit profile of the two doses studied.

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in the major amendment to pembrolizumab BLA125514 Supplement 14. Based on the review of the entire dataset, we recommend the following:

- Both the 2 mg/kg Q3W and 10 mg/kg Q2W dosing regimens should be available for the treatment of MSI-H patients given the effectiveness of both regimens and incremental benefit of the higher dose.
- Further evaluation of accumulating data to determine whether both dose regimens should be made available for approved indications including melanoma and NSCLC.

No baseline patient-specific factors are identified to determine which starting regimen should be recommended. This is not uncommon for drug approvals where multiple dose regimens are available and described in labeling. In the absence of identified baseline factors, OCP recommends the starting dose regimen be left to the discretion of the practitioner without explicit recommendations in labeling.

Signatures:

Hongshan Li, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Ping Zhao, Ph.D. PBPK Lead Division of Pharmacometrics
Jiang Liu, Ph.D. Pharmacometrics Team Leader Division of Pharmacometrics	Brian D. Furmanski, Ph.D. Reviewer Division of Clinical Pharmacology V

Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V	Yaning Wang, Ph.D. Acting Division Director Division of Pharmacometrics
Nam Atiqur Rahman, Ph.D. Division Director Division of Clinical Pharmacology V	

Cc: DOP2: RPM – S Sickafuse; DD – P Keegan; MTL – S Lemery; MO – L Marcus
DCPV: DDD - B Booth; DD - A Rahman

2.1. Summary of Major Amendment

The major amendment provided the following updated information:

- Updated data with longer duration of follow-up for KN164 (extended to ≥54 weeks from ≥27 weeks) and KN158 (extended to ≥36 weeks from ≥18 weeks) for the patients presented in the sBLA.
- No updated data is provided for Trials KN016, KN012, and KN028 that demonstrated the effectiveness of 10 mg/kg Q2W dose.
- Supportive data in 65 additional MSI-H cancer patients, which included 58 new patients enrolled in KN158 and 7 patients with gastric cancer who received pembrolizumab in the third line (3L)+ setting from KN059.
- Results of 6 patients from French ATU program.
- Physiologically based pharmacokinetic (PBPK) analysis of pembrolizumab PD-1 engagement across multiple tumor types. (b) (4)

2.2. **Key Review Questions**

2.2.1. What dose should be recommended in pembrolizumab label?

We consider that both 200 mg Q3W and 10 mg/kg Q2W doses have demonstrated significant benefit for MSI-H patients. Based on the consistently observed trend towards better effectiveness of pembrolizumab 10 mg/kg Q2W, this dose should be made available for the treatment of

MSI-H patients. However, 200 mg Q3W dose is also acceptable as a starting dose based on the physician's discretion.

Based on the amended efficacy data for S14, the ORRs increased to 27.9% from 24.6% for Trial KN164 and to 36.8% from 31.6% for Trial KN158 for the 200 mg Q3W dosing regimen, with mean of 30.0% (95% CI: 20.3, 41.3), which remains lower than the mean of 50.7% (95% CI: 38.4, 63.0) for the 10 mg/kg Q2W dose (**Table 1**) with 2.9% overlap of confidence intervals. The complete response rate was 13% (9/69) with the 10 mg/kg Q2W dose versus 2.5% (2/80) with 200 mg Q3W dose.

Table 1: Summary of Response Results of the Five Trials in sBLA (with Updated Information for KN164 and KN158).

Response	10 mg/kg Q2W				200 mg Q3W	
	KN016-A (n=28)	KN016-C (n=30)	KN012 (n=6)	KN028 (n=5)	KN164 (n=61)	KN158 (n=19)
Complete Response (%)	4 (14.3)	5 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)
Partial Response (%)	10 (35.7)	9 (30.0)	3 (50.0)	4 (80.0)	17 (27.9)	5 (26.3)
CR+PR (%), (95% CI†)	**14 (50), (30.6,69.4)**	**14 (46.7), (28.3,65.7)**	**3 (50.0), (11.8,88.2)**	**4 (80.0), (28.4,99.5)**	**17 (27.9), (17.1,40.8)**	**7 (36.8), (16.3,61.6)**
Pooled CR+PR (%), (95% CI†)	**35 (50.7) (38.4, 63.0)**				**24 (30.0) (20.3, 41.3)**	

For trials not listed in Table 1, the ORRs was 33% for ATU (2 mg/kg Q3W, N=6), and 57% for KN059 (200 mg Q3W, N=7). Combining the 58 additional patients with those from the initial submission yields a total of 77 patients with ≥18 weeks of follow-up in KN158 with an IRC confirmed ORR of 29.9% and Investigator assessed confirmed and unconfirmed ORR of 37.7%.

Supporting Evidence for 10 mg/kg Dose

As discussed in the documented clinical pharmacology review for S14, accumulated clinical data have demonstrated that pembrolizumab 10 mg/kg Q2W or Q3W showed a trend towards better efficacy than the 200 mg or 2 mg/kg Q3W dose in indications including melanoma, NSCLC, and MSI-H without compromising the safety profile as shown below:

MSI-H cancer

- For MSI-H colorectal cancer (CRC), the ORR is consistently higher at 10 mg/kg Q2W dosing regimen:

- 50% (with 95% CI 30.6%, 69.4%) for 10 mg/kg Q2W vs. 27.9% (with 95% CI: 17.1%, 40.8%) for 200 mg Q3W with no overlap of confidence intervals;
- ORR separation is evident between the two trials after 4 months of treatment;
- The evident separation between the two trials was also observed in Kaplan Meier plot of progression free survival (PFS).

- For the overall MSI-H indication across various tumor types the ORRs are consistently higher for the 10 mg/kg Q2W regimen as compared to 200 mg Q3W regimen (Table 1).
- There were 9/69 (13.0%) complete responders with the 10 mg/kg Q2W dose versus 2/80 (2.5%) with 200 mg dose.

Ipilimumab-Refractory Melanoma (KN002, N=440)

The overall survival (OS) of pembrolizumab 10 mg/kg Q3W dosing regimen was higher than chemotherapy and showed a trend toward better survival compared to 2 mg/kg Q3W dosing regimen (

- **Table 2**):
  - The median OS times are 11.0, 13.4, and 14.7 months for the control, pembrolizumab 2 mg/kg Q3W, and 10 mg/kg Q3W, respectively. While 2 mg/kg Q3W dose prolonged OS by 2.4 months over control, the 10 mg/kg Q3W dose provided additional 1.3 months in OS.
  - The OS hazard ratio of 10 mg/kg Q3W to 2 mg/kg Q3W is 0.87 (95%CI: 0.67, 1.12), which appears to be comparable to that of 2 mg/kg Q3W to the control, 0.86 (95%CI: 0.67, 1.10).
  - The numerically better OS of pembrolizumab 10 mg/kg Q3W than that of 2 mg/kg Q3W appeared to be even more evident in PD-L1 negative melanoma patients.

Previously treated NSCLC (KN010, N=1033, TPS>1%)

The OS of pembrolizumab at 10 mg/kg Q3W dose was significantly higher than docetaxel and showed a trend toward better survival than 2 mg/kg Q3W dosing regimen (

- **Table 2**):
  - The median OS were 8.5, 10.4, and 12.7 months for the control, pembrolizumab 2 mg/kg Q3W, and 10 mg/kg Q3W, respectively. While pembrolizumab 2 mg/kg

Q3W prolonged OS by 1.9 months over the control, 10 mg/kg Q3W provided additional 2.3 months in OS.

- Numerically longer OS of pembrolizumab 10 mg/kg Q3W than that of 2 mg/kg Q3W appeared to be even more evident in PD-L1 weakly positive NSCLC patients.

Table 2: Consistently Better Overall Survival of Pembrolizumab 10 mg/kg Q3W Dose Than That of 2 mg/kg Q3W Dose in Melanoma and NSCLC

	2 mg/kg vs. control	10 mg/kg vs. 2 mg/kg
Melanoma		
OS Hazard Ratio (95%CI)	0.86 (0.67, 1.10)	0.87 (0.67, 1.12)
Median OS (month)	13.4 vs. 11.0	14.7 vs. 13.4
NSCLC		
OS Hazard Ratio (95%CI)	0.71 (0.58, 0.88)	0.85 (0.69, 1.06)
Median OS (month)	10.4 vs. 8.5	12.7 vs. 10.4

Safety

- The number of patients studied for each pembrolizumab dose was approximately 180 in KN002, 280 in KN006, and 350 in KN010, and the safety profiles of the two doses are generally comparable. Refer to clinical study reports for KN002, KN006 and P010 for more information.
- For pembrolizumab 10 mg/kg Q2W dose, the safety profile in patients with MSI-H was consistent with that in patients with melanoma (KN006).
- Safety profile was also comparable between 200 mg Q3W and 10 mg/kg Q2W. Discontinuation due to toxicity was 11% (3/28) for KN016-A (10 mg/kg Q2W) and 7% (4/60) for KN164 (200 mg Q3W). Although dose interruption rate in KN016A is higher than that in KN164, the outcome was drug being held temporarily and majority of the

events were resolved. Moreover, the higher dose interruption with 10 mg/kg Q2W did not cause a compromised ORR compared to that with the 200 mg Q3W dosing.

2.2.2. Does the PBPK analysis support the dosing regimen of 200 mg Q3W proposed by Merck for the treatment of MSI-H cancer?

The objective of this PBPK analysis was to predict PD-1 engagement across cancer types (considering higher PD-1 expression which can be associated with MSI-H) and tumor regions (including poorly vascularized regions) to inform dose choice. To achieve this objective, the model should consider heterogeneity in PD-1 expression and tumor heterogeneity for different types of cancer to allow adequate characterization of receptor binding and tumor distribution of pembrolizumab.

(b) (4)

In summary, Merck's PBPK analysis is exploratory. The model remains to be verified with regard to its ability to represent heterogeneity in PD-1 expression and tumor heterogeneity.

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

/s/

BRIAN D FURMANSKI
05/10/2017

HONG ZHAO
05/10/2017
I concur.

HONGSHAN LI
05/10/2017

PING ZHAO
05/10/2017

JIANG LIU
05/10/2017

YANING WANG
05/10/2017

NAM ATIQUR RAHMAN
05/10/2017
I concur.

Clinical Pharmacology Review	
BLA (supplement)	125514 (S-14)
Submission Date:	November 11th, 2016
Brand Name:	Keytruda ®
Generic Name:	Pembrolizumab (MK-3475)
Formulation/Strength:	50 mg lyophilized powder and 100 mg/4 mL (25 mg/mL) solution in a single-use
Sponsor:	Merck
Submission Type; Code:	Efficacy Supplement
Dosing regimen:	200 mg once every 3 weeks (Q3W) and 10 mg/kg once every two weeks (Q2W) as a 30 minute intravenous (IV) infusion
Proposed Indication:	(b) (4)
Pharmacometrics Reviewer:	Hongshan Li, Ph.D.
Pharmacometrics Team Leader:	Jiang Liu, Ph.D.
OCP Reviewer:	Brian D. Furmanski, Ph.D.
OCP Team Leader:	Hong Zhao, Ph.D.
OCP Divisions:	Division of Clinical Pharmacology V Division of Pharmacometrics
ORM Division:	Division of Oncology Products 2 (DOP2)

Table of Contents

2.2.2. Does the dose- and exposure-response relationship from the efficacy and safety trials support the dose regimen of 200 mg Q3W and10 mg/kg Q2W for the proposed indication of MSI-H/MMR deficient cancer?

2.2.3. What is the incidence (rate) of the formation of the anti-drug antibodies (ADA)? Do the ADAs have neutralizing activity?

2.2.4. What bioanalytical methods are used to assess pembrolizumab concentrations?

2.2.5. What immunogenicity assays are used to assess pembrolizumab ADA incidence in patients with MSI-H/MMR deficient cancer?

1. Executive summary

Pembrolizumab (Keytruda) is a human programmed death receptor-1 (PD-1)-blocking antibody that is indicated for indications of melanoma (2 mg/kg Q3W) and NSCLC (non-small cell lung cancer) (200 mg Q3W). Pembrolizumab has also received accelerated approval for the indication of head and neck squamous cell carcinoma (HNSCC) (200 mg Q3W).

In support of an accelerated approval of the indication for MSI-H/MMR deficient cancer, Merck submitted safety and efficacy data from multiple trials in patients with 15 different histologic types of MSI-H/MMR deficient cancer. The primary efficacy endpoint is objective response rate (ORR). The efficacy results demonstrate that both pembrolizumab dose regimens of 200 mg Q3W and 10 mg/kg Q2W are effective in the treatment of patients with MSI-H cancer, however, the ORR is consistently higher across trials for the 10 mg/kg Q2W regimen than the 200 mg Q3W regimen after 4 months of treatment . Furthermore, the dose-response data assessing relationship between dose and PFS or OS in MSI-H, melanoma, and non-small-cell-lung cancer (NSCLC) suggest that 10 mg/kg Q2W or Q3W provides additional efficacy compared to the 200 mg Q3W dose. The adverse event profile for pembrolizumab at 10 mg/kg Q2W and 200 mg Q3W in the MSI-H patient population is similar to, and consistent with the previously reported results in patients with melanoma, HNSCC and NSCLC.

The following clinical pharmacology pertinent information was submitted to support the use of pembrolizumab (b) (4)

- A pooled comparative analysis of pembrolizumab exposure and clearance across multiple tumor types was conducted. Pembrolizumab plasma exposure and clearance in the MSI-H/MMR deficient cancer population was comparable to patients with other tumor types.

- A pooled comparative analysis of the immunogenicity rate of pembrolizumab across multiple tumor types was submitted. The rate of anti-drug antibody (ADA) formation in the MSI-H/MMR deficient cancer population was 1.9% which is the same as the overall studied population for pembrolizumab. The effect of ADA formation on pembrolizumab safety and pharmacokinetic profile is minimal and is not clinically meaningful.

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in Supplement 14 of BLA125514. Given the consistently higher objective response rates and lack of patient characteristics, markers, demographics to select a specific dose, we recommend that patients receive pembrolizumab at 10 mg/kg IV Q2W and that the dose be modified to as low as 200 mg IV Q3W based on patient tolerability and safety.

1.2. Post Marketing Requirements or Commitments

There are no postmarketing requirements (PMR) or postmarketing commitment (PMC) studies requested by the Office of Clinical Pharmacology.

Signatures:

Hongshan Li, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Jiang Liu, Ph.D. Pharmacometrics Team Leader Division of Pharmacometrics
Brian D. Furmanski, Ph.D. Reviewer Division of Clinical Pharmacology V	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V

Cc: DOP2: RPM – S Sickafuse; DD – P Keegan; MTL – S Lemery; MO – L Marcus
DCPV: DDD - B Booth; DD - A Rahman

2.1. Introduction

Pembrolizumab (Keytruda) is a humanized monoclonal antibody that binds to the human programmed cell death-1 (PD-1) receptor and blocks the interaction between PD-1 and its 2 ligands: PD-1 ligand 1 (PD-L1) and PD-1 ligand 2 (PD-L2).

2.1.1. Clinical pharmacology study design to support labeling claims

BLA125514 Supplement 14 includes results of population PK (popPK) analysis and immunogenicity assessment for trials KN164 (N=58) and KN012 (N=6).

KN012 is an ongoing open label trial that is assessing the activity of pembrolizumab at 10 mg/kg Q2W in patients with PD-L1-positive advanced solid tumors in Cohorts A (triple negative breast cancer), C (urothelial tract cancer), and D (gastric cancer), who were previously treated with standard of care (SOC) chemotherapies. The MSI analysis was not used for biomarker selected enrollment and 6 patients were identified as MSI-H upon retrospective analysis.

KN164 is an ongoing open label trial that is assessing the activity of pembrolizumab at 200 mg Q3W in patients with MSI-H colorectal cancer (CRC) who were previously treated with approved standard therapies (must have included fluoropyrimidine, oxaliplatin, and irinotecan).

Additional trials not included in the clinical pharmacology section used to support the safety and efficacy of Pembrolizumab in the MSI-H population include, KN016-A, KN016C and KN028 (10 mg/kg Q2W) and KN158 (200 mg Q3W).

PK and immunogenicity sampling schedules for trial KN164 and KN012

KN012: PK samples were collected at pre-dose and 30 min after the start of infusion on Cycles 1 and 2. Thereafter starting with Cycle 5 pre-dose samples were collected every 4 cycles through Cycle 37. Additional samples were taken 30 days after discontinuation of trial drug, and 3 months and 6 months after discontinuation of trial drug. Also PK time matched antibodies immunogenicity samples were collected prior to infusion of pembrolizumab at the cycles indicated above.

KN164: PK and immunogenicity samples were collected within 24 hours before infusion at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter, 30 days after discontinuation of trial drug.

2.1.2. Formulation and Dose Regimen

Sterile solution available as a 100 mg/ 4 mL single use vial

200 mg administered as an intravenous (IV) infusion over 30 minutes Q3W

2.2. Key Review Questions

2.2.1. What are the findings in the population pharmacokinetics (PopPK) report of this efficacy supplement?

PK data of 6 MSI-H patients from KN012 (with dose of 10 mg/kg Q2W), and 58 MSI-H patients from KN164 (with dose of 200 mg Q3W) were combined with PK data of non-MSI-H patients from Trials KN01, KN02 and KN06 for a population pharmacokinetics (PPK) analysis using a static clearance model. The PPK parameters are comparable between MSI-H and other patients (**Table 1 below, also see section 4 appendix 1**). Individual post-hoc PK parameters are also comparable (**Table 1 below, also see section 4 appendix 1**). In addition, the exposures for MSI-H patients receiving 200 mg Q3W pembrolizumab demonstrated no clinically meaningful difference in PK variability compared to weight-based dosing (**Error! Reference source not found. below, also see section 4 appendix 1**). The population exposure of 200 mg Q3W was numerically higher than 2 mg/kg Q3W dose, but significantly lower than 10 mg/kg Q2W and Q3W doses.

Table 1. Comparisons of Descriptive Statistics of Individual PK Parameters (CL, Vc) and Derived Parameters (t1/2, Vd_{SS}, T_{SS}) between MSI-H and non- MSI-H Patients

	MSI-H				Non-MSI-H			
	N	Mean	Median	Standard deviation	N	Mean	Median	Standard deviation
CL (L/day)	64	0.214	0.205	0.0894	2189	0.235	0.205	0.12
Vc (L)	64	3.23	3.24	0.729	2189	3.43	3.38	0.785
Half life (days)	64	27.4	27	6.48	2189	27.5	27	8.81
Vd_{ss} (L)	64	7.17	7.15	1.44	2189	7.53	7.41	1.53
T_{ss}; Time to steady state (days)	64	137	135	32.4	2189	137	135	44
Source: Table 6 of modeling and simulation report file "04gf2t-ppk-extended-to-MSI.pdf".								

Table 2: Mean (CV%) Comparison of Descriptive Statistics of Post-hoc Individual PK Parameters and Derived Parameters between MSI-H and non-MSI-H Patients Based on Time-Dependent PPK Analysis

	MSI-H (n=79)	Non-MSI-H (n=2189)
CL (L/d)	0.240 (39%)	0.253 (46%)
CLss (L/d)	0.221 (44%)	0.238 (52%)
Vss (L)	6.72 (19%)	6.96 (20%)
$T_{1/2\ \beta}$ (day)	24.8 (26%)	25.2 (35%)
Source: FDA reviewer's analysis.		

2.2.2. Does the dose-exposure relationship for efficacy and safety from related trials support the dose regimen of 200 mg Q3W and 10 mg/kg Q2W for the proposed indication of MSI-H/MMR deficient cancer?

The efficacy results demonstrate that both pembrolizumab dose regimens of 200 mg Q3W and 10 mg/kg Q2W are effective in the treatment of patients with MSI-H cancer, however, the ORR is consistently higher across trials for the 10 mg/kg Q2W regimen than the 200 mg Q3W

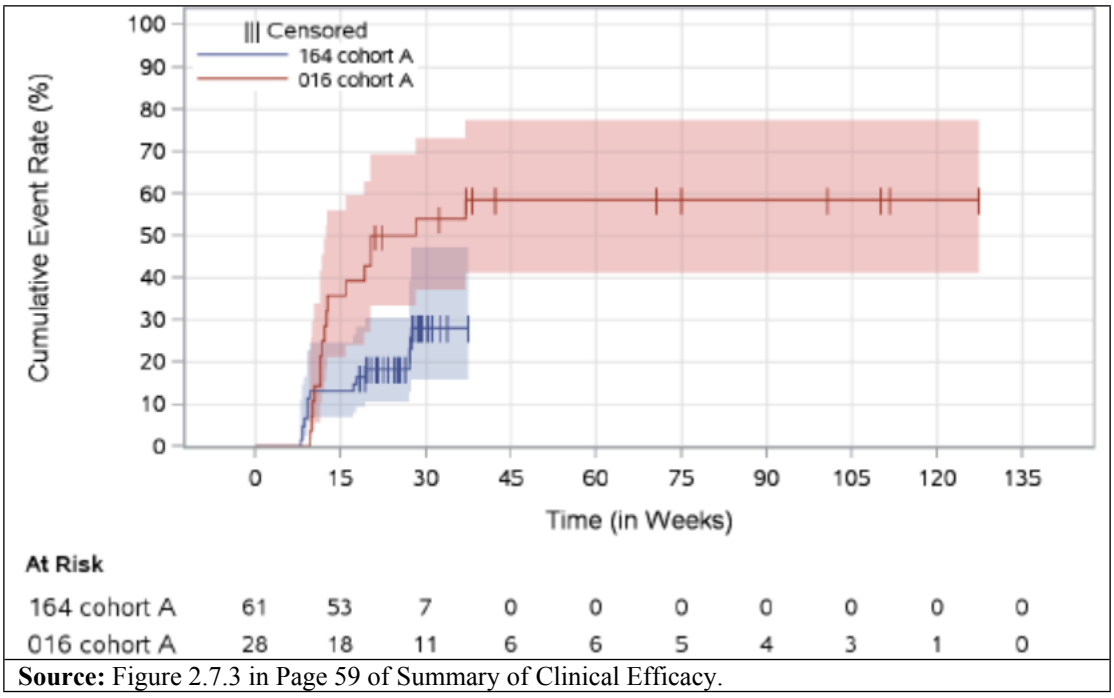
regimen after 4 months of treatment . Furthermore, the dose-response data assessing relationship between dose and PFS or OS in MSI-H, melanoma, and non-small-cell-lung cancer suggest that 10 mg/kg Q2W or Q3W provide additional efficacy compared to the 200 mg Q3W dose.:

- KN016-A and KN164 are two trials in patients with MSI-H colorectal cancer (CRC), where pembrolizumab dose are 10 mg/kg Q2W and 200 mg Q3W, respectively. The ORR separation is evident between the two trials after 4 months of treatment (**Figure 1 below, also see section 4 appendix 1**); 10 mg/kg Q2W in Trial KN016-A clearly showed better efficacy than 200 mg Q3W in Trial KN164. The evident separation between the two trials was also observed in Kaplan Meier plot of progression free survival (PFS) as shown in **Figure 3 below (also see section 4 appendix 1)**. This suggests 10 mg/kg Q2W dose level could be more efficacious.
- Across the 6 trials/cohorts for the MSI-H indication listed in **Table 2 below (also see section 4 appendix 1)** each of the four with pembrolizumab 10 mg/kg Q2W showed better efficacy (CR + PR) than each of the two with 200 mg Q3W dose. There were 9 complete responders at the 10 mg/kg Q2W dose versus 1 complete responder at 200 mg Q3W dose.

In addition, Trial KN002 in melanoma patients and Trial KN010 in NSCLC patients consistently demonstrated numerically better efficacy (overall survival) of pembrolizumab 10 mg/kg Q3W than 2 mg/kg Q3W dose, especially in PD-L1 negative melanoma or PD-L1 weakly positive NSCLC patients (

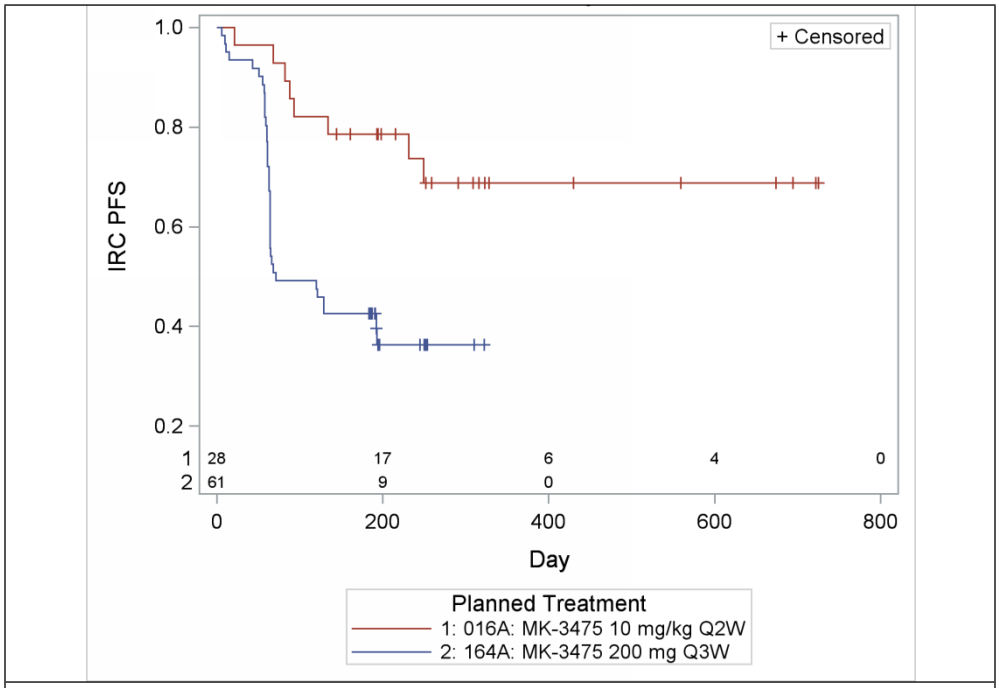
- **Figure 4 and Figure 5 below, also see section 4 appendix 1**).
- The number of patients studied for each pembrolizumab dose was about 180 in KN002 and 350 in KN010, and the safety profile of the two doses are generally comparable. KN06 studied pembrolizumab 10 mg/kg Q2W (n=279) and 10 mg/kg Q3W (n=277), and the safety profile was also acceptable. Refer to clinical trial reports for KN002, KN006 and P010 for more information.
- The overall number, type, and frequency of AEs reported in the MSI-H safety population are consistent with the safety profile previously described for pembrolizumab at 10 mg/kg Q2W dose level. Discontinuation due to toxicity is also comparable between KN016-A (11% (3/28)) and KN164 (7% (4/60)). Although dose interruption rate of KN016A at 10 mg/kg Q3W is higher than that of KN164 at 200 mg Q3W (**Figure 6 below, also see section 4 appendix 1**), the overall result was drug held temporarily and majority of the events were resolved. This observation suggested both doses are clinically meaningful; patients with frequent dose interruption at 10 mg/kg Q3W starting dose may transit to 200 mg/kg Q3W as needed.

Figure 1. Kaplan-Meier Curve of Time to Response (Confirmed and Unconfirmed Combined) Based on IRC Assessment per RECIST 1.1 (Cohort A of KN016 and KN164, ASaT Population)



Source: Figure 2.7.3 in Page 59 of Summary of Clinical Efficacy.

Figure 2. Kaplan-Meier Curve of PFS (Cohort A of KN016 (10 mg/kg Q2W, Blue) and KN164 (200 mg Q3W, Red))

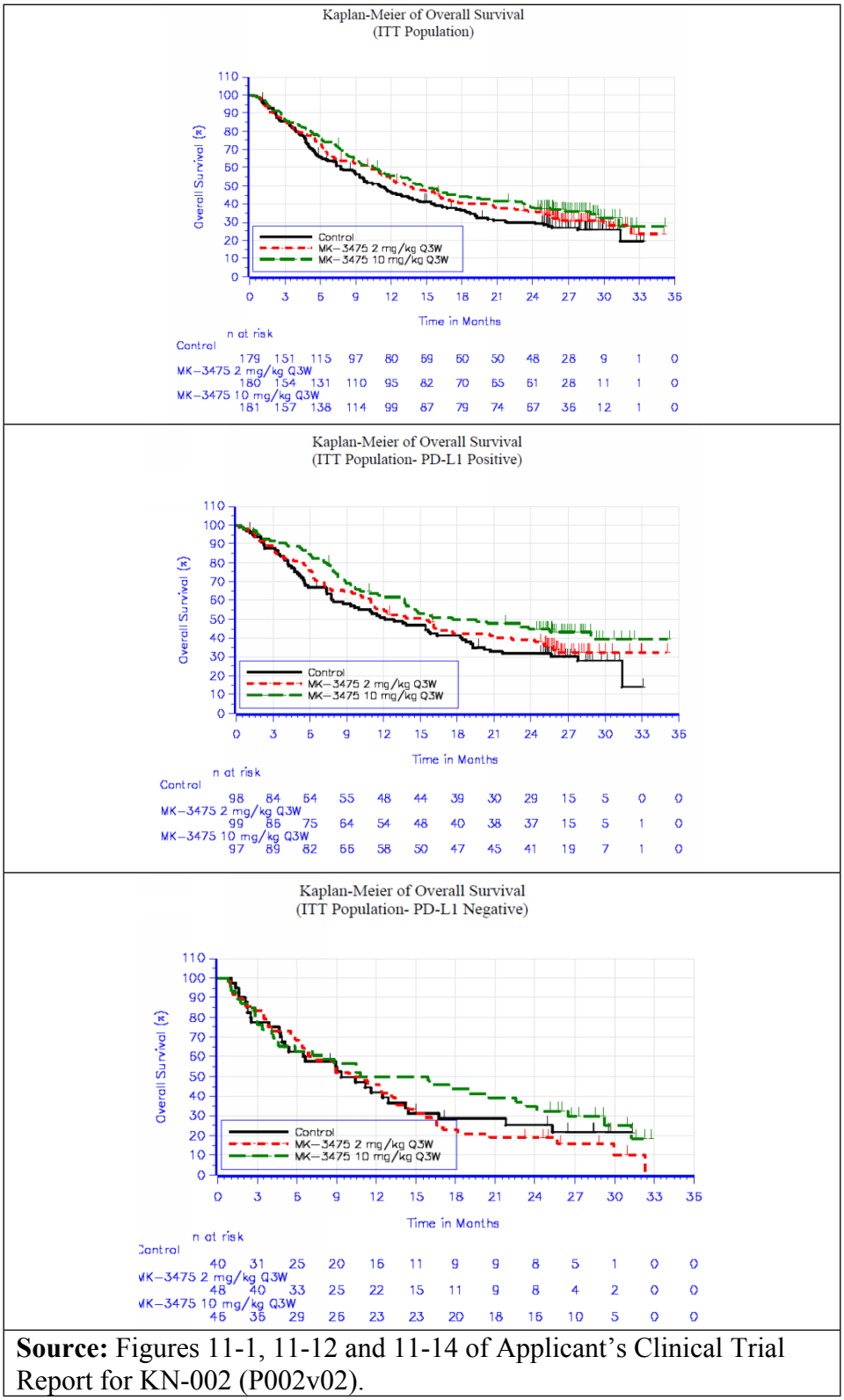


Source: Reviewer's exploratory analysis.

Table 2. Summary of Response Results of the Five Trials

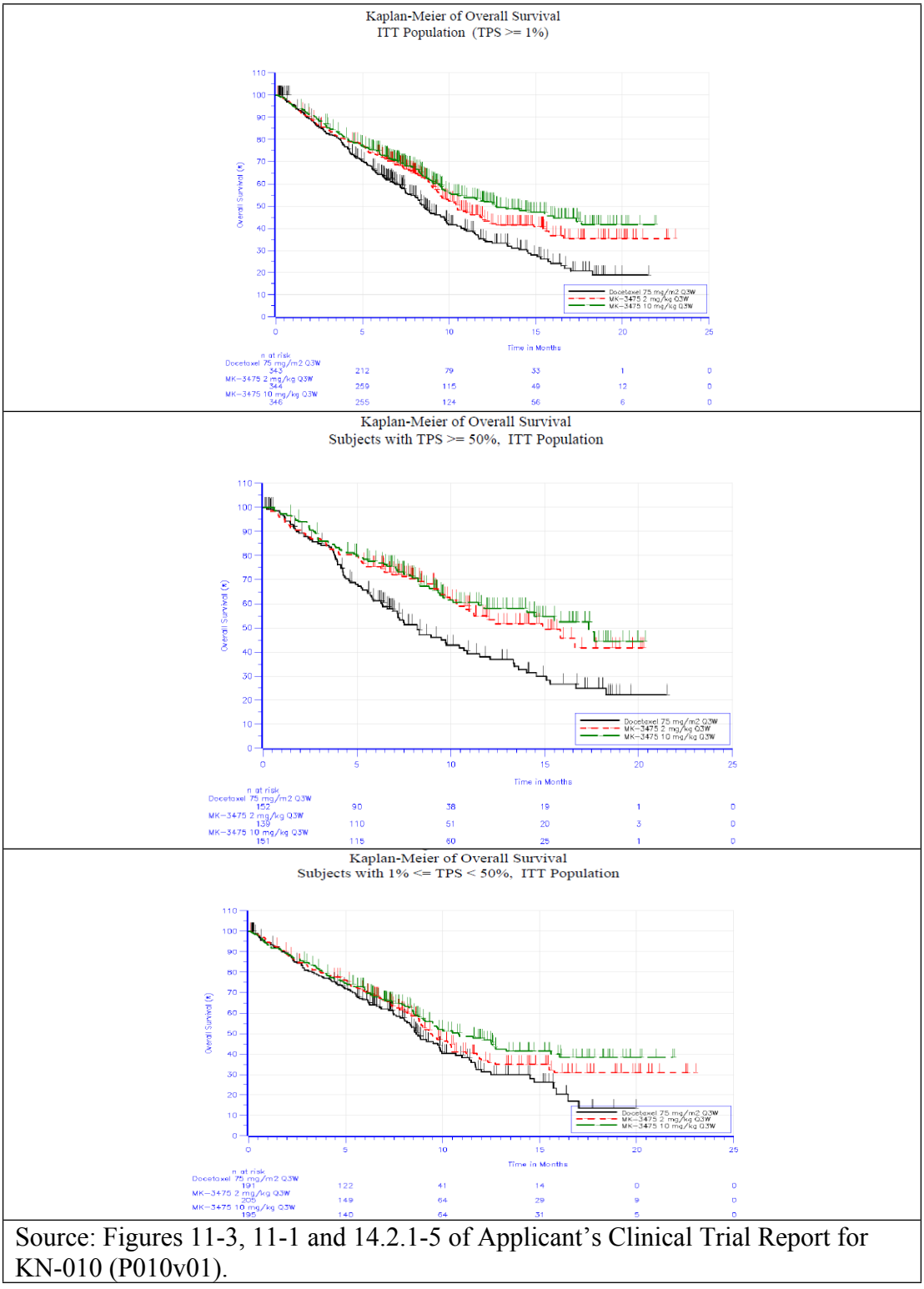
Response	10 mg/kg Q2W				200 mg Q3W	
	KN016-A (n=28)	KN016-C (n=30)	KN012 (n=6)	KN028 (n=5)	KN164 (n=61)	KN158 (n=19)
Complete Response (%)	4 (14.3)	5 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Partial Response (%)	10 (35.7)	9 (30.0)	3 (50.0)	4 (80.0)	13 (21.3)	4 (21.1)
CR+PR (%), (95% CI†)	**14 (50), (30.6-69.4)**	**14 (46.7), (28.3-65.7)**	**3 (50.0), (11.8-88.2)**	**4 (80.0), (28.4-99.5)**	**15 (24.6), (14.5-37.3)**	**6 (31.6), (12.6-56.6)**
Stable Disease (%)	9 (32.1)	5 (16.7)	0 (0.0)	0 (0.0)	18 (29.5)	8 (42.1)
Disease Control* (%), (95% CI†)	**23 (82.1), (63.1-93.9)**	**19 (63.3), 43.9-80.1)**	**3 (50.0), (11.8-88.2)**	**4 (80.0), (28.4-99.5)**	**31 (50.8), (37.7-63.9)**	**Not reported**
Source: Table 2.7.3 in Page 22 of Summary of Clinical Efficacy.						

Figure 4. Kaplan-Meier Curve of Time to Overall Survival for Trial KN-002 in Ipilimumab Refractory Melanoma Patients



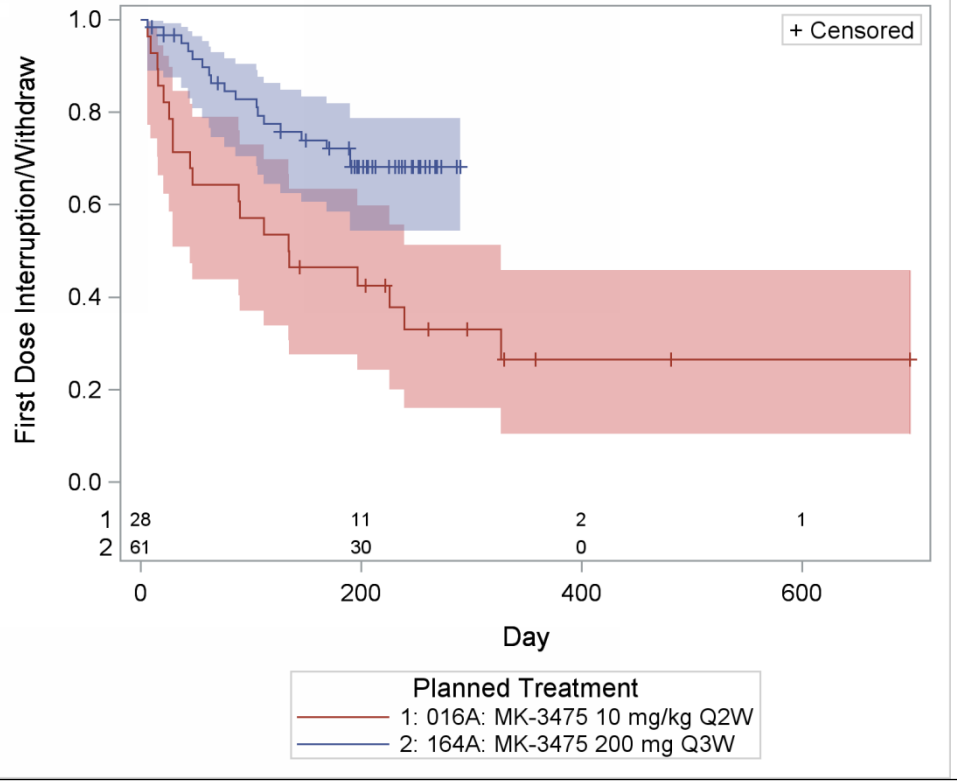
Source: Figures 11-1, 11-12 and 11-14 of Applicant's Clinical Trial Report for KN-002 (P002v02).

Figure 5. Kaplan-Meier Curve of Time to Overall Survival for Trial KN-010 in Non-small Cell Lung Cancer Previously Treated with Platinum Based Chemotherapy



Source: Figures 11-3, 11-1 and 14.2.1-5 of Applicant's Clinical Trial Report for KN-010 (P010v01).

Figure 6. Kaplan-Meier Curve of First Dose Interruption/Withdrawal (Cohort A of KN016 (10 mg/kg Q2W, Blue) and KN164 (200 mg Q3W, Red))



Source: Reviewer's sensitivity analysis, censored data were imputed from the last observation in the OS dataset

In summary, both pembrolizumab 200 mg Q3W and 10 mg Q2W are effective for patients with MSI-H tumors. The high dose of 10 mg/kg Q2W may provide additional benefit with acceptable safety in the MSI-H population.

2.2.3. What is the incidence (rate) of the formation of the anti-drug antibodies (ADA), including the rate of pre-existing antibodies, the rate of ADA formation during and after the treatment, time profiles and adequacy of the sampling schedule? Do the ADAs have neutralizing activity?

In patients with MSI-H positive tumors, 1 of 54 (1.9%) evaluable patients (51 negative, 2 non-treatment emergent positive) had treatment emergent ADA, **see table 4 below**. In trial KN012, six patients were identified as MSI-H. Per Merck, three patients are classified as ADA inconclusive and three were ADA negative. Patients from KN012 were not included in the integrated analysis of pembrolizumab immunogenicity. Neutralizing capacity for the confirmed one positive ADA sample in trial KN164 is pending.

Merck also submitted an integrated immunogenicity analysis across multiple tumor types (melanoma, NSCLC, HNSCC, urothelial cancer (UC) and MSI-H) from 1427 evaluable out of 3048 treatment patients. Pre- and post-baseline serum samples from patients treated with

pembrolizumab were analyzed for ADAs. The observed incidence of pembrolizumab treatment emergent ADA in evaluable patients based on a pooled analysis of patients is 1.9% (28 out of 1437), **see table 4 below**. Incidence of ADA induction was also stratified by dose regimen (2 mg/kg, 10 mg/kg, or 200 mg pembrolizumab). Immunogenicity rate did not increase with increasing dose, **see table 5 below**.

Table 4. Summary of immunogenicity assessments stratified by indication following treatment with pembrolizumab at dose of 2 mg/kg, 10 mg/kg, or 200 mg

Immunogenicity status	**Melanoma**	**NSCLC**	**HNSCC**	**UC**	**MSI-H**
Assessable patients	1535	1237	101	121	54
Inconclusive patients	1101	444	39	27	0
Evaluable patients	434	793	62	94	54
Negative	427 (98.4%)	765 (96.5%)	59 (95.2%)	93 (98.9%)	51 (94.4%)
Non-Treatment emergent positive	4 (0.9%)	6 (0.8%)	2 (3.2%)	0 (0%)	2 (3.7%)
Treatment emergent Positive	3 (0.7%)	22 (2.8%)	1 (1.6%)	1 (1.1%)	1 (1.9%)

Data Source: Table 5 of immunogenicity report [Ref. 5.3.5.3: 04D4CF]

Table 5. Summary of immunogenicity results stratified by pembrolizumab dose pooled across multiple tumor types

Immunogenicity status	**All treatments**	**Treatment**		
		2 mg/kg	**10 mg/kg**	**200 mg**
Assessable patients	3048	706	2014	328
Inconclusive patients	1611	136	1469	6
Evaluable patients	1437	570	545	322
Negative	1395 (97.1%)	555 (97.4%)	530 (97.2%)	310 (96.3%)
Non-Treatment emergent positive	14 (1.0%)	7 (1.2%)	4 (0.7%)	3 (0.9%)
Treatment emergent Positive	28 (1.9%)	8 (1.4%)	11 (2.0%)	9 (2.8%)

Data Source: Table 5 of immunogenicity report [Ref. 5.3.5.3: 04D4CF]

Among the 28 patients who tested positive for treatment emergent anti-pembrolizumab antibodies, only 4 patients were tested for neutralizing antibodies and one was positive. Per

Merck, during the course of the trial, measurement of the ADA samples has been transferred from (b) (4) to another vendor, (b) (4). As part of this transfer the neutralizing assay is being optimized at (b) (4). At this moment only results from the neutralizing assay (b) (4) from 4 patients are available and the majority of the confirmed positive samples the results of the neutralizing assay are still pending, because the optimization of the neutralizing assay at (b) (4) has not finalized yet.
One patient with an ADA screening negative result that was classified as inconclusive but inadvertently tested for neutralizing ADA capacity and showed a positive result, **see table 6 below**.

Table 6. Neutralizing ADA positive patient

Study	TRT	AN	Visit code	TAFD (day)	TALD (day)	MK-3475 conc (µg/mL)	Result ADA assay			Result Neutralizing assay		
							Screening[a]	Confirmatory[b]	Titer[c]	Screening	Confirmatory	Final
MK3475-002	10 mg/kg	(b) (6)	C1W0	0	0	0.00	Negative		.			
			C3W6	43	21	78.3	Negative		.	Positive	Positive	Positive
			C6W15	108	22	197	Negative		.			
			C9W24	185	22	198	Negative					
			C13W36	276	28	233	Negative		.			
			C16W45	339	21	149	Negative		.			

TRT: Treatment; AN: Allocation Number
TAFD: Time After First Dose; TALD: Time After Last Dose
a: A positive result for the screening assay is reported by (b) (4) as "Positive" and by (b) (4) as "Potential Positive", both meaning the same
b: For samples with a screening negative result, the confirmatory result is reported by (b) (4) as "." and by (b) (4) as "N/A", both meaning the same
c: For samples with a screening negative result, the Titer result is reported by (b) (4) as "." and by (b) (4) as "N/A", both meaning the same

Data Source: Table 9 of immunogenicity report [Ref. 5.3.5.3: 04D4CF]

In conclusion, overall the observed incidence of treatment emergent ADA in evaluable MSI-H patients was 1.9 % (1 of 58 patients). No impact of ADA on pembrolizumab exposure was observed, and no hypersensitivity events or infusion site reactions associated with neutralizing antibodies have yet been identified.

2.2.4. What bioanalytical methods are used to assess pembrolizumab concentrations?

The electrochemiluminescence (ECL) bioanalytical method was utilized in the quantitation of pembrolizumab serum samples. The ECL assay reviewed in the original BLA was developed by (b) (4) and subsequently was transferred to (b) (4). The history of the bioanalytical method was previously detailed in Supplements 4 and 6. The bioanalytical method validation was reviewed earlier as part of Supplements 4 and 6.

Per Merck, the lower limit of quantitation (LLOQ) for the 3rd generation assay at (b) (4) was raised on 27 May 2016 from 10 ng/mL (b) (4) to 25 ng/mL (b) (4). All samples tested before that date are reported with an LLOQ of 10 ng/mL and all samples tested from 27 May 2016 onwards are using an LLOQ of 25 ng/mL. The original 10 ng/ml concentration was used as an anchor point in method (b) (4).

Method (b) (4), with an LLOQ of 10 ng/ml was used to determine the serum concentration in trial KN012. (b) (4), with an LLOQ of 25 ng/ml was used to determine the serum concentration of in trial KN164.

Reviewer's Comment: The increase in LLOQ unlikely to influence PK data quality as the majority of trough samples are above 10 ug/ml or 400 times above the LLOQ of 25 ng/ml.

2.2.5. What methods are used to assess pembrolizumab ADA incidence in SCCHN patients?

The validated bridging electrochemiluminescence (ECL) immunoassay used for the detection of anti-pembrolizumab antibodies in human serum was reviewed earlier as part of supplement 8.

3. Detailed Labeling Recommendations

Only relevant clinical pharmacology sections are included. The sponsor's proposed additions are underlined and deletions have a strikethrough line. The sponsor proposed additions are represented by red strikethrough lines.

---------- **DOSAGE AND ADMINISTRATION** ----------

- NSCLC: 200 mg every 3 weeks. (2.3)
- HNSCC: 200 mg every 3 weeks. (2.4)
- MSI-H Cancer: 200 mg every 3 weeks. (2.5)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

2.5 Recommended Dosage for Microsatellite Instability-High (MSI-H) Cancer

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.4)]*.**[2]**

12.3 Pharmacokinetics

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2841 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Pembrolizumab clearance (CV%) is approximately ~~20~~21% lower [geometric mean, ~~212~~ 196 mL/day (~~46~~41%)] (b) (4) at steady state ~~than that after~~ (b) (4) the first dose [~~267~~ 249 mL/day (~~43.1~~38%)]; this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for volume of distribution at steady state is ~~6.1~~6.0 L (21%) and for terminal half-life ($t_{1/2}$) is ~~23~~ 22 days (~~30~~32%).

Steady-state concentrations of pembrolizumab were reached by ~~19~~ 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-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.**[18]**

Reviewer's Comment: Merck is proposing not to update the label for immunogenicity. Per Merck, FDA feedback provided for S-008 and S-012 for NSCLC that the database of 1289

evaluable patients is sufficient to characterize the incidence of anti-pembrolizumab antibodies. Therefore no revision to section 6.2 is proposed at this time.

Also Merck proposes to revise PK parameter values introduced by FDA on 19Sep2016 for NSCLC (S-008 and S-012). Per Merck, the values provided by FDA are based on arithmetic mean and %CV calculations. The revised values proposed by Merck represent calculations based on geometric mean and geometric %CV as described in the text.

4. Appendix 1) Pharmacometrics review office of clinical pharmacology: pharmacometric review

BLA Number	125514/s14
Drug Name	Keytruda® (pembrolizumab)
Dose Regimen	200 mg intravenous infusion over 30 minutes every 3 weeks
Indication	For the treatment of patients with microsatellite instability high (MSI-H) tumors
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Jiang Liu, Ph.D.
Sponsor	Merck & Co. Inc.

Table of Contents

SUMMARY OF FINDINGS

Pembrolizumab BLA125514 Supplement 14 (s14) included efficacy and safety data from 5 trials for a total of 149 patients with different types of microsatellite instability-high (MSI-H) tumors from 5 trials (KN016, KN012, KN028, KN164, and KN 158), where the objective response rate (ORR) is the primary efficacy endpoint.

- In Trials KN164 (n=61) and KN158 (n=19), pembrolizumab 200 mg were administered every 3 weeks (Q3W), and the percent ORRs (95% CI) were 24.6 (14.5-37.3) and 31.6 (12.6-56.6), respectively.
- In Trials KN012 (n=6), KN016-A (n=28), KN016-C (n=30), and KN028 (n=5), pembrolizumab 10 mg/kg were administered every 2 weeks (Q2W), and the percent ORRs (95% C) were 50.0 (11.8-88.2), 50.0 (30.6-69.4), 46.7 (28.3-65.7) and 80.0 (28.4-99.5), respectively.

The efficacy data based on cross-trial comparison showed that the high dose of 10 mg/kg Q2W is more efficacious than 200 mg Q3W in the MSI-H population with overall safety profile demonstrated acceptable in pembrolizumab development program. We therefore recommend the 10 mg/kg Q2W dosing to be approved for patients with MSI-H cancer.

1.1. KEY REVIEW QUESTIONS

The purpose of this review was to address the following key question.

1.1.1. Is the proposed pembrolizumab dose of 200 mg Q3W optimal for patients with MSI-H tumors?

In context of the limited data provided in this application, both pembrolizumab 200 mg Q3W and 10 mg Q2W are effective for patients with MSI-H tumors. The high dose of 10 mg/kg Q2W can provide additional benefit with acceptable safety in the MSI-H population.:

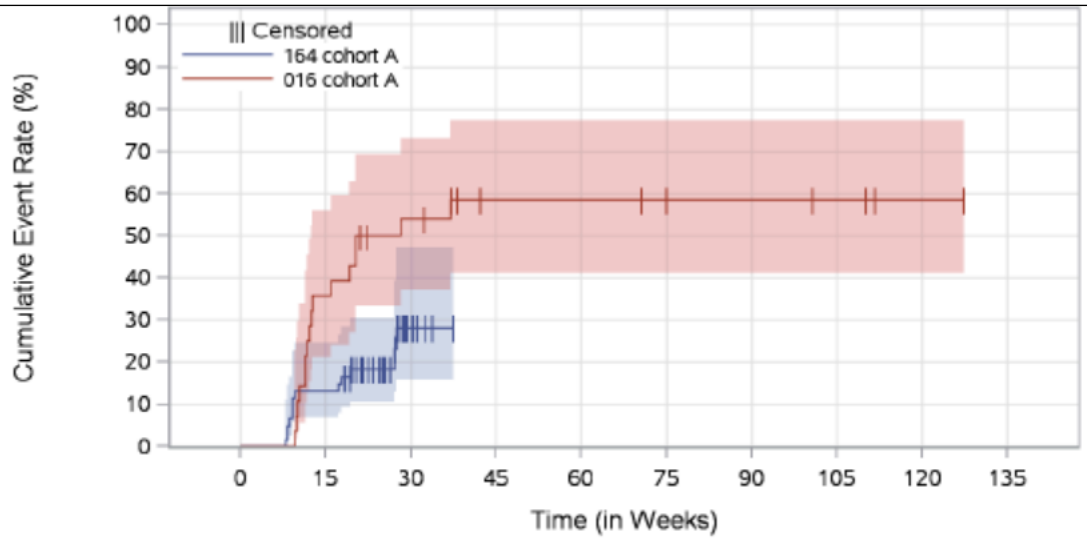
- KN016-A and KN164 are two trials in patients with MSI-H colorectal cancer (CRC), where pembrolizumab dose are 10 mg/kg Q2W and 200 mg Q3W, respectively. The ORR separation is evident between the two trials after 4 months of treatment (**Figure 1**); 10 mg/kg Q2W in Trial KN016-A clearly showed better efficacy than 200 mg Q3W in Trial KN164. The evident separation between the two trials was also observed in Kaplan Meier plot of progression free survival (PFS) as shown in (**Error! Reference source not found.** This suggests 10 mg/kg Q2W dose level could be more efficacious.
- Across the 6 trials/cohorts listed in **Table 2**, each of the four with pembrolizumab 10 mg/kg Q2W showed better efficacy than each of the two with 200 mg Q3W dose.

In addition, Trial KN002 in melanoma patients and Trial KN010 in non-small cell lung cancer (NSCLC) patients consistently demonstrated numerically better efficacy of pembrolizumab 10

mg/kg Q3W than 2 mg/kg Q3W dose, especially in PD-L1 negative melanoma or PD-L1 weakly positive NSCLC patients (

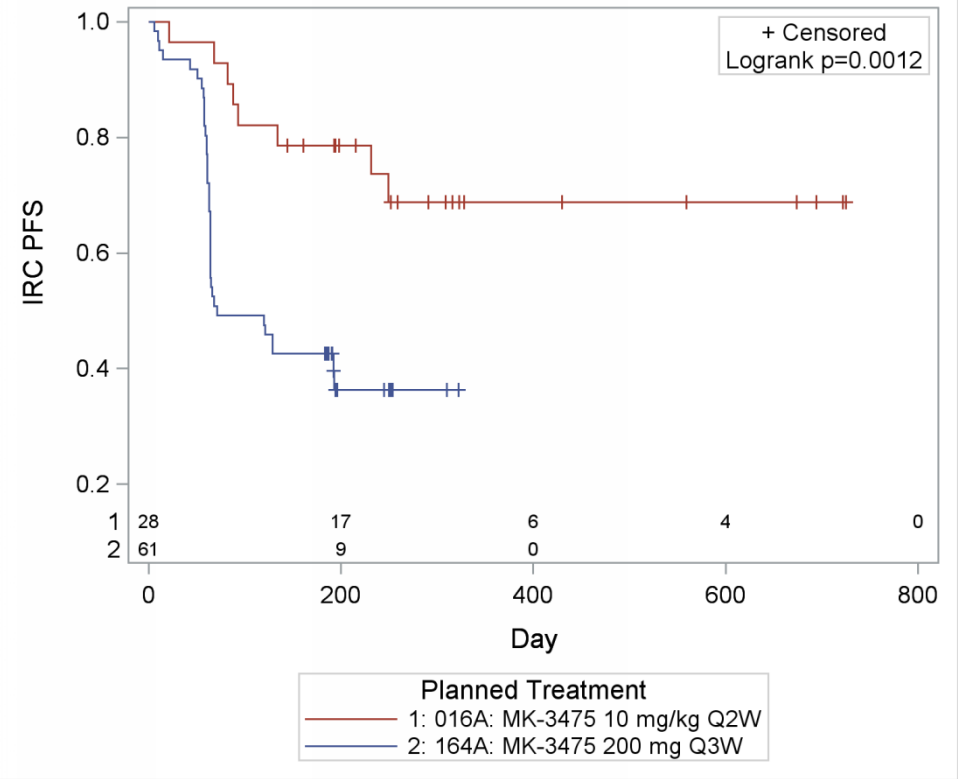
- **Figure** and **Figure**).
- The number of patients studied for each pembrolizumab dose was about 180 in KN02 and 350 in KN010, and the safety profile of the two doses are generally comparable. KN06 studied pembrolizumab 10 mg/kg Q2W (n=279) and 10 mg/kg Q3W (n=277), and the safety profile was also acceptable. Refer to clinical trial reports for KN002, KN006 and P010 for more information.
- The overall number, type, and frequency of AEs reported in the MSI-H safety population are consistent with the safety profile previously described for pembrolizumab at 10 mg/kg Q2W dose level. Discontinuation due to toxicity is also comparable between KN016-A (11% (3/28)) and KN164 (7% (4/60)). Although dose interruption rate of KN016A at 10 mg/kg Q3W is higher than that of KN164 at 200 mg Q3W (**Figure**), the overall result was drug held temporarily and majority of the events were resolved. This observation suggested both doses are clinically meaningful; patients with frequent dose interruption at 10 mg/kg Q3W starting dose may transit to 200 mg/kg Q3W as needed.

Figure 3: Kaplan-Meier Curve of Time to Response (Confirmed and Unconfirmed Combined) Based on IRC Assessment per RECIST 1.1 (Cohort A of KN016 and KN164, ASaT Population)



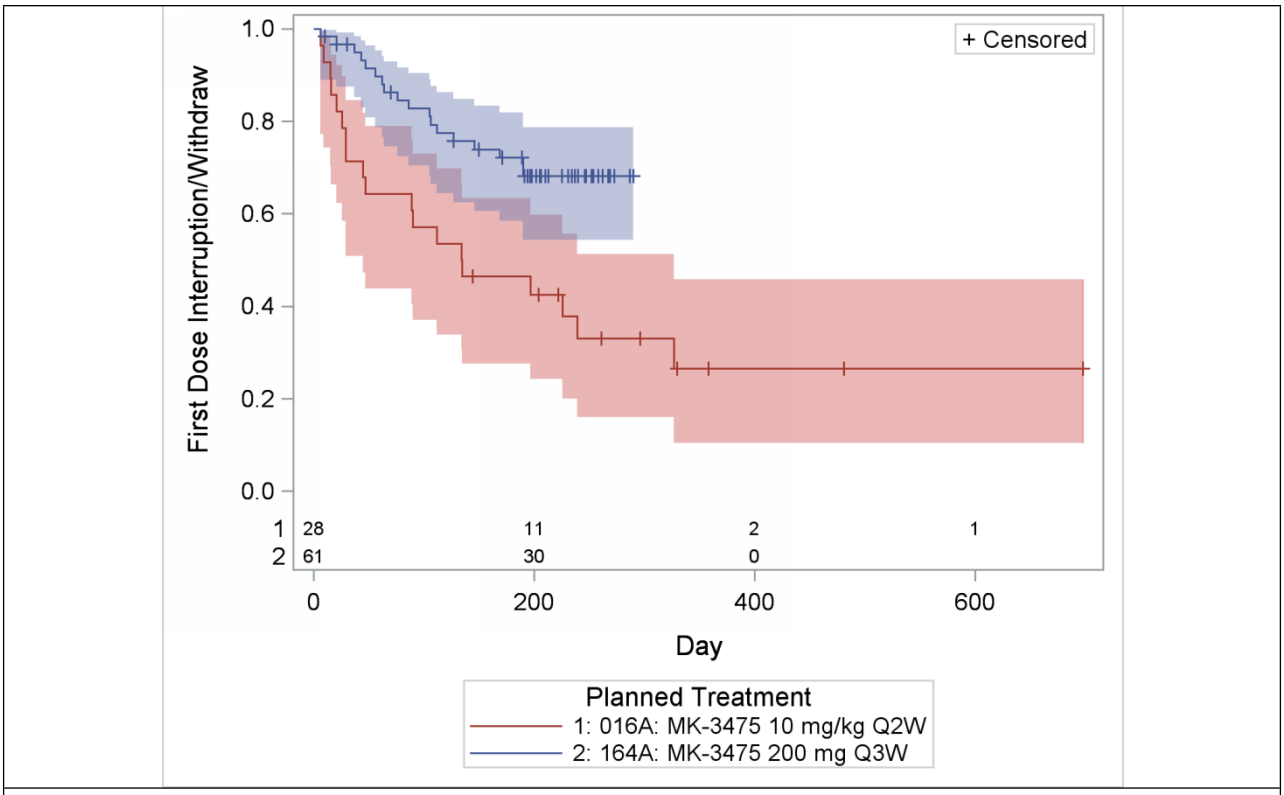
Source: Figure 2.7.3 in Page 59 of Summary of Clinical Efficacy.

Figure 4: Kaplan-Meier Curve of PFS (Cohort A of KN016 (10 mg/kg Q2W, Blue) and KN164 (200 mg Q3W, Red))



Source: Reviewer's exploratory analysis.

Figure 5: Kaplan-Meier Curve of First Dose Interruption/Withdrawal (Cohort A of KN016 (10 mg/kg Q2W, Blue) and KN164 (200 mg Q3W, Red))



Source: Reviewer's sensitivity analysis, censored data were imputed from the last observation in the OS dataset

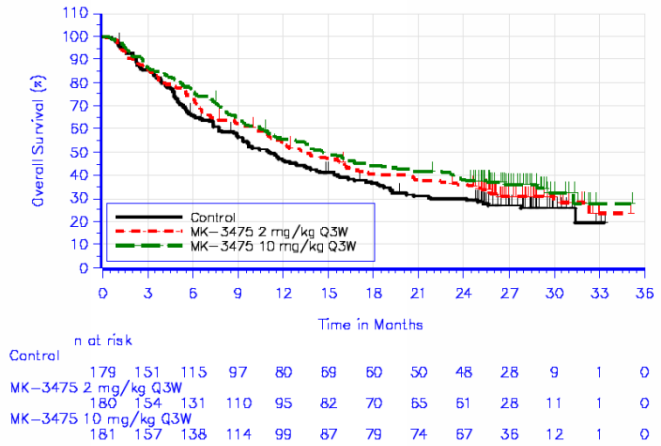
Table 3: Summary of Response Results of the Five Trials

Response	10 mg/kg Q2W				200 mg Q3W	
	KN016-A (n=28)	KN016-C (n=30)	KN012 (n=6)	KN028 (n=5)	KN164 (n=61)	KN158 (n=19)
Complete Response (%)	4 (14.3)	5 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Partial Response (%)	10 (35.7)	9 (30.0)	3 (50.0)	4 (80.0)	13 (21.3)	4 (21.1)
CR+PR (%, 95% CI†)	**14 (50, 30.6-69.4)**	**14 (46.7, 28.3-65.7)**	**3 (50.0, 11.8-88.2)**	**4 (80.0, 28.4-99.5)**	**15 (24.6, 14.5-37.3)**	**6 (31.6, 12.6-56.6)**
Stable Disease (%)	9 (32.1)	5 (16.7)	0 (0.0)	0 (0.0)	18 (29.5)	8 (42.1)
Disease Control* (%, 95% CI†)	**23 (82.1, 63.1-93.9)**	**19 (63.3, 43.9-80.1)**	**3 (50.0, 11.8-88.2)**	**4 (80.0, 28.4-99.5)**	**31 (50.8, 37.7-63.9)**	**Not reported**

Source: Table 2.7.3 in Page 22 of Summary of Clinical Efficacy.

Figure 6: Kaplan-Meier Curve of Time to Overall Survival for Trial KN-002 in Ipilimumab Refractory Melanoma Patients

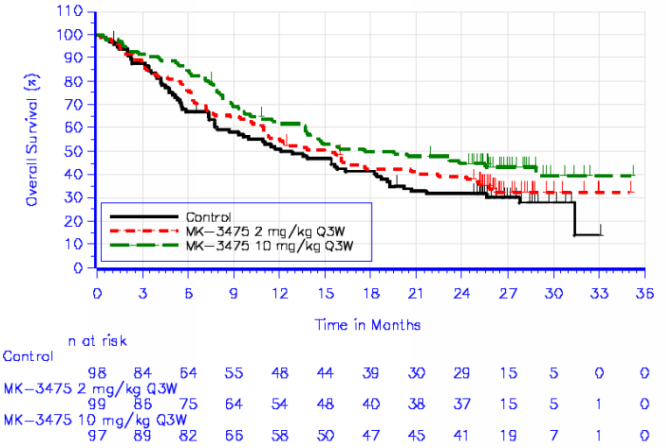
Kaplan-Meier of Overall Survival
(ITT Population)



n at risk

Control	179	151	115	97	80	69	60	50	48	28	9	1	0
MK-3475 2 mg/kg Q3W	180	154	131	110	95	82	70	65	61	28	11	1	0
MK-3475 10 mg/kg Q3W	181	157	138	114	99	87	79	74	67	36	12	1	0

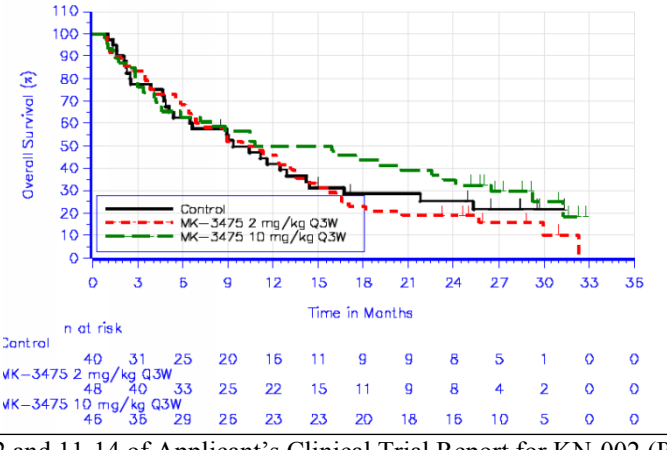
Kaplan-Meier of Overall Survival
(ITT Population- PD-L1 Positive)



n at risk

Control	98	84	64	55	48	44	39	30	29	15	5	0	0
MK-3475 2 mg/kg Q3W	99	86	75	64	54	48	40	38	37	15	5	1	0
MK-3475 10 mg/kg Q3W	97	89	82	66	58	50	47	45	41	19	7	1	0

Kaplan-Meier of Overall Survival
(ITT Population- PD-L1 Negative)

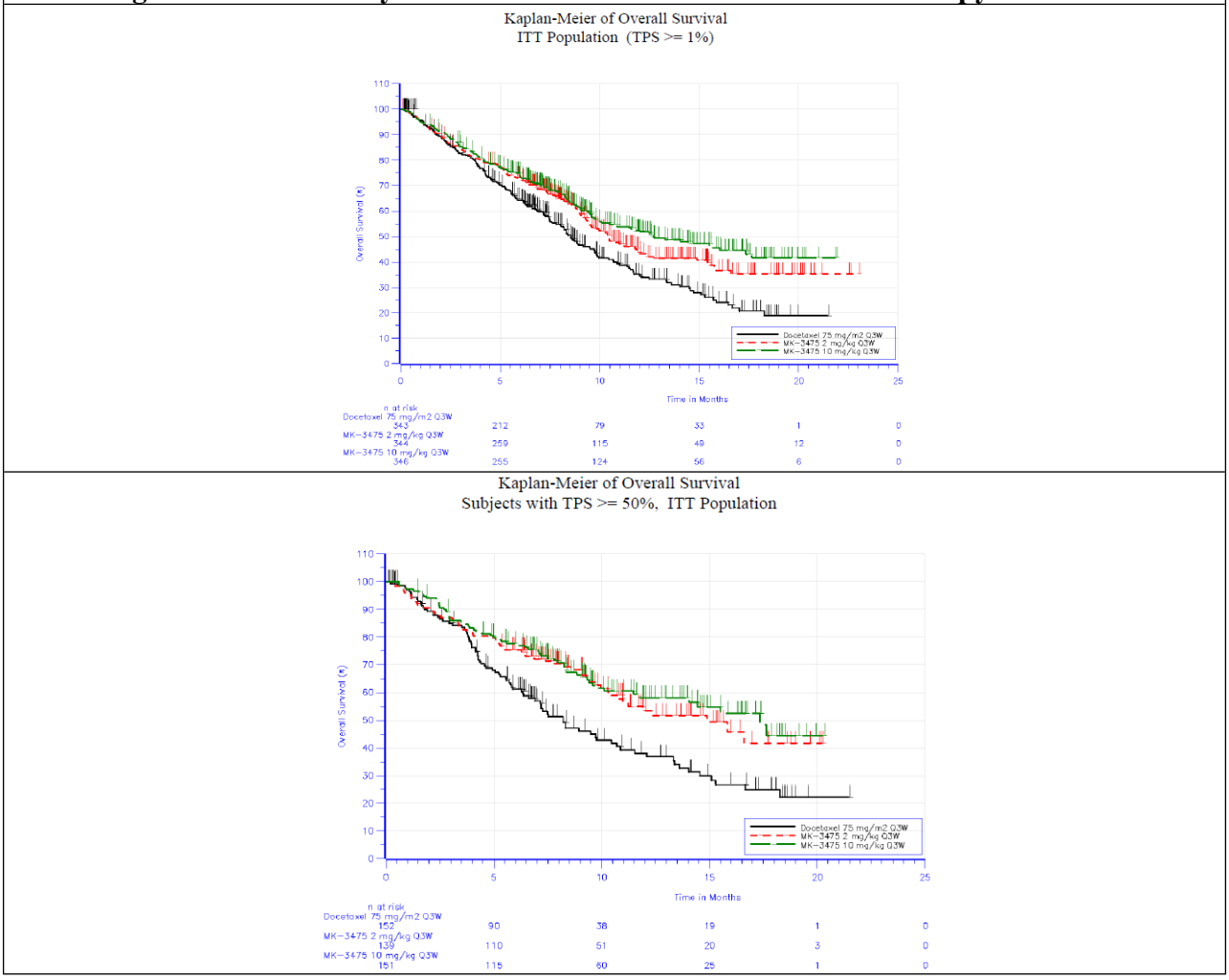


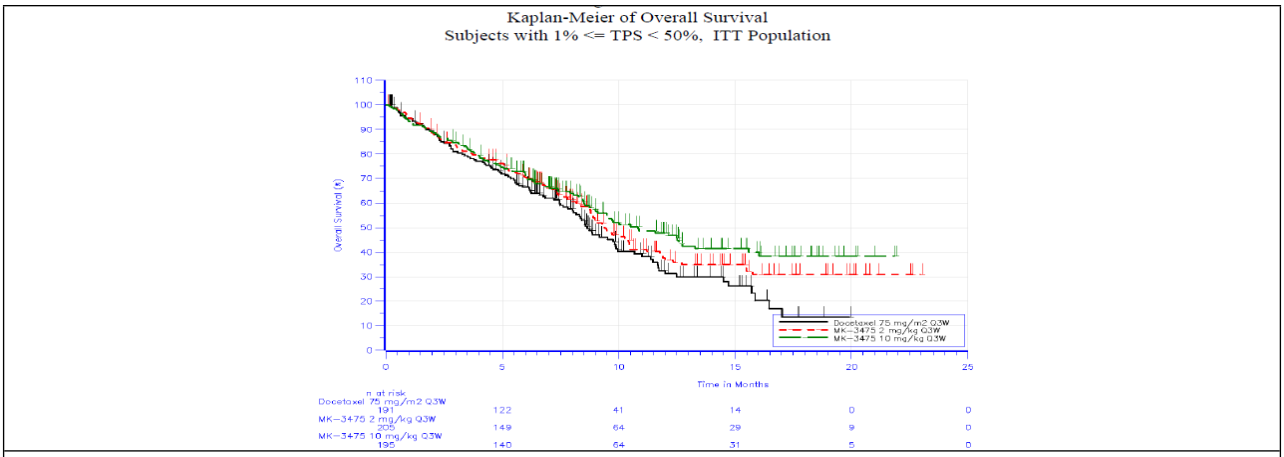
n at risk

Control	40	31	25	20	16	11	9	9	8	5	1	0	0
MK-3475 2 mg/kg Q3W	48	40	33	25	22	15	11	9	8	4	2	0	0
MK-3475 10 mg/kg Q3W	46	36	29	26	23	23	20	18	16	10	5	0	0

Source: Figures 11-1, 11-12 and 11-14 of Applicant's Clinical Trial Report for KN-002 (P002v02).

Figure 7: Kaplan-Meier Curve of Time to Overall Survival for Trial KN-010 in Non-small Cell Lung Cancer Previously Treated with Platinum Based Chemotherapy





Source: Figures 11-3, 11-1 and 14.2.1-5 of Applicant's Clinical Trial Report for KN-010 (P010v01).

In summary, both pembrolizumab 200 mg Q3W and 10 mg Q2W are effective for patients with MSI-H tumors. The high dose of 10 mg/kg Q2W can provide additional benefit with acceptable safety in the MSI-H population..

1.2. LABELING CHANGE

Associated with FDA action on S-008 and S-012, time-dependent population pharmacokinetics parameters (based on an expanded dataset, n=2841 including KN001, KN002, KN006 and KN010) appeared in Section 12.3 of the USPI. The label text refers to geometric means, but the values were based on arithmetic mean and %CV calculations. With an amendment submitted on 11/23/2016 under BLA125514 s14, (\\cdsesub1\evsprod\bla125514\0308\m1\us\efficacy-information-amendment-23nov2016.pdf), Merck proposes to revise the PK parameter values. The corrected values proposed here represent calculations based on geometric mean and geometric %CV using the same PPK dataset and the same time-dependent PK model.

Proposed labeling with corrected geometric mean and geometric %CV values

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2841 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Pembrolizumab clearance (CV%) is approximately 21~~20~~% lower [geometric mean, 196~~212~~ mL/day (41~~46~~%)] (b) (4) at steady state (b) (4) ~~than that after~~ the first dose [249~~267~~ mL/day (38~~43.1~~%)]; this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for volume of distribution at steady state is 6.0 ~~6.1~~ L (21%) and for terminal half-life ($t_{1/2}$) is 22~~23~~ days (32~~30~~%).

Steady-state concentrations of pembrolizumab were reached by 16~~19~~ weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-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.

Reviewer's comments: *The proposed values are verified to be correct so the proposed revisions are necessary although the differences are not significant.*

2. PERTINENT REGULATORY BACKGROUND

This supplementary submission is for the approval of pembrolizumab 200 mg Q3W for patients with microsatellite instability high (MSI-H) solid tumors based on efficacy and safety data of 149 patients from 5 trials.

Key highlights of the US regulatory history on pembrolizumab include grant of orphan drug designation for Stage IIB-IV melanoma on 20-Nov-2012, grant of breakthrough therapy designation on 17-Jan-2013, and the grant of a pediatric waiver based on orphan drug status on 17-Apr-2013.

On 04-Sept-2014, pembrolizumab (Keytruda®) received the FDA's accelerated approval as a breakthrough therapy for the treatment of patients with unresectable or metastatic melanoma who have been previously treated with ipilimumab (BLA125514). The accelerated approval was based on ORR data of Trial P001 Part B2, a randomized (1:1) Phase I trial of pembrolizumab 2 mg/kg Q3W (n=89) versus 10 mg/kg Q3W (n=84) in the treatment of ipilimumab-refractory melanoma patients. The primary objective was to compare the ORR between the two treatments. The confirmed ORR was 26% (95% CI: 17-37%) for 2 mg/kg Q3W dose and 26% (95% CI: 17-38%) for 10 mg/kg Q3W dose by independent central review (based on IRO assessment) using RECIST 1.1.

On 25-Mar-2015: the supplement (sBLA 125514-s4, Seq 253) was submitted for the approval of pembrolizumab for the treatment of ipilimumab treated, unresectable or metastatic melanoma based on efficacy and safety result of P002V01, a randomized, Phase II trial of MK-3475 versus

chemotherapy in patients with advanced melanoma. This was a partially blinded, randomized, Phase II trial of intravenous (IV) MK-3475 (2 or 10 mg/kg Q3W) versus investigator-choice (standard of care) chemotherapy in a 1:1:1 ratio in patients with advanced melanoma.

On 19-Jun-2015: the supplement (sBLA 125514-s6, Seq 310) was submitted for the approval of pembrolizumab for the treatment of non-ipilimumab treated, unresectable or metastatic melanoma based on efficacy and safety result of P006, a multicenter, randomized, controlled, three-arm, phase III trial to evaluate the safety and efficacy of two dosing schedules of MK-3475 (10 mg/kg Q2W and 10 mg/kg Q3W) compared to ipilimumab in patients with advanced melanoma.

On 24-Dec-2015: the supplement (sBLA 125514-s8, Seq 516) was submitted for the approval of pembrolizumab for the treatment of previously treated PDL-1 positive NSCLC patients based on efficacy and safety result of P010, a Phase II/III randomized trial of two doses of MK-3475 (2 mg/kg Q3W and 10 mg/kg Q3W) versus docetaxel in previously treated PDL-1 positive patients with non-small cell lung cancer.

On 09-Feb-2016: the supplement (sBLA 125514-s9, Seq 547) was submitted for the approval of pembrolizumab for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy based on efficacy and safety result of P055, a Phase II clinical trial of single agent, pembrolizumab, in patients with recurrent or metastatic head and neck squamous Cell carcinoma (HNSCC) who have failed platinum and cetuximab. Patients received 200 mg of pembrolizumab administered every 3 weeks (Q3W).

On 24-Jun-2016: the supplement (sBLA 125514-s12, Seq 679) was submitted for the approval of pembrolizumab for the first-line treatment of PDL-1 positive NSCLC patients based on efficacy and safety result of P024, a randomized open-label Phase III trial of MK-3475 versus platinum based chemotherapy in first line patients with PD-L1 Strong metastatic NSCLC. Patients received 200 mg of pembrolizumab administered every 3 weeks (Q3W).

On 12-Aug-2016: the supplement (sBLA 125514-s13, Seq 776) was submitted for the approval of pembrolizumab 200 mg Q3W for melanoma based on PK tables and figures for MK-3475 Trial PN037, a phase I/II trial exploring the safety, tolerability and efficacy of MK-3475 in combination with INCB024360 in patients with selected solid tumors, where 200 mg Q3W dose was administered to 143 patients including 25 melanoma patients. Modeling and simulation component was submitted for dose justification.

On 08-Sep-2016: the supplement (sBLA 125514-s14, Seq 775) was submitted for the approval of pembrolizumab 200 mg Q3W for patients with microsatellite instability high (MSI-H) solid tumors based on efficacy and safety data of 149 patients from 5 trials:

Trial	MSI-H Patient and Pembrolizumab Dose Information
KN012 (n=6)	A Phase Ib multi-cohort trial of pembrolizumab in patients with advanced solid tumors. Six patients (*4 gastric, 1 breast and 1 bladder)* were identified as MSI-

	H patients retrospectively out of 297 patients studied. Pembrolizumab dose is 10 mg/kg Q2W
KN016 (n=28 for Cohort A, and n=30 for Cohort C)	Phase 2 trial of MK-3475 in patients with microsatellite unstable (MSI) tumors. Three cohorts of patients were enrolled to receive pembrolizumab: patients with MSI-H colorectal cancer (CRC) with at least 2 prior cancer therapy regimens (Cohort A, n=28); patients with MSI-H negative CRC and at least 2 prior cancer therapy regimens (Cohort B); and patients with MSI-H solid tumor malignancies other than CRC and at least 2 prior cancer therapy regimens (Cohort C, n=30, Endometrial 9, Amp/biliary 7, Pancreatic 4, Small bowel 4, Gastric 3, 1 each of sarcoma, prostate, thyroid). Pembrolizumab dose is 10 mg/kg Q2W.
KN028 (n=5)	Multi-disease cohorts PD-L1+. Total 5 out of 475 were identified as MSI-H patients retrospectively. The MSI-H tumors on this trial were esophageal, cholangio, breast endometrial, CRC. Pembrolizumab dose is 10 mg/kg Q2W.
KN158 (n=19)	MSI-H cohort of multi-cohort rare tumor basket trial. Total 19 of 713 patients were identified as MSI-H. Cohort k consisted of prospectively identified MSI-H 16 patients (4 endometrial cancer, 4 small intestinal cancer, 3 cholangio-carcinoma, 2 gastric cancer, 2 pancreatic cancers, 1 kidney cancer, 1 prostate cancer, 1 retroperitoneal adenocarcinoma, and 1 small cell lung cancer), along with 3 additional MSI-H patients identified retrospectively by PCR from cohorts B and D c/o SCLC, gastric, pancreatic, and SB. Pembrolizumab dose is 200 mg Q3W.
KN164 (n=61)	A Phase II trial of pembrolizumab as monotherapy in patients with previously treated locally advanced unresectable or metastatic (Stage IV) mismatched repair deficient or microsatellite instability-high CRC. The dose of pembrolizumab dose is 200 mg Q3W.
Source: mid-cycle meeting slides by medical officer Leigh Marcus.	

3. RESULTS OF SPONSOR'S ANALYSIS

3.1. PPK ANALYSIS

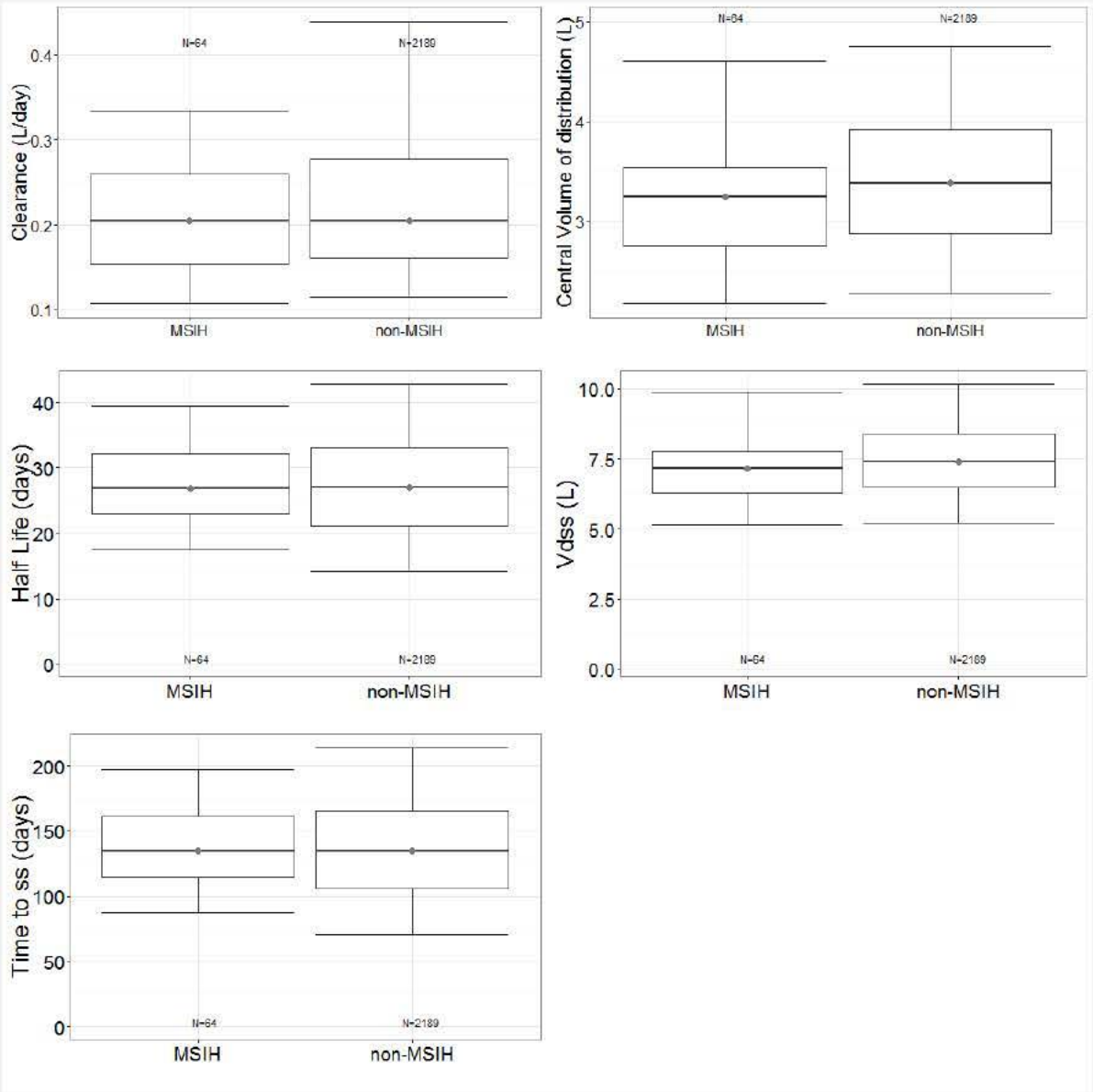
PK data of 6 MSI-H patients of KN012 (with dose of 10 mg/kg Q2W), and 58 MSI-H patients of KN164 (with dose of 200 mg Q3W) were combined with PK data of non-MSI-H patients from Trials KN01, KN02 and KN06 for a population pharmacokinetics (PPK) analysis using a static clearance model. The PPK parameters are comparable between MSI-H and other patients (**Table 1**). Individual post-hoc PK parameters are also comparable (**Table 1**).In addition, the exposures for MSI-H patients receiving 200 mg Q3W pembrolizumab demonstrated no clinically meaningful difference in PK variability compared to weight-based dosing (**Error! Reference source not found.**). The population exposure of 200 mg Q3W was numerically higher than 2 mg/kg Q3W dose, but significantly lower than 10 mg/kg Q2W and Q3W doses.

Table 4: Comparisons of Descriptive Statistics of Individual PK Parameters (CL, Vc) and Derived Parameters (t1/2, Vd_{ss}, T_{ss}) between MSI-H and non- MSI-H Patients

	MSI-H				Non-MSI-H			
	N	**Mean**	**Median**	**Standard deviation**	**N**	**Mean**	**Median**	**Standard deviation**
CL (L/day)	64	0.214	0.205	0.0894	2189	0.235	0.205	0.12
Vc (L)	64	3.23	3.24	0.729	2189	3.43	3.38	0.785
Half life (days)	64	27.4	27	6.48	2189	27.5	27	8.81
Vd_{ss} (L)	64	7.17	7.15	1.44	2189	7.53	7.41	1.53
T_{ss}; Time to steady state (days)	64	137	135	32.4	2189	137	135	44

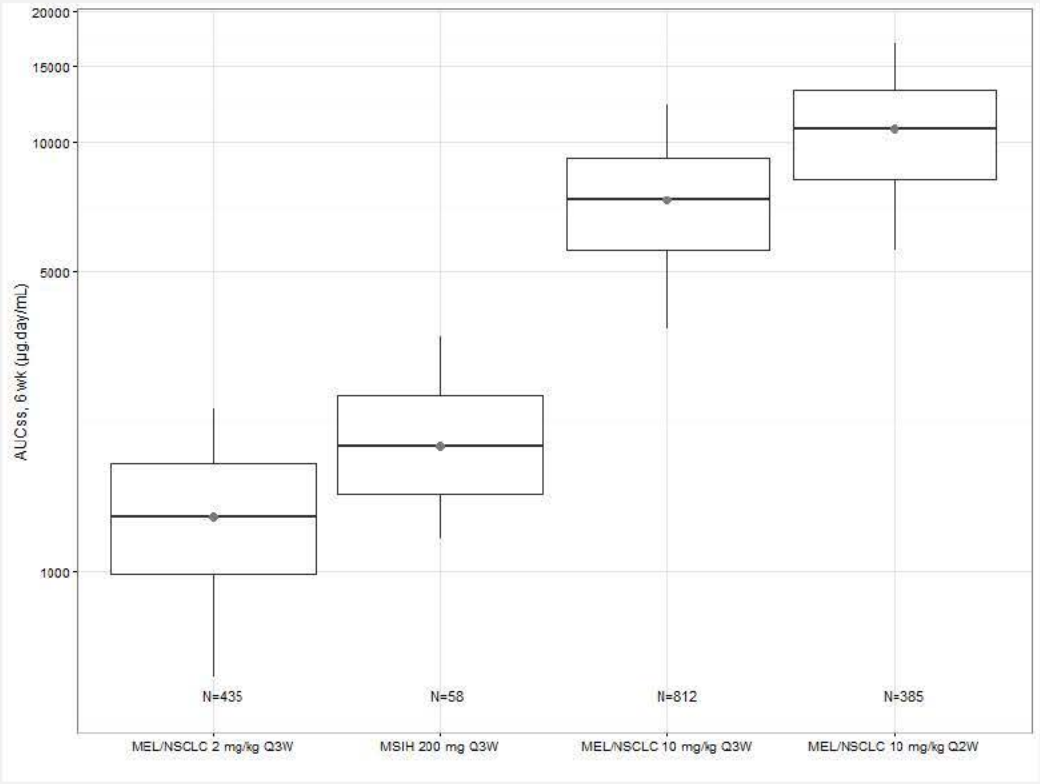
Source: Table 6 of modeling and simulation report file "04gf2t-ppk-extended-to-MSI.pdf".

Figure 8: Individual Post-hoc PK Parameters (CL, V, t1/2, Vd_{ss}, T_{ss}) between MSI-H and non-MSI-H Patients



Source: Figures 2 of modeling and simulation report file "04gf2t-ppk-extended-to-MSI.pdf".

Figure 9: Pembrolizumab (MK-3475) Exposure across Indications at Clinically Tested Dose Regimens (Log Scale)



Source: Figures 3 of modeling and simulation report file "04gf2t-ppk-extended-to-MSI.pdf".

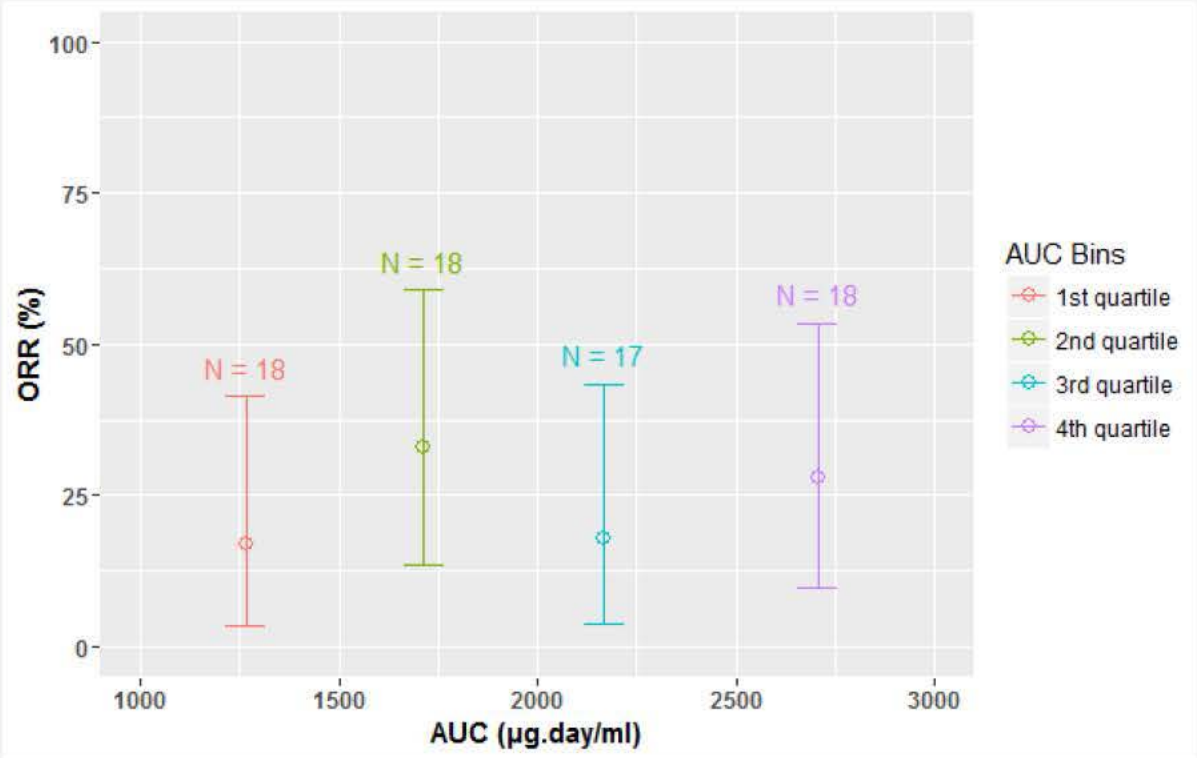
FDA Reviewer's Comments: *Labeling Section 12.3 (clinical pharmacology) for pembrolizumab sBLA 125514 s8 and s12 was based on time-dependent PPK model, while the modeling and prediction for this submission is based static-PK model, so the analysis is outdated. However, this did not change the conclusion that the PK is similar between MSI-H and non-MSI-H patients, as demonstrated in the FDA reviewer's analysis.*

3.2. ANALYSIS OF COUNFOUNDING FACTORS ON RESPONSE

Upon FDA reviewer's request, the applicant submitted an analysis exploring confounding effect on objective response. **Error! Reference source not found.** shows the flat exposure-ORR relationship. The applicant concluded the response with this sentence: "In summary, there is no evidence to indicate an influence of patient characteristics, trial conduct, or drug exposure on the efficacy of pembrolizumab in patients with MSI-H cancer enrolled in the 5 trials." Refer to

report \\cdsesub1\evsprod\bla125514\0306\m1\us\efficacy-information-amendment-21nov2016.pdf for more information.

Figure 10: Pembrolizumab (MK-3475) Exposure across Indications at Clinically Tested Dose Regimens (Log Scale)



Note: Open circles represent the observed ORR (%) for each quartile of AUC, plotted at the median of the quartile; 95% CI: Vertical bars representing the 95% exact confidence intervals corresponding to the observed ORR (%)
Source: Figures 1 of applicant's response to FDA pharmacometrics reviewer's information request Item 2. The report was named "efficacy-information-amendment-21nov2016.pdf.

4. REVIEWER'S ANALYSIS

4.1. OBJECTIVE

The objectives of FDA reviewer's PPK analyses were:

- To apply the time-dependent PPK (TDPK) model used by Supplement 8 to the PPK data of Supplement 14.
- To compare the steady-state exposure between pembrolizumab 10 mg/kg Q2W and 200 mg Q3W in MSI-H patients based on the TDPK model.

4.2. METHODS

4.2.1. Data Set and Code Files

File	Link

PPK data (s14new3.csv)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pembrolizumab_BLA125514s14_HLi\PopPK
PPK output list file (run0074.lst)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pembrolizumab_BLA125514s14_HLi\PopPK
PPK output table (patab0074)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pembrolizumab_BLA125514s14_HLi\PopPK
making nm dataset includingp12p158p164-Version2	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pembrolizumab_BLA125514s14_HLi\PopPK
TDM parameter estimates.R	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pembrolizumab_BLA125514s14_HLi\PopPK

4.2.2. Software

R (v3.2.2) and NONMEM (v7.3) were used for the reviewer's analysis.

4.2.3. Method

The applicant provided static PPK analysis results based on dataset "p12p158p164poppk.csv", as shown in Section 3.1, where PK data of only 64 MSI-H patients were provided. The applicant provided more PK data in "p1p2p6p12msihp164poppk.csv" upon FDA information request, but didn't provide associated PPK analysis. The FDA reviewer combine the two PPK datasets into a new dataset named as "s14new3.csv" and conducted PPK analysis using the TDPK model, with pembrolizumab clearance decreases with time, which can be described by Equations 1-2.

$$CL = TVCL \cdot TDPK \cdot \left(\frac{WT}{75}\right)^{\alpha} CoCov \cdot CaCov \cdot e^{\eta_1} \qquad \text{Equation 1}$$

$$TDPK = 1 + \frac{(I_{\max} + \eta_3) \cdot Time^{\gamma}}{TI_{50}{}^{\gamma} + Time^{\gamma}} \cdot \left(\frac{BSLD}{91}\right)^{\theta} \cdot \left(\frac{\lambda \cdot 40}{ALB + 40}\right) \qquad \text{Equation 2}$$

Where α, γ, θ, and λ are parameters to be estimated, and η_1 and η_3 are inter-individual variability. After PPK parameters are estimated, individual exposure values at steady-state (AUCss) are imputed and the descriptive statistics is graphically presented.

4.3. RESULTS

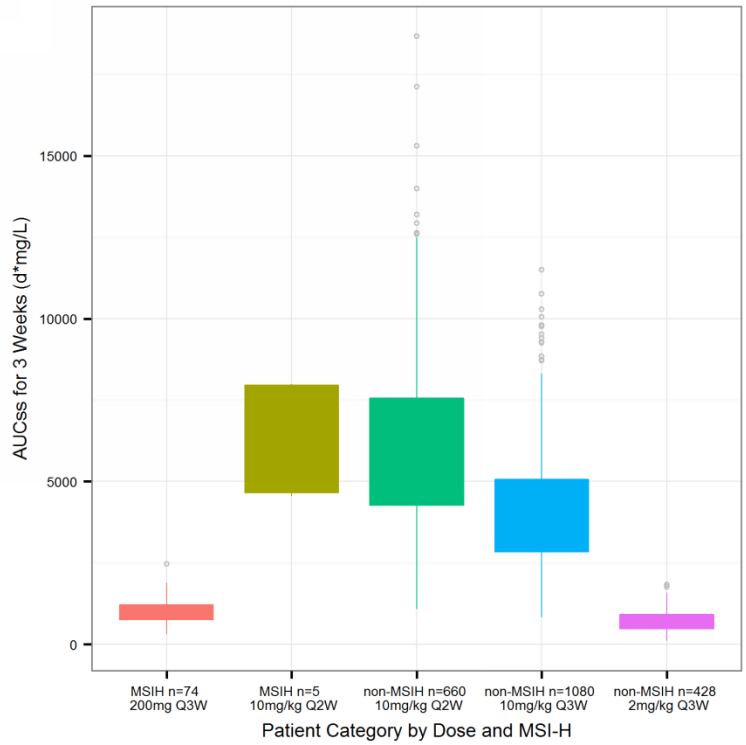
The results of FDA reviewer's exploratory analysis are presented in **Error! Reference source not found.** and **Figure 11**

Table 5: Mean (CV %) Comparison of Descriptive Statistics of Post-hoc Individual PK Parameters and Derived Parameters between MSI-H and non-MSI-H Patients Based on Time-Dependent PPK Analysis

	MSI-H (n=79)	Non-MSI-H (n=2189)
CL (L/d)	0.240 (39%)	0.253 (46%)
CLss (L/d)	0.221 (44%)	0.238 (52%)
Vss (L)	6.72 (19%)	6.96 (20%)

$T_{1/2\ \beta}$ (day)	24.8 (26%)	25.2 (35%)
Source: FDA reviewer's analysis.		

Figure 11: TDPK Generated Pembrolizumab Exposure across Indications at Clinically Tested Dose Regimens



Source: FDA reviewer's analysis.

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

/s/

BRIAN D FURMANSKI
02/16/2017

HONGSHAN LI
02/16/2017

JIANG LIU
02/16/2017

NAM ATIQUR RAHMAN
02/17/2017
I agree with the team's recommendation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: March 3, 2017

To: Sharon Sickafuse
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nick Senior, PharmD, JD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Comments on the proposed product labeling for BLA 125514 KEYTRUDA (pembrolizumab) for injection, for intravenous use; injection, for intravenous use

---

OPDP has reviewed the proposed product labeling (PI) for KEYTRUDA (pembrolizumab) for injection, for intravenous use; injection; for intravenous use (Keytruda) as requested in the consult dated September 21, 2016. The following comments, using the proposed substantially complete, marked-up version of the PI emailed to OPDP by Sharon Sickafuse on February 17, 2017, are provided below.

OPDP conferred with and concurs with the Patient Labeling Team's comments on the draft Med Guide.

If you have any questions, please feel free to contact me (contact information: 240-402-4256; Nicholas.Senior@fda.hhs.gov)

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

30 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

NICHOLAS J SENIOR
03/03/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	March 1, 2017
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name): Dosage Form and Route:	KEYTRUDA (pembrolizumab) for injection, for intravenous use KEYTRUDA (pembrolizumab) injection, for intravenous use
Application Type/Number:	BLA 125514
Supplement Number:	S-014
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On September 8, 2016, Merck Sharp & Dohme Corp. submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved Biologics License Application (BLA) 125514/S-014 for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection. KEYTRUDA was originally approved on September 4, 2014.

In this supplement, the Applicant proposes revision to the approved KEYTRUDA (pembrolizumab) Prescribing Information (PI) to reflect the addition of a proposed new indication for the treatment of (b) (4)

(b) (4)

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Oncology Products 2 (DOP2) on September 22, 2016, for DMPP to review the Applicant's proposed Medication Guide (MG) for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection.

2 MATERIAL REVIEWED

- Draft KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) for intravenous use MG received on September 8, 2016.
- Draft KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) for intravenous use Prescribing Information (PI) received on September 8, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on February 17, 2017.
- Approved KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) for intravenous use labeling dated October 24, 2016.

3 REVIEW METHODS

In our focused review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.

- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SHARON R MILLS
03/01/2017

BARBARA A FULLER
03/01/2017

LASHAWN M GRIFFITHS
03/02/2017

Clinical Inspection Summary

Date	February 10, 2017
From	Lauren Iacono-Connors, Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Sharon Sickafuse, Regulatory Project Manager Leigh Marcus, Clinical Reviewer Division of Oncology Products 2
sBLA #	125514 S-014
Applicant	Merck Sharp & Dohme Corp.
Drug	Keytruda® (pembrolizumab)
NME	No
Therapeutic Classification	Priority
Proposed Indication	(b) (4)
Consultation Request Date	September 20, 2016
Summary Goal Date	February 14, 2017
Action Goal Date	March 8, 2017
PDUFA Date	March 8, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study MK-3475-016 were submitted to the Agency in support of sBLA 125514 S-014. One clinical site, Dr. Dung T. Le (Site 1) was selected for audit.

The primary efficacy endpoint, immune related objective response rate (irORR), was corroborated with the source records generated at the inspected clinical site. The inspection of Dr. Le found no significant deficiencies associated with the conduct of Study MK-3475-016.

II. BACKGROUND

Merck Sharp & Dohme Corp. (Merck) seeks approval of Keytruda® (pembrolizumab) for the treatment of (b) (4). This request is based on the results from primarily Study MK-3475-016. The study planned to enroll 25 subjects into each

study Cohort (A, B and C). The current submission reports on the data from 28 MSI-H CRC patients enrolled in Cohort A only.

Study Period: First subject enrolled: September 11, 2013
Data cut-off date for primary analysis: February 19, 2016

Primary efficacy endpoint: irORR is the proportion of subjects with a best overall response (BOR) of Complete (CR) or Partial Response (PR), using RECIST v1.1 and immune-related response criteria as assessed by a blinded independent review committee (BIRC).

Objectives of Inspection:

a. Verify key secondary efficacy endpoints as determined by the clinical investigator and Overall Survival (OS).
b. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
c. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Dung T. Le (Site 1) 1650 Orleans Street Room 410 Baltimore, MD 21287	Protocol: MK-3475-016 Number of Subjects Enrolled: 20 (Cohort A)	November 28-29, 2016	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Dung T. Le, M.D. (Site 1)

The inspection reviewed the conduct of one clinical study (MK-3475-016). The site screened 29 subjects and 20 were enrolled into Cohort A at the time of the inspection. Six subjects had completed the 2 year treatment period, five withdrew early for disease progression and have died, one died early in the study for reasons not related to the study medication or disease and four are continuing in the study.

The records for 16 Cohort A subjects, specifically those whose data were submitted to sBLA 125514 S-014, were inspected. Each subject met eligibility criteria, and

informed consent was properly obtained prior to participation in the study. Study procedures were performed per the study protocol. Adverse events (AEs) identified in the study files matched the AEs in the data listings submitted to the application. Efficacy assessments as determined by the BIRC were corroborated by study records reviewed at the site. However, it was noted that efficacy endpoints as determined by the clinical investigator were different than that determined by the BIRC for 2 subjects.

The inspection revealed no significant deficiencies. The efficacy endpoint data as determined by the clinical investigator was verifiable. There was no evidence of under-reporting of AEs.

The data from Site 1, associated with Study MK-3475-016 appear reliable.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. sBLA #125514 S-014
DOP2/Division Director/Patricia Keegan
DOP2/Clinical Team Leader/Steven Lemery
DOP2/Project Manager/Sharon Sickafuse
DOP2/Medical Officer/Leigh Marcus
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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

/s/

LAUREN C IACONO-CONNORS
02/10/2017

SUSAN D THOMPSON
02/10/2017

KASSA AYALEW
02/10/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123482

MEETING MINUTES

Merck Sharp and Dohme Corp.
Attention: Nahid Latif
Executive Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000, UG-2C029
North Wales, PA 19454

Dear Ms. Latif:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Pembrolizumab (MK-3475)."

We also refer to the meeting between representatives of your firm and the FDA on July 13, 2016. The purpose of the meeting was to discuss the content and format of a sBLA for the treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) cancers.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sharon Sickafuse, Senior Regulatory Project Manager at (301) 796-1462.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	pre-sBLA
Meeting Date and Time:	July 13, 2016 / 2:00 – 3:00 PM (EST)
Meeting Location:	WO 21 Room 1537
Application Number:	123482
Product Name:	Keytruda **(**pembrolizumab)
Indication:	Treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) cancers
Sponsor/Applicant Name:	Merck Sharp and Dohme Corp. (Merck)
Meeting Chair:	Steven Lemery
Meeting Recorder:	Leah Her

FDA ATTENDEES

Martha Donoghue	Associate Director (Acting), OHOP/DOP2
Steven Lemery	Clinical Team Lead, OHOP/DOP2
Leigh Marcus	Clinical Reviewer, OHOP/DOP2
Lorraine Pelosof	Clinical Reviewer, OHOP/DOP2
Leah Her	Regulatory Health Project Manager, OHOP/DOP2
Jonathan Meyer	Observer (Pharmacy Student), DOP2
Kun He	Statistical Team Lead, OTS/OB/DBV
Weishi (Vivian) Yuan	Statistical Reviewer, OTS/OB/DBV
Hong Zhao	Clinical Pharmacology Team Lead, OTS/OCP/DCPV
Brian Furmanski	Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Donna Roscoe	Branch Chief, CDRH/OIR/DMGP/MGB
Prakash Jha	Medical Officer, CDRH/OIR/DMGP/MGB
Janaki Veeraraghavan	Reviewer, CDRH/OIR/DMGP/MGB

SPONSOR ATTENDEES

Merck Sharp and Dohme Corp. (Merck)

Julie Lepin	Vice President, Regulatory Affairs
Nahid Latif	Executive Director, Regulatory Affairs
Roger Dansey	Senior Vice President, Clinical Research
Peter Kang	Executive Director, Clinical Research

Andrew Joe	Executive Director, Clinical Research
Scott Pruitt	Director, Clinical Research
Baohoang Lam	Director, Clinical Research
Christine Gause	Executive Director, Biostatistics
Honghong Zhou	Director, Biostatistics
Tomoko Freshwater	Associate Principal Scientist, Quantitative Sciences
Lina AlJuburi	Director, Regulatory Policy
Mary Savage	Director, Companion Diagnostics
Lokesh Jain	Principal Scientist, Quantitative Pharmacology and Pharmacometrics

Johns Hopkins Sidney Kimmel Comprehensive Cancer Center

Luiz Diaz	Associate Professor of Oncology

BACKGROUND

Regulatory History

On May 18, 2016, Merck submitted a pre-sBLA meeting request (SDN 285) to discuss the format and content of a proposed sBLA for the treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) cancers. The meeting package was submitted on June 13, 2016, as SDN 292.

Keytruda is approved in the U.S. for the treatment of patients with unresectable or metastatic melanoma. FDA also granted accelerated approval to Keytruda for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1, as determined by an FDA-approved companion diagnostic test, and who have disease progression on or after platinum-containing chemotherapy.

Merck is developing pembrolizumab for the treatment of patients with MSI-H tumors under two INDs: 127548 for non-colorectal cancers (CRC) and 123482 for CRC. Additionally, a Type B meeting to discuss Study KN158 was initially held under IND 110080; however, based on FDA request, the study was submitted under a separate IND (127548).

On May 12, 2015, a meeting was held between FDA and Merck under IND 123482 to discuss the design of Study KN164, entitled "A Phase IIB Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Unresectable Locally Advanced or Metastatic Microsatellite Instability-High Colorectal Adenocarcinoma," in order to support accelerated approval. During this meeting, FDA stated that whether Study KN164 will support accelerated approval would depend upon the magnitude of response observed, the duration of response, and the risk-benefit profile of pembrolizumab in patients with previously treated MSI-H CRC. In the meeting package, Merck summarized the results of Study KN016, entitled "Phase 2 study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors." Study KN016 was conducted under a separate IND, primarily at Johns Hopkins. During the meeting, based on the magnitude of the effect observed in Study KN016 in patients with MSI-H CRC, FDA recommended that Merck submit a request for Breakthrough Therapy Designation as an IND amendment.

On July 10, 2015, a meeting was held between FDA and Merck under IND 110080 to discuss the design of Study KN158, a study that was initially intended to enroll patients across ten different primary tumors based on PD-1 tumor expression, microsatellite instability, or a specific gene expression profile signature (using Nanostring-based RNA analysis). The meeting package indicated that Merck would use the Promega MSI Analysis System to identify patients as MSI-H in Study KN158.

On September 29, 2015, under new IND 127548, Merck requested FDA's agreement with a proposal to (b) (4). On October 27, 2015, FDA responded by email that the Agency did not agree with the proposal based on (b) (4). FDA stated that an alternative to central testing would be required to ensure the same reagents, protocol, and result reporting are used at all testing sites. On February 16, 2016, Merck submitted an amendment to IND 127548 containing a proposal stating that MSI-H testing could be performed using IHC or one of two specific PCR assays. Merck stated that the case report forms would collect information about methodology used to identify MSI-H status, including reagents, assay protocols, and results.

Keytruda received Breakthrough Therapy Designation on October 29, 2015 for the treatment of MSI-H metastatic colorectal carcinoma (CRC). Merck submitted a request for Breakthrough Therapy Designation for the treatment of patients with MSI-H metastatic non-CRC on June 21, 2016.

Proposed Content of the sBLA

To support the sBLA for pembrolizumab in the treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) cancers, Merck proposes to submit data on objective response rate and duration of response from at least 146 patients with MSI-H metastatic cancer. These include patients from the following studies:

Study	Title	Number of patients with MSI-H
KN016	Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors (Hopkins Study)	CRC: 28 Non-CRC: 30
KN164	Phase 2B Study of Pembrolizumab (MK-3475) in Subjects with Unresectable Locally Advanced or Metastatic Microsatellite Instability-High Colorectal Adenocarcinoma	61
KN012	A Phase 1B Multi-Cohort Study of MK-3475 in Subjects with Advanced Solid Tumors	6
KN028	A Phase 1B Study of Pembrolizumab (MK-3475) in Subjects with Select Advanced Solid Tumors	5
KN158	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors	At least 16
KN059	A Phase 2 Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin plus 5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma	TBD (MSI results pending)
Total		**At least 146**

In the meeting package, Merck provided summary data from Studies KN016, KN012, and KN028. MSI-H status from patients in Studies KN012 (n=165) and KN028 (n=450) were retrospectively identified based on PCR-based MSI testing (of patients with available samples) using the Promega MSI Analysis System v1.2. The following table summarizes the available efficacy data from the three studies as described in the meeting package:

	KN016*		KN012	KN028	Total
(n)	**CRC (28)**	**Non-CRC (30)**	**Non-CRC (6)**	**CRC (1) / non-CRC (4)**	**MSI-H (69)**
CR %	11	30	0	0	17%
PR %	46	23	50	80	39
ORR %	**57**	**53**	**50**	**80**	**56**
Median DOR	NR	NR	NA	NA	NR
Median follow-up (mo) (range)	11 (5, 27)	11 (5, 24)	18 (1.8, 31)	20 (5, 22)	

*Investigator-assessed

On July 6, 2016, Merck provided an update of the clinical data regarding the development program for MSI-H tumors. The following table summarizes the updated data. Median follow-up time of patients in Study KN164 is 5.4 months (range 0.2 to 8.7). The data for Study KN164 includes both confirmed and unconfirmed responses (due to shorter follow-up compared to Study KN016). To date, the *confirmed* overall response rate (ORR) per independent review committee (IRC) according to RECIST v1.1 is 14.8%. An estimated 56% of patients experienced some degree of maximum target lesion shrinkage per IRC.

	KN016		KN012	KN028	KN164[#]	KN158[@]	Total
(n)	**CRC (28)[*]**	**Non-CRC (30)**	**Non-CRC (6)**	**CRC (1)/ non-CRC (4)**	**CRC (61)**	**Non-CRC (16)**	**146**
CR %	14	30	0	0	0	1	10
PR %	36	23	50	80	21	25	28
ORR %	**50**	**53**	**50**	**80**	**21**	**31**	**38**
Median DOR	NR	NR	NA	NA	NR	NA	
Median follow up (mo)(range)	11 (5, 27)	11 (5, 24)	18 (2, 31)	20 (5, 22)	5.4 (0.2, 8.7)	(2.2, 4.3)	

[*] confirmed and IRC-assessed per RECIST (median time to response was 2.7 months); non-CRC group is based on investigator assessment
[#] includes confirmed and unconfirmed responses (due to shorter follow-up compared to KN016)
[@] preliminary assessment based on unconfirmed-investigator determination

FDA sent Preliminary Comments to Merck on July 11, 2016. Merck's responses were received on July 12, 2016. On July 13, 2016, Merck submitted slides for review during the meeting.

DISCUSSION

1. *Does the Agency concur that a submission comprised of data from 146+ patients with MSI-H cancers from 6 studies across multiple different tumor types could support approval of pembrolizumab for the treatment of patients with metastatic MSI-H cancers, agnostic of tissue type?*

   FDA Response: FDA agrees that, pending review of the data, the application could potentially support approval of pembrolizumab for the treatment of patients with metastatic MSI-H cancers, agnostic of tissue type.

   Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's response and stated that no further discussion is required during the meeting.

2. *The Sponsor intends to submit the sBLA to support approval of pembrolizumab for the treatment of patients with metastatic MSI-H cancers. Does the Agency concur with this position?*

   FDA Response: FDA agrees that Merck can submit the sBLA with the proposed indication; however, because the proposed effect is based on a surrogate endpoint or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality and because limited data will be submitted in the sBLA for certain tumor types (e.g., prostate cancer), if approved, FDA may approve pembrolizumab for the treatment of MSI-H cancer under the accelerated approval regulations. Furthermore, if approved, the indication, including qualifications regarding prior therapy and whether any tumor histology is excluded from the indication, will be determined during the review of the sBLA.

   FDA acknowledges that there may be challenges in conducting randomized trials in certain groups of patients with MSI-H tumors. During the review of the sBLA, FDA will consider what data would be necessary to support regular approval (e.g., data from Study KN177 or confirmatory data on ORR and duration of response (DOR) in a larger clinical experience).

   Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's response and requested discussion during the meeting.

   Discussion During the Meeting of 7/13/16: Merck proposed to submit additional data from Studies KN164 (~121 patients with MSI-H CRC across two cohorts) and KN158 (~120 patients with non-MSI-H CRC) to support regular approval. Merck stated that both studies would be fully enrolled with a minimum follow up of at least 9 months by the 4th quarter of 2017. FDA stated that Merck's approach was reasonable; however, FDA will need to further consider during the review of the sBLA what data will be necessary to confirm the clinical benefit of pembrolizumab in patients with MSI-H advanced cancers. FDA stated that it is possible that single-arm data could confirm the clinical benefit of pembrolizumab, depending on the results; however, FDA also stated

that data from Study KN177 (the randomized mCRC trial) could also be used for confirmation of clinical benefit.

FDA also stated that the Agency would be amenable to Merck providing additional data from a registry study in patients with MSI-H tumors; in this case, images from responding patients would need to be collected in order to facilitate independent confirmation of response.

3. *Does the Agency agree that the approach for presenting safety analyses from KN016 (Cohort A) and KN164 only, comparing to the combined reference safety information from KN001, KN002, KN006, and KN010, will enable evaluation of the proposed sBLA?*

FDA Response: Yes.

Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's response and stated that no further discussion is required during the meeting.

4. *Does the Agency agree that the contents of the proposed submission dataset package will support the sBLA submission?*

FDA Response: FDA does not object to Merck's proposal; however FDA requests that a single dataset containing all demographic and tumor response data from all patients be submitted in the sBLA.

Additionally, provide clinical pharmacology datasets and population PK and exposure response analyses including results of Study KN059 in support of the 200 mg Q3W regimen in patients with MSI-H cancer. Please refer to the following guidance for general expectations on submitting pharmacometrics data and models: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Finally, if Merck does not plan to include data from Study KN059 in the population PK and exposure response analyses, the sBLA should provide justification for this approach.

Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's response and requested discussion during the meeting.

Discussion During the Meeting of 7/13/16: Regarding Merck's single dataset containing integrated demographics and tumor response data, FDA stated that the Agency would prefer to have the demographics and response data from Cohort C of Study KN016 integrated within the dataset. FDA stated that Merck should submit the ADaM-like datasets (ADSL and ADORR) into the legacy folder. FDA will provide the location of the non-CDISC dataset for submission in a subsequent communication. Merck acknowledged FDA's response.

Merck proposed to submit an integrated population PK data dataset and PK analysis from Studies KN164 and KN012. FDA acknowledged this proposal and stated that FDA will request additional information during the review of the sBLA, if needed.

Merck also proposed not to submit exposure-response analyses for MSI-H patients. FDA stated that specific MSI-H exposure-response analyses will not be required to file the sBLA.

Post Meeting Addendum: Both tabulation and analysis data have a legacy folder. Please place the non-CDISC tabulation datasets in the legacy folder under the tabulation folder, and the non-CDISC analysis datasets in the legacy folder under the analysis folder.

OSI

5. *Merck plans to provide site level datasets in the sBLA to aid the Office of Scientific Investigation (OSI) in identifying clinical trial sites for inspections. Financial disclosure information will not be included in the summary level dataset since this information is sensitive and has extremely limited distribution within Merck. This information is provided by a separate group within Merck and will be available within Module 1.3.4 of the sBLA. Does the Agency agree that providing site level datasets with no financial disclosure information will satisfy OSI requirements?*

FDA Response: Yes.

Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's response and stated that no further discussion is required during the meeting.

ADDITIONAL FDA COMMENTS:

6. Please refer to FDA Guidance for Industry (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf) regarding the integrated summary of safety (ISS) and integrated summary of effectiveness (ISE). For this application, FDA agrees that it is acceptable for the ISE and ISS to be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and any appendices of tables, figures, and datasets, as appropriate, located in section 5.3.5.3. Ensure that there is a clear explanation, both in Module 2 and in Module 5 of where parts of the application are located.

   Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's comment and stated that no further discussion is required during the meeting.

7. In the sBLA, please describe the tests that will be used to identify the subset of patients with MSI-H tumors across the range of tumor types. Provide evidence that specific commercial and laboratory developed tests can accurately identify MSI-H tumors

regardless of primary site of origin for the purposes of patient selection and where risk/benefit assessment is favorable.

Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's comment and stated that no further discussion is required during the meeting.

8. Please provide a plan to provide an update of the ORR and DOR data from Studies KN164, 158, and 059 during the review of the sBLA.

Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's comment and requested discussion during the meeting.

Discussion During the Meeting of 7/13/16: Merck proposed not to include Study KN059 data in the upcoming MSI-H cancer sBLA. Merck stated that this was because MSI testing was not originally planned in Study KN059; therefore, tissue was not specifically allocated for testing and only a minority of patients appear to have specimens available. Merck stated that they plan to retrospectively test patients that have available tumor specimens and that these data will be planned for submission in a sBLA for a gastric cancer indication targeted for 2017.

FDA acknowledged Merck's plans and stated that data from Study KN059 would not be required in order to file a sBLA in the intended indication.

Merck proposed to submit a Day 60 efficacy update containing ORR and DOR data from Studies KN164 and KN158. FDA acknowledged and agreed with this approach.

9. In the sBLA, provide a discussion regarding the potential reason(s) for the discrepancies in the data between Studies KN016 and KN164 and whether it is scientifically appropriate to pool the data to provide an estimation of the ORR. The discussion should include whether there were any differences in MSI testing (e.g., was testing in Study KN016 more specific), differences in enrolled populations, and any other factors deemed relevant.

Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's comment and stated that no further discussion is required during the meeting.

Discussion During the Meeting of 7/13/16: FDA expressed concern that the 200 mg every three week dose may be insufficient for the treatment of patients with MSI-H tumors. FDA noted that the differences in response rates between studies could potentially be related to differences in the dose between studies, which resulted in almost a log difference in exposure (per AUC). Merck believed that the 200 mg dose (every three weeks) was sufficient based on PK analyses and analyses of receptor saturation from lung and melanoma studies (non-MSI-H studies) and that the differences in response rates were likely due to other factors. FDA stated that the Agency would consider Merck's position and the data submitted to the sBLA when determining whether

further actions are necessary to optimize the dose of pembrolizumab for the treatment of patients with MSI-H cancers.

10. In the sBLA, provide a narrative summary of all patients who developed progression/recurrence limited to the central nervous system. The summary should include whether the patient had CNS imaging at baseline, what treatment the patient received for the CNS metastasis, whether the patient continue to receive pembrolizumab (and for how long), and any other information deemed relevant.

    Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's comment and stated that no further discussion is required during the meeting.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) no later than 210 calendar days before submission of the sBLA. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

We acknowledge your November 30, 2015, Agreed iPSP for the treatment of colorectal cancer. Unless you have Orphan Drug Designation at the time of sBLA submission for the other indications, you will need to submit iPSPs for these indications; however, at this time, FDA is determining the type and scope of the iPSP that will need to be submitted [i.e., whether Merck should conduct study(ies) in pediatric patients with MSI-H tumors (agnostically) versus whether the scope would involve requests for studies (or waivers) of individual tumor types].

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

Merck's Emailed Response of 7/12/16: Merck acknowledged FDA's comment and stated that no further discussion is required during the meeting. Merck will await further guidance as to the type and scope of iPSP that will need to be submitted, for the sBLA submission for MSI-H cancers.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is

the actual physical site(s) where documents are maintained and would be available for inspection

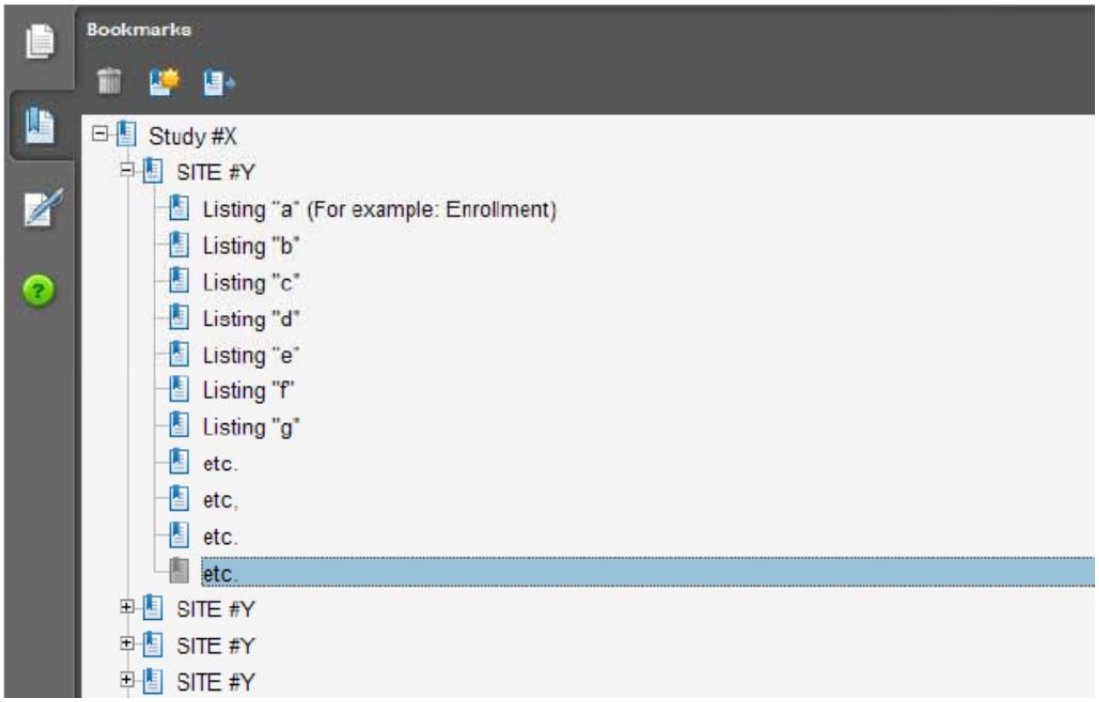
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

Action Item/Description	Owner	Due Date
Location of the non-CDISC dataset for submission in the sBLA.	FDA	Refer to the *Post Meeting Addendum* under Question 4.
Proposal for MSI testing methodology	Merck	Prior to sBLA
Determination of the type and scope of an initial Pediatric Study Plan (iPSP) needed to support this sBLA indication	FDA	Prior to sBLA

ATTACHMENTS AND HANDOUTS

- Final MSI-H slides for FDA 13 JUL 2016.pptx

MK-3475 Pembrolizumab
Pre sBLA – MSI-H Cancer Meeting

July 13 2016

Focus of Meeting Discussion

- Merck appreciates the thorough review and considered feedback to our briefing document and the questions we posed.
- Responses to Questions 1, 3 and 5, are acknowledged with no further discussion required.
- Additional FDA comments 6, 9 and 10, are acknowledged with no further discussion required.
- Merck would like to discuss the following topics
  - Question 2, discussion regarding data to support regular approval
  - Question 4, clarification regarding request that a single dataset containing all demographic and tumor response data from all patients be submitted in the sBLA
  - Comment 8, discussion regarding request to provide a plan to provide an update of the ORR and DOR data from studies during the review of the sBLA
  - Question 4, discussion regarding request to provide clinical pharmacology datasets and population PK and exposure response analyses
- Regarding PREA requirements, Merck acknowledges the Agency's response, and will await further guidance as to the type and scope of iPSP that will need to be submitted for the sBLA submission for MSI-H cancers.
- Regarding comment 7, Merck intends to return to FDA with a proposal regarding methodology of MSI testing

Agenda

Topic	Time
Introductions	
Question 2 Discussion regarding data to support regular approval	5 min
Question 4 Clarification regarding request that a single dataset containing all demographic and tumor response data from all patients be submitted in the sBLA Discussion regarding request to provide clinical pharmacology datasets and population PK and exposure response analyses	15 min 15 min
Question 8 Discussion regarding request to provide a plan to provide an update of the ORR and DOR data from studies during the review of the sBLA	15 min

Question 2

During review of the sBLA, FDA will consider what data would be necessary to support regular approval (e.g. data from KN177 or confirmatory data on ORR and DOR in a larger clinical experience).

- Merck proposes that the following studies, fully enrolled with sufficient follow up (9m min by Q4 2017), will provide confirmatory data required to support regular approval:
  - KN164 Cohort B (~60 MSI-H CRC patients)
  - KN164 Cohort A (61 MSI-H CRC patients)
  - KN158 (~120 MSI-H non CRC patients)

Update KN059 Status

- Upon further evaluation of MSI testing, Merck proposes to not include KN059 data in the MSI-H cancer sBLA
- As MSI testing was not originally planned, tissue was not specifically allocated for testing and only a minority of patients appear to have specimens available
- KN059 is a key study within the gastric cancer development program, and will be included in an upcoming sBLA submission

Question 4

FDA does not object to Merck's proposal for the contents of the proposed submission dataset package; however FDA requests that a single dataset containing all demographic and tumor response data from all patients be submitted in the sBLA.

- Merck proposes to submit the following tables, listings, and figures pooled across MSI-H subjects that represent a single summary in the sBLA
  - Demographics (KN16-A, KN164, KN012, KN028, KN158)
  - ORR and DOR
    - Centrally reviewed (IRC): KN16-A, KN164, KN16-C, KN012, KN028
    - Site reviewed: KN16-A, KN164, KN012, KN028, KN158 (confirmed and unconfirmed)
  - Swimlane plots of responders

Question 4 – Initial sBLA

- Merck would like clarification as to whether SAS datasets are required containing all demographic and tumor response data
- Merck can provide the following ADaM-like analysis datasets across multiple studies for demographics and efficacy

Dataset	IRC or Site	KN16-A (N=28)	KN164 (N=61)	KN16-C (N=30)	KN012 (N=6)	KN028 (N=5)	KN158 (N=19)
Demographics (ADSL)	--	X	X	*	X	X	X
Response (ADORR)							
RECIST 1.1 ORR	IRC	X	X	X	X	X	
DOR RECIST 1.1	IRC	X	X	X	X	X	
RECIST 1.1 ORR	Site	X	X	*	X	X	X
DOR RECIST 1.1	Site	X	X	*	X	X	X
Confirmed and Unconfirmed ORR	IRC	X	X	X	X	X	
Confirmed and Unconfirmed ORR	Site	X	X	*	X	X	X

* Directly from JHU

Comment 8

Please provide a plan to provide an update of the ORR and DOR data from studies KN164, 158 and 059 during review of this sBLA.

- Merck proposes to provide an efficacy (ORR and DOR) update at day 60 following submission, which will comprise of the following additional information

- KN164, N=61
  - 27 wk FU
  - Efficacy (Central Review)
  - Update report

- KN158, N=16 Group K + 3 Group D (endometrial)
  - 18 wk FU
  - Efficacy (Central Review)
  - Update report

Question 4 – Data Provided for Efficacy Update

- Merck can provide the following single ADaM-like analysis datasets across multiple studies for demographics and efficacy update at Day 60

Dataset	IRC or Site	KN16-A (N=28)*	KN164 (N=61)	KN16-C (N=30)*	KN012 (N=6)	KN028 (N=5)	KN158 (N=19)
Demographics (ADSL)	--	X	X	X	X	X	X
Response (ADORR)							
RECIST 1.1 ORR	IRC	X	X	X	X	X	X
DOR RECIST 1.1	IRC	X	X	X	X	X	X
RECIST 1.1 ORR	Site	X	X	X	X	X	X
DOR RECIST 1.1	Site	X	X	X	X	X	X
Confirmed and Unconfirmed ORR	IRC	X	X	X	X	X	X
Confirmed and Unconfirmed ORR	Site	X	X	X	X	X	X

* Data cutoff will be the same as for sBLA, data for Cohort C will be converted from JHU format into ADaM-like format

Question 4:

- *Additionally, provide clinical pharmacology datasets and population PK and exposure response analyses including results of study KN059 in support of the 200 mg Q3W regimen in patients with MSI-H cancer.*

Merck Response for Population PK:

- The PK data available at the time of sBLA submission will be provided as an integrated population PK dataset along with the population PK analysis report.
  - KN164 (N=61) at 200 mg Q3W
  - KN012 (N=6) at 10 mg/kg Q2W
  - No PK data were collected from KN016 and KN028 evaluating 10 mg/kg Q2W
  - Propose to not include data from KN158 (N=19) at 200 mg, since we have a sufficient number of PK observations from KN164 at 200 mg Q3W to evaluate PK
    - If needed, can be provided at day 60 efficacy update

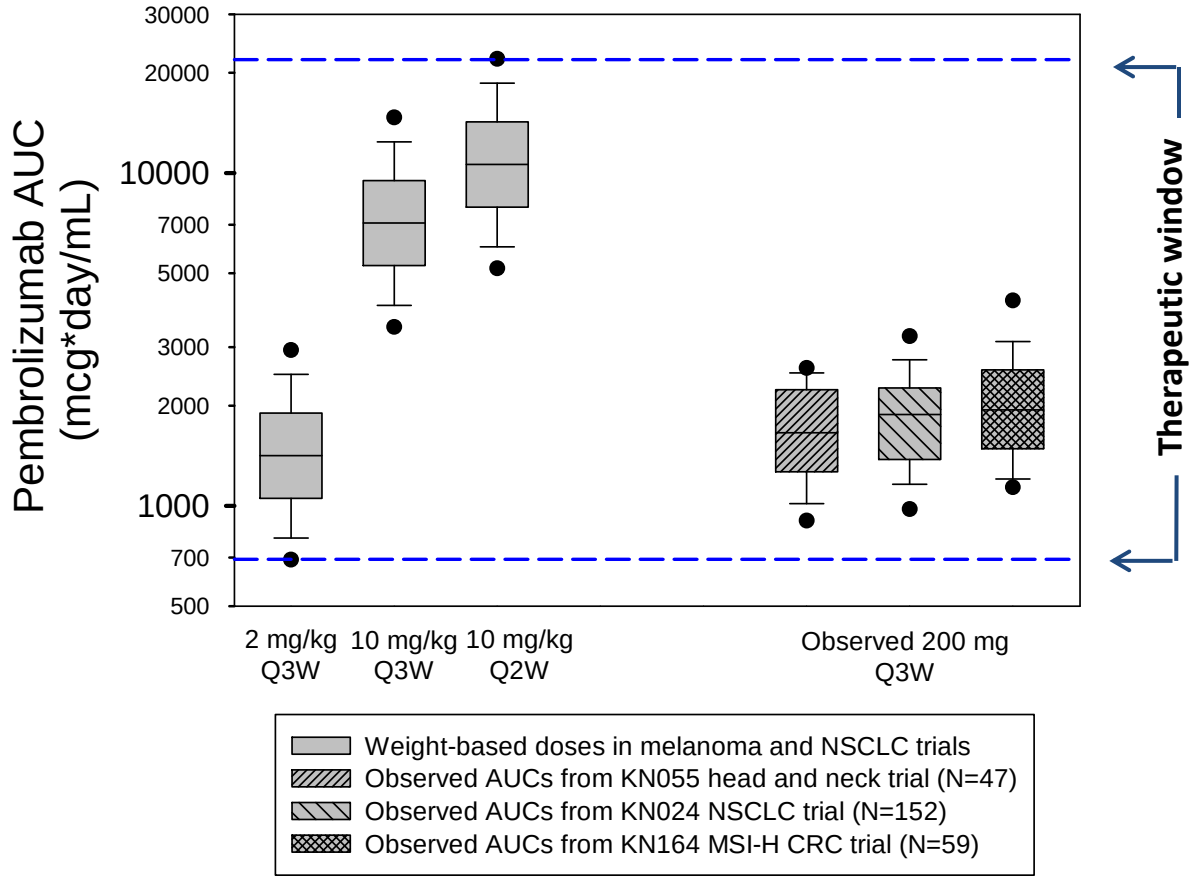
Question 4 (cont'd):

Merck Response (cont'd) for Exposure-Response:

- Merck does not plan to conduct exposure-response analysis for MSI-H patients
  - Anti-tumor effect of pembrolizumab is driven through immune system activation and not direct binding to cancer cells; therefore, the shape of the exposure-response relationship among indications is expected to be similar
  - Available PK data show that PK in patients with MSI-H is consistent with PK in other indications
  - No indication of differences in target engagement between MSI-H and MEL/NSCLC based on similarity of clearance values
  - If conducted, exposure-response analysis will be confounded and results will be difficult to interpret
    - Available PK data are from a small number of subjects
    - Majority of PK data are at 200 mg Q3W dose

Pharmacokinetics of Pembrolizumab in Various Indications is Similar Including MSI-H Population

- Exposures for 200 mg Q3W are contained within the range of exposures shown to have similar efficacy and safety and are associated with maximal efficacy for MEL and NSCLC
- Observed concentrations in CRC patients at 200 mg Q3W in MSI-H are similar to other indications



Horizontal dashed lines represent the range of exposures (5th percentile of 2 mg/kg Q3W and 95th percentile of 10 mg/kg Q2W) from dose regimens demonstrated to have comparable efficacy and tolerability in melanoma and NSCLC trials.

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

/s/

LEAH S HER
07/22/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123482

MEETING MINUTES

Merck Sharp and Dohme Corporation
Attention: Chandrika Kumar, Ph.D.
Director, Global Regulatory Affairs
126 East Lincoln Ave.
RY 34-B212
Rahway, NJ 07065

Dear Dr. Kumar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Pembrolizumab (MK3475)."

We also refer to the meeting between representatives of your firm and the FDA on May 12, 2015. The purpose of the meeting was to discuss a proposed Phase 2 study, Protocol KEYNOTE (KN)-164 entitled "A Phase IIB Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Unresectable Locally Advanced or Metastatic Microsatellite Instability-High Colorectal Adenocarcinoma."

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-5890.

Sincerely,

{See appended electronic signature page}

Tina M. Ennis, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Single-Arm Clinical Trial to Support Accelerated Approval

Meeting Date and Time: Tuesday, May 12, 2015, 1:00 PM - 2:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 21, Conference Room: 1537
Silver Spring, Maryland 20903

Application Number: 123482
Product Name: Pembrolizumab
Indication: (b) (4)

Sponsor/Applicant Name: Merck Sharp & Dohme Corp. (Merck)

Meeting Chair: Joseph Gootenberg, M.D.
Meeting Recorder: Tina Ennis, M.S.

FDA ATTENDEES
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Oncology Products 2

Joseph Gootenberg, M.D.	Division Deputy Director
Steven Lemery, M.D., M.H.S.	Medical Officer Team Lead
Leigh Marcus, M.D.	Medical Officer
Jeanne Fourie Zirkelbach, Pharm.D.	Clinical Pharmacology Team Lead
Elimika Pfuma, Ph.D.	Clinical Pharmacology Reviewer
Kun He, Ph.D.	Biometrics Team Lead
Weishi (Vivian) Yuan, Ph.D.	Biometrics Reviewer
Sharon Sickafuse, M.S.	Senior Regulatory Health Project Manager
Tina Ennis, M.S.	Regulatory Health Project Manager

Center for Devices and Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Division of Molecular Genetics and Pathology

Elizabeth Mansfield	Director
Robert Becker	Medical Officer Team Lead

Merck Sharp and Dohme Corp.

Joseph Arena Ph.D	Vice President, Regulatory Affairs
Chandrika Kumar Ph.D.	Director, Regulatory Affairs
Koshiji Minori M.D., Ph.D.	Executive Director, Clinical Research Oncology
Roger Dansey M.D.	Senior Vice President, Oncology
Linda Sun Ph.D.	Senior Principal Scientist, Biostatistics
Anna Georgieva Kondic, Ph.D., MBA	Oncology TA Lead, Quantitative Pharmacology and Pharmacometrics
Tomoko Freshwater Ph.D.	Associate Principal Scientist Quantitative Sciences, PPDM
Mary Savage Ph.D.	Senior Principal Scientist Molecular Biomarkers and Diagnostics
Siddhartha Mathur, MBS	Principal Scientist, Regulatory Affairs

INTRODUCTION

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 12, 2015, between Merck and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

FDA sent Preliminary Comments to Merck on May 6, 2015. Merck submitted a response via email on May 8, 2015.

BACKGROUND

Regulatory:

On March 18, 2015, Merck submitted a meeting request (SDN 95) to discuss Protocol KEYNOTE (KN)-164 entitled “A Phase IIB Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Unresectable Locally Advanced or Metastatic Microsatellite Instability-High Colorectal Adenocarcinoma” to support accelerated approval. The meeting background package was received on April 13, 2015, as SDN 127.

Pembrolizumab received marketing approval in the U.S. on September 4, 2014, for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Pembrolizumab is also under development as a treatment for patients with NSCLC, gastric cancer, head and neck cancer, and other malignancies.

Clinical:

In the meeting package, Merck summarized the results of study KN016 entitled a "Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors" that accrued 41 patients with microsatellite instability-high (MSI-H) colorectal cancer (CRC) (n=11), microsatellite instability-stable (MSI-S) CRC (n=21), and MSI-H non-CRC (n=9). All but 1 patient received > 2 chemotherapy regimens (median = 4). Patients in KN016 received 10 mg/kg pembrolizumab every two weeks and response was assessed using both RECIST v1.1 and immune-related response criteria (irRC). Six patients (1 with MSI-H CRC, 3 with MSI-S CRC, and 2 with MSI-H non-CRC) were not included in the response assessment because they discontinued prior to evaluation. The meeting package stated that 4 of 10 (40%) patients with MSI-H CRC and 5 of 7 patients with MSI-H non-CRC (71%) had a response. No responses were observed among 18 evaluable patients with MSI-S CRC. The meeting package stated that the median duration of response has not yet been reached; however, the duration of follow-up for response was not reported.

KEYNOTE-164
KEYNOTE-164 is a single arm, open-label, multi-site trial of pembrolizumab to be conducted in patients with previously-treated locally advanced unresectable or metastatic (Stage IV) MSI-H CRC. Approximately 60 patients with MSI-H CRC will receive single agent pembrolizumab, 200 mg as an intravenous infusion every 3 weeks.

To be eligible for KEYNOTE-164, patients are required to have measurable disease per RECIST 1.1 and to have been previously treated with at least two lines of approved standard therapies, including a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab (if KRAS wild type). Patients also will be required to provide an archival or newly obtained tumor sample and a blood sample for central laboratory evaluation and confirmation of MSI-high status.

The primary objective of this trial is to determine the overall response rate (ORR) per RECIST of pembrolizumab administered as monotherapy. Beginning with screening, all imaging assessments will be submitted for central imaging vendor review and will be evaluated using RECIST 1.1 for determination of eligibility and assessment of response. Imaging assessments will be performed every 9 weeks.

Patients will continue to receive pembrolizumab until progressive disease, unacceptable adverse events, intercurrent illness that prevents further administration of pembrolizumab, investigator's decision to withdraw the patient, withdrawal of consent, pregnancy, noncompliance with trial

treatment or procedure requirements, administrative reasons, or the patient has received 35 doses of pembrolizumab.

The proposed sample size of 60 patients will provide for 92% power with a one sided type I error rate of 2.5% to reject the null hypothesis of an ORR of 10% assuming the true ORR is 27%.

Determination of MSI-H Status:
MSI-H status will be confirmed by Merck and determined by comparing CRC tumor DNA allelic profiles of microsatellite markers with normal DNA using a PCR-based assay followed by capillary electrophoresis. The meeting package stated that patients will be assessed using the MSI Analysis System using fluorescently labeled primers for co-amplification of seven markers, including five nearly monomorphic mononucleotide repeat markers and two highly polymorphic pentanucleotide repeat markers. At least two MSI loci are required to be evaluable and greater than 2 loci will need to be abnormal to consider a patient as having MSI-H CRC.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical

Background for Question 1:

To be eligible for pembrolizumab as monotherapy, previously treated subjects must meet the key inclusion criteria listed below:

- Have a histologically proven locally advanced unresectable or metastatic CRC (Stage IV).
- Confirmed MSI-H CRC by the sponsor.
  Had been previously treated with at least two lines of approved standard therapies, which must include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS wild type), if approved in the respective country. Subjects who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent before progression of disease will also be eligible.
- Must have an ECOG performance status of 0 or 1.
- Have at least one measureable lesion by RECIST v1.1 for response assessment.

1. Does the Agency agree that the key patient eligibility criteria for the previously treated MSI- H CRC patient population proposed below define a population with significant unmet medical need and that the results of the proposed single-arm study could be considered as a basis for accelerated approval in this population?

FDA Response:
The meeting package contained insufficient information for FDA to answer the question on unmet medical need because Merck did not address all available therapies in the position statement regarding Question #1. Nevertheless, because the response rate of regorafenib is approximately 1%, Merck can make a reasonable argument in support of

accelerated approval that pembrolizumab is better than available therapy based on the results of a single arm study if a response rate of a sufficient magnitude (and with a sufficient duration) is observed in the proposed patient population.

Merck Response Received Via Email on May 8, 2015:
Merck accepts the Agency's input on the proposed single arm study to support accelerated approval and no further discussion is needed at the F2F meeting.

2. Does the Agency agree with the proposed study design and statistical analysis plan of KN164 to support consideration for accelerated approval in previously treated (b) (4) metastatic MSI-H-CRC?

FDA Response:
No. Study KN164 is designed to only rule out a 10% response rate. FDA recommends that Merck power the study to rule out a higher (e.g., at least 15%) lower bound of the 95% confidence interval of the response rate. Ultimately, whether KN164 will support accelerated approval depends upon the actual magnitude of response observed, the duration of response, and the risk-benefit profile when pembrolizumab is administered to patients with previously treated MSI-H mCRC.

Merck Response Received Via Email on May 8, 2015:
Merck acknowledges Agency's recommendation and agrees to design the study to rule out a response rate of 15%.

Discussion During the Meeting:
Merck proposed to conduct an interim analysis when 40 patients have been enrolled and followed for at least 18 weeks. FDA recommended that Merck submit a meeting request to discuss results from the planned interim analysis.

FDA requested Merck submit a revised protocol.

(b) (4)

FDA ADDITIONAL CLINICAL COMMENTS

4. FDA would not object to Merck revising the eligibility criteria to exclude patients who have received a monoclonal antibody within two weeks (rather than 4 weeks).

Merck Response Received Via Email on May 8, 2015:
Merck agrees to revise the eligibility criteria accordingly.

5. In the informed consent document, describe available therapies (e.g., regorafenib) that patients would be willing to forgo in order to enroll into the trial.

Merck Response Received Via Email on May 8, 2015:
Merck acknowledges Agency's comment and agrees to provide available therapy information for inclusion in the ICF. No further discussion is required at the F2F meeting.

6. FDA recommends that Merck consider allowing patients with HIV on highly active antiretroviral therapy and an intact immune system to enroll into the clinical trial.

Merck Response Received Via Email on May 8, 2015:
Merck acknowledges Agency's comment and will take this into consideration. No further discussion required at the F2F meeting.

7. FDA recommends that Merck consider enrolling a cohort of patients with MSI-H small intestinal cancer.

Merck Response Received Via Email on May 8, 2015:
Merck acknowledges Agency's recommendation and would like to discuss this further at the F2F meeting to get better understanding of the recommendation.

Discussion During the Meeting:
Rather than include patients in an "umbrella protocol," FDA encouraged Merck to enroll patients with MSI-H small intestinal cancer and other gastrointestinal malignancies in a dedicated protocol in order to expedite development of pembrolizumab for these patient populations.

8. FDA recommends that Merck test tumor samples for BRAF V600E mutations in addition to MSI-high status.

Merck Response Received Via Email on May 8, 2015:
Merck acknowledges the Agency's comment and will take this into consideration. No further discussion required at the F2F meeting.

ADDITIONAL SPONSOR QUESTION NOT CONVEYED IN MEETING PACKAGE:

9. Merck requests feedback from the Agency whether the data from MSI-H CRC trial "Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors" (KN016) would be sufficient to support the submission of a breakthrough therapy designation application for MSI-H CRC. The clinical activity data is provided in section 5.2.4.2 of the briefing package and Merck plans to share data update at the F2F meeting.

Discussion During the Meeting:
FDA recommended that Merck submit a request for Breakthrough Therapy (BT) designation as an IND amendment. FDA would further discuss the proposal internally in order to determine whether to grant the request. FDA recommended that the BT request include the results from an independent review of responses.

PREA REQUIREMENTS
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov.
For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA web Page entitled "CDER/CBER Position on Use of SI Units for Lab Tests" found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm .

ACTION ITEMS

Action Item/Description	Owner	Due Date
Design the study to rule out a response rate of 15% and revise the eligibility criteria to exclude patients who have received a monoclonal antibody within two weeks (rather than 4 weeks).	Merck	TBD

Submit a revised protocol.		
Submit a meeting request to discuss results from the planned interim analysis.	Merck	TBD
(b) (4)	Merck	TBD
	Merck	TBD
Submit a request for Breakthrough Therapy designation. Include the results from an independent review of responses.	Merck	TBD
Revise the informed consent document to provide available therapy information.	Merck	TBD

ATTACHMENTS AND HANDOUTS
Merck's presentation

POST-MEETING ADDENDUM
After further discussion, FDA will agree to review a request for breakthrough designation prior to full independent review of responses from Study KN016. FDA continues to recommend that Merck obtain the independent review as soon as possible and prior to a sBLA submission.

OHOP's End-of-Phase 2
General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

FDA's methodology and submission structure for regulatory applications supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. Our methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. The sponsor/applicant should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications*). Study analyses datasets should be traceable to the tabulations datasets.

The *PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017* guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsors/Applicants should design and implement data standardization in all research protocols to be included in regulatory submissions, as required, based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. The sponsor/applicant should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (*CDASH*) standard for design and implementation of data collection instruments.

The *Study Data Specifications* provide the current specifications for submissions. The specifications provide the most conducive data content definition and structure for the review team. The review team assigned to the submission determines the acceptability. Therefore, you are encouraged to follow this best practice noted in the *Study Data Specifications*, "prior to submission, sponsors should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset and the organization of the data within the file".

In addition, please reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions. The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration. In addition to the information and guidance provided at the above FDA link and CDISC links contained therein, the Division Oncology Products 2 (DOP2) has attached a

separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions. These domains and variable specifications have been developed by CDISC and will be included in the implementation guidance in the near future. DOP2 is using these domains.

Additional Links:

Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application, we encourage you to provide justification and discuss it with us.

GENERAL
Special Protocol Assessment (SPA) Requests
1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.
SPA Requests for a Single Trial Intended to Support Marketing Approval *Note: You may also apply these concepts to a trial for which you are not seeking SPA agreement.*
2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document: • Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. *See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products'*). • A description of your drug development plan, including each indication that is being (or has been) studied and a timetable for submission of the planned studies. You should also include information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.
Additional Content for SPA Request Submission

Note: You may also apply some of the concepts below to trials for which you are not seeking SPA agreement.

3) Please submit/address the items below in your SPA request.
   - The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
   - If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
   - If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
   - If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
   - If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:
     - How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
     - Applicability of comparator treatment or of disease characteristics to U.S. population
   - Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot be performed. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on single arm trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)) in your SPA request and NDA/BLA submission. Under §314.510 and 601.41, confirmatory trials would usually be underway at the time of accelerated approval. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on the timing and number of confirmatory trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).
   - If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format

CLINICAL
1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format)
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset h) listing of raw data definitions i) analysis data definitions j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item) k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).
8) Pediatric Studies: All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the FDA Pediatric Team at Pedsdrugs@fda.hhs.gov. You may also refer to the following FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm
9) Quantitative Safety Analysis Plan (QSAP): The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation.

The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:

a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
b) Safety endpoints for Adverse Events of Special Interest (AERI)
c) Definition of Treatment Emergent Adverse Event (TEAE)
d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))
e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:
a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)
b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)

11) Perform the following Standard MedDRA Queries (SMQs) on the ISS adverse event data and include the results in your ISS report. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application

13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

14) References:

There should be active links from lists of references to the referenced article.

Studies, Data And Analyses

15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).

16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:

a) Site number
b) Principle investigator
c) Location: City State, Country
d) Number of subjects screened
e) Number of subjects randomized
f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)
g) Number of protocol violations (Major, minor, including definition)

17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).

18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:
a) subject age and gender
b) signs and symptoms related to the adverse event being discussed
c) an assessment of the relationship of exposure duration to the development of the adverse event
d) pertinent medical history
e) concomitant medications with start dates relative to the adverse event
f) pertinent physical exam findings
g) pertinent test results (for example: lab data, ECG data, biopsy data)
h) discussion of the diagnosis as supported by available clinical data
i) a list of the differential diagnoses, for events without a definitive diagnosis
j) treatment provided
k) re-challenge and de-challenge results (if performed)
l) outcomes and follow-up information
m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and

patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
b) Exposure-Response Relationships – important exposure-response assessments.
c) Less common adverse events (between 0.1% and 1%).
d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
f) Marked outliers and dropouts for laboratory abnormalities.
g) Analysis of vital signs focused on measures of central tendencies.
h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
l) Standard analyses and explorations of ECG data.
m) Overdose experience.
n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
o) Explorations for:
    i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
    ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.

iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
iv) Drug-demographic interactions
v) Drug-disease interactions

p) Drug-drug interactions
i) Dosing considerations for important drug-drug interactions.
ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

Physician's Labeling Rule

Highlights

1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]

4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).

6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5

sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].
11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights
12) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]
Table of Contents
15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows: 8.1 Pregnancy 8.3 Nursing Mothers *(not 8.2)* 8.4 Pediatric Use *(not 8.3)*

8.5 Geriatric Use *(not 8.4)*
20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."
Full Prescribing Information (FPI)
22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
24) Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]
26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

31) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.
33) Refer to the Institute of Safe Medication Practices’ website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Slides for discussion on May 12th 2015 Type B Face to Face Meeting

Reference ID: 3775897

Q1: Eligibility Criteria

Merck accepts the Agency's input on the proposed single arm study to support accelerated approval and no further discussion is needed.

KN-016 A Phase 2 Study of Pembrolizumab in Patients with MSI Tumors

Primary Objective: To determine the immune-related progression free survival (irPFS) rate at 20 weeks and objective response rate (irORR) in patients with MSI positive and negative colorectal adenocarcinoma and non-colorectal solid tumor malignancies treated with MK-3475 using immune related response criteria (irRC).

- **Trial Design**
- **Open-label, 2-stage, phase 2 study**
- **MK-3475 10mg/kg every 14 days**
- **Co-primary endpoints for CRC cohorts (A & B): immune-related PFS at 20 weeks and objective response rate using immune related response criteria**
- **Primary endpoint for cohort C: immune-related PFS at 20 weeks**
- **Secondary endpoints: disease control rate, PFS, OS, and safety**
- **Markers of MSI status: BAT-25, BAT-26, MON0-27, NR-21 and NR-24**

- **Investigators –**

• Dung Le, M.D. (Protocol Chair)	Sidney Kimmel Comprehensive Cancer Center
• Luis Diaz, M.D. (IND sponsor)	Sidney Kimmel Comprehensive Cancer Center
• Todd Crocenzi, M.D.	Providence Medical Center
• George Fischer, M.D., Ph.D.	Stanford University
• Tim Greten, M.D.	National Cancer Institute
• Richard M. Goldberg, M.D.	The Ohio State University
• James Lee, M.D., Ph.D.	University of Pittsburgh

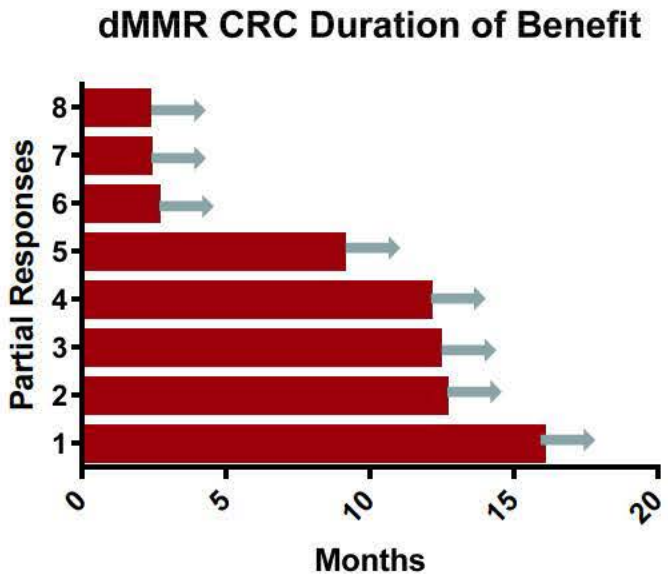
Updated Data from KN016 Study

Response to Treatment				
	Initial Data in the briefing document		Updated Data	
	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient CRC	MMR-proficient CRC
Type of Response-no (%)	n=10	n=25	n=13	n=25
Complete Response	0 (0)	0 (0)	0 (0)	0 (0)
Partial Response	4 (40)	0 (0)	8 (62)	0 (0)
Stable Disease (Week 12)	5 (50)	4 (16)	4 (30)	4 (16)
Progressive Disease	1 (10)	14 (56)	1 (8)	14 (56)
Not Evaluable[1]	0 (0)	7 (28)	0 (0)	7 (28)
Objective Response Rate (%)	40	0	62	0
95% CI	12-74	0-14	32-86	0-14
Disease Control Rate (%)[2]	90	16	92	16
95% CI			64-100	5-36

[1]Patients were considered not evaluable if they did not undergo a 12 week scan due to clinical progression.

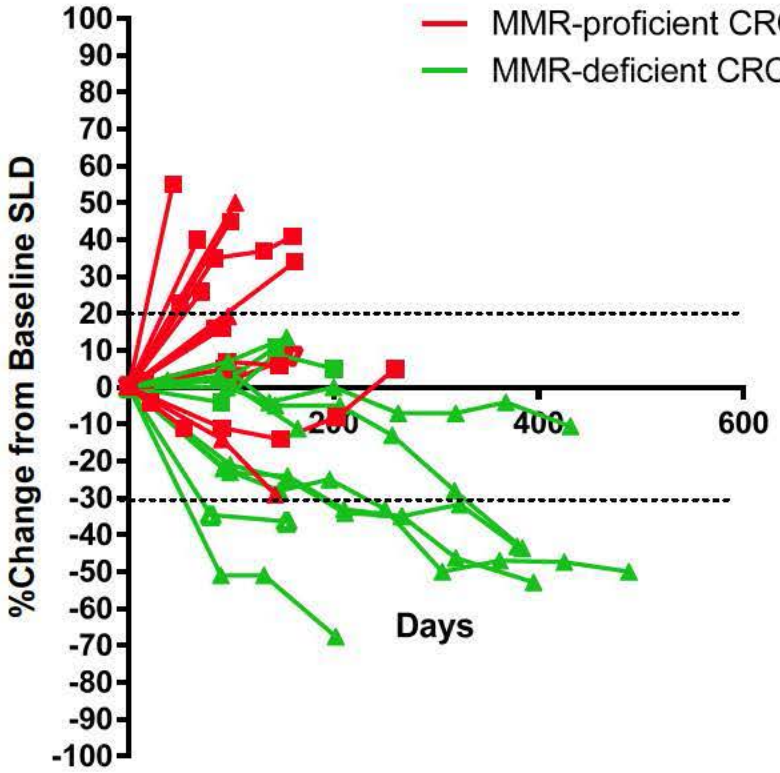
[2]The rate of disease control was defined as the percentage of patients who had a complete response, partial response or stable disease for 12 weeks or more.

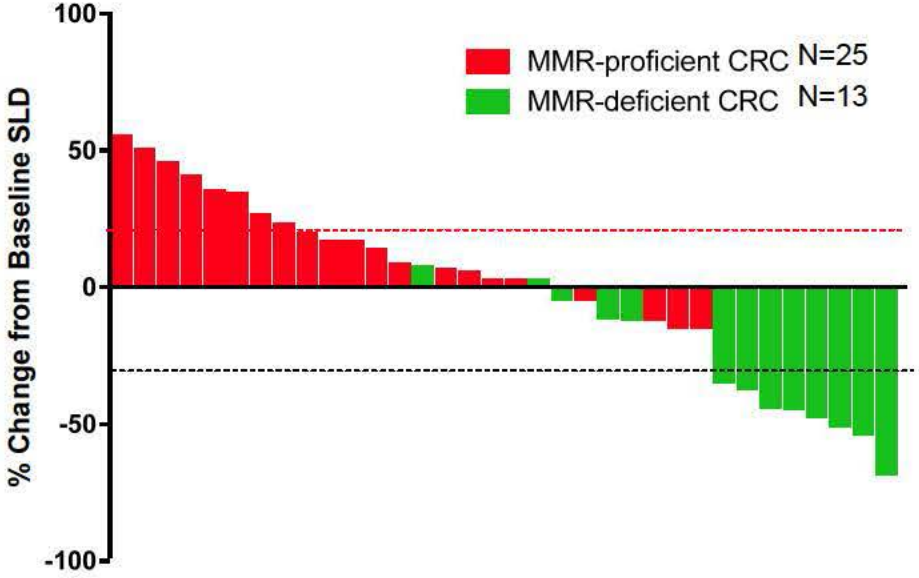
KN-016-Duration of Clinical Benefit in MSI-H CRC patients



Reference ID: 3775897

Maximum Percentage Change From Baseline in Tumor Size (RECIST v1.1)



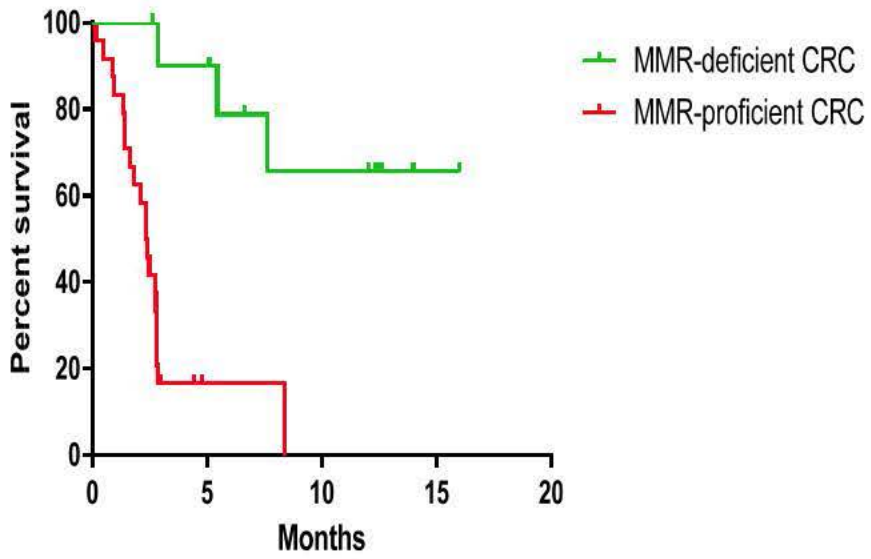


MERCK
Be well

Reference ID: 3775897

Kaplan-Meier Estimates of Survival in CRC cohorts

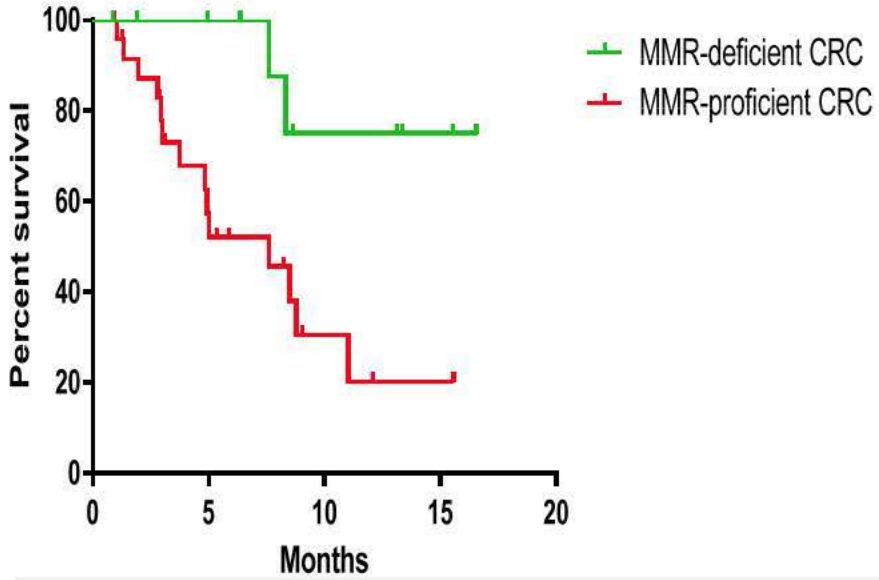
PFS



•PFS = 2.3 mos. (MMR-proficient CRC) vs. Not Reached (MMR-deficient CRC)

• HR 0.1300 (95% CI, 0.07251 to 0.3599), p < 0.0001

OS



•OS = 7.6 mos. (MMR-proficient CRC) vs. Not Reached (MMR-deficient CRC)

• HR 0.1713 (95% CI, 0.09492 to 0.6793), p < 0.0072

MERCK Be well

Reference ID: 3775897

Q2: Proposed Statistical Assumption

	Original Design	Updated Design
Null hypothesis	ORR = **10%**	ORR = **15%**
Alternative hypothesis	ORR = 27%	ORR = 35%
Sample size	N = 60	N = 60
Power	92%	93%
Statistical Success Criterion at Final Analysis (FA)	Observed ORR ≥ 20% (12/60)	Observed ORR ≥ 26.7% (16/60)
Statistical Success Criterion at Interim Analysis (IA)	Observed ORR ≥ 25% (10/40)	Observed ORR ≥ 32.5% (13/40)

Q3: MSI Testing

(b) (4)

Additional Clinical comment #7

- Merck would like to discuss what data package for MSI-H small intestinal cancer will be considered sufficient for inclusion in the label.
- An Investigator Initiated Study of small intestinal cancer (n=25) including MSI-H evaluation is planned.

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

/s/

TINA M ENNIS
06/08/2015