

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125514Orig1s024

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125514/S-24
Priority or Standard	Priority
Submit Date(s)	March 22, 2017
Received Date(s)	March 22, 2017
PDUFA Goal Date	September 24, 2017
Division / Office	DOP2/OHOP
Reviewer Name(s)	Lola Fashoyin-Aje, MD, MPH
Review Completion Date	September 8, 2017
Established Name	Pembrolizumab (MK- 3475)
(Proposed) Trade Name	Keytruda
Therapeutic Class	Programmed death 1 (PD-1) receptor blocking antibody
Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	50mg lyophilized powder for reconstitution; 100 mg/4 mL (25 mg/mL) solution in a single-dose vial.
Dosing Regimen	200 mg IV every 3 weeks
Indication(s)	For the treatment of patients with recurrent locally advanced or metastatic gastric or gastro-

esophageal junction
adenocarcinoma

(b) (4)

Intended Population(s) Adults $\geq$ 18 years of age

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment	8
1.2.1.	Disease Background	8
1.2.2.	Unmet Need	9
1.2.3.	Benefit	10
1.2.4.	Risks	11
1.2.5.	Uncertainties	11
1.2.6.	Overall Risk Benefit Assessment.....	12
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ..	13
1.4	Recommendations for Postmarket Requirements and Commitments	13
2	INTRODUCTION AND REGULATORY BACKGROUND	14
2.1	Product Information	14
2.2	Tables of Currently Available Treatments for Proposed Indications.....	15
2.2.1	Treatment of Advanced Gastric Cancer	15
2.2.2.	Microsatellite instability (MSI)- high/ mismatch repair deficient (dMMR) Gastric Cancer	17
2.3	Availability of Proposed Active Ingredient in the United States	18
2.4	Important Safety Issues With Consideration to Related Drugs.....	18
2.5	Summary of Presubmission Regulatory Activity Related to Submission	19
2.6	Other Relevant Background Information	21
3	ETHICS AND GOOD CLINICAL PRACTICES.....	22
3.1	Submission Quality and Integrity	22
3.2	Compliance with Good Clinical Practices	23
3.3	Financial Disclosures	23
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	24
4.1	Chemistry Manufacturing and Controls	24
4.2	Clinical Microbiology	24
4.3	Preclinical Pharmacology/Toxicology	24
4.4	Clinical Pharmacology	24
4.4.1	Mechanism of Action	24
4.4.2	Pharmacodynamics	25
4.4.3	Pharmacokinetics	25
5	SOURCES OF CLINICAL DATA.....	25
5.1	Tables of Studies/Clinical Trials.....	25
5.2	Review Strategy	26
5.2.1.	Efficacy Review	27
5.2.2.	Safety Review	27

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

5.3	Discussion of Individual Studies/Clinical Trials	28
5.3.1	KEYNOTE- 059	28
5.3.2	KEYNOTE-012	40
6	REVIEW OF EFFICACY	42
	Efficacy Summary	42
6.1	Indication	42
6.1.1	Methods.....	42
6.1.2	Demographics	43
6.1.3	Subject Disposition	47
6.1.4	Analysis of Primary Endpoint(s)	48
6.1.5	Analysis of Secondary Endpoints(s).....	49
6.1.6	Other Endpoints	50
6.1.7	Subpopulations.....	52
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	52
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects	53
6.1.10	Additional Efficacy Issues/Analyses	53
7	REVIEW OF SAFETY	56
	Safety Summary.....	56
7.1	Methods	56
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	56
7.1.2	Categorization of Adverse Events	56
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	58
7.2	Adequacy of Safety Assessments	58
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	58
7.2.2	Explorations for Dose Response.....	58
7.2.3	Special Animal and/or In Vitro Testing	58
7.2.4	Routine Clinical Testing.....	58
7.2.5	Metabolic, Clearance, and Interaction Workup	59
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class...59	
7.3	Major Safety Results.....	59
7.3.1	Deaths	59
7.3.2	Nonfatal Serious Adverse Events.....	67
7.3.3	Dropouts and/or Discontinuations	68
7.3.4	Significant Adverse Events.....	70
7.3.5	Submission Specific Primary Safety Concerns	70
7.4	Supportive Safety Results	71
7.4.1	Common Adverse Events.....	71
7.4.2	Laboratory Findings.....	72
7.4.3	Vital Signs	73
7.4.4	Electrocardiograms (ECGs)	73
7.4.5	Special Safety Studies/Clinical Trials	74

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

7.4.6	Immunogenicity	74
7.5	Other Safety Explorations	74
7.5.1	Dose Dependency for Adverse Events	74
7.5.2	Time Dependency for Adverse Events	76
7.5.3	Drug-Demographic Interactions	77
7.5.4	Drug-Disease Interactions	78
7.5.5	Drug-Drug Interactions	78
7.6	Additional Safety Evaluations	78
7.6.1	Human Carcinogenicity	78
7.6.2	Human Reproduction and Pregnancy Data	78
7.6.3	Pediatrics and Assessment of Effects on Growth	78
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	78
7.7	Additional Submissions / Safety Issues	79
8	POSTMARKET EXPERIENCE	79
9	APPENDICES	80
9.1	Literature Review/References	80
9.2	Labeling Recommendations	81
9.3	Advisory Committee Meeting	82

Table of Tables

Table 1. Agents Evaluated Following Fluoropyrimidine and Platinum-containing Chemotherapy in Randomized Trials	16
Table 2. Protocol Deviations in KEYNOTE-059	22
Table 3. Studies Providing Evidence of Safety and Efficacy in BLA	26
Table 4. Dose Modification ^A Guidelines for Drug-Related ^B Adverse Events	34
Table 5. Protocol-specified Schedule of Clinical Assessments	37
Table 6. Demographics Characteristics (n=259)	44
Table 7. Baseline Characteristics KEYNOTE-059 (n=259)	44
Table 8. Summary of Prior Treatments (n=259)	45
Table 9. Study and Treatment Disposition of Patients in KEYNOTE-059: (n=259)	47
Table 10. Results of Response Evaluation: KEYNOTE-059 (n=259)	48
Table 11. Results of Response Evaluation: KEYNOTE-059 (n=252)	49
Table 12. Duration of Response KEYNOTE-059 (n=259)	50
Table 13. Responder Disposition at Data Cut-off (n=30)	50
Table 14. Duration of Response KEYNOTE-059 (n=252)	50
Table 15. ORR by Microsatellite Status; KEYNOTE- 059- (n=259)	51
Table 16. Results of Response Evaluation by Line of Therapy: KEYNOTE-059	51
Table 17. ORR by Pembrolizumab Dose: KEYNOTE-059 vs KEYNOTE-012	52
Table 18. PD-L1 Positive Rate by Age of Tumor Specimen	54
Table 19. PD-L1 Test Results by Specimen Type: Archival versus Newly Obtained	54
Table 20. Disposition of Patients Enrolled in KEYNOTE-012 (Cohort D)	55
Table 21. Efficacy Summary: KEYNOTE-012 (Cohort D)	55
Table 22. Overview of Safety: KEYNOTE-059 (n=259)	57
Table 23. Duration of Pembrolizumab Exposure in KEYNOTE-059 (n=259)	58
Table 24. Incidence of Fatal Serious Adverse Events (N=33)	60
Table 25. Deaths: Patient Narratives	60
Table 26. Non-Fatal Serious Adverse Events (≥1%)	67
Table 27. Reasons for Treatment Discontinuation (n=259)	68
Table 28. Adverse Events of Special Interest (AEOSI)	70
Table 29. Common Adverse Events ^c (≥ 10%): Safety Population (n=259)	71
Table 30. Common (≥2%) AE: Grade 3-4: Safety Population (n=259)	72
Table 31. Laboratory Abnormalities Worsened ^A from Baseline Higher in Incidence in KEYNOTE-059 Compared to Reference Safety Dataset.	73
Table 32. Summary* Adverse Events (AEs) in KEYNOTE-059 and KEYNOTE-012	75
Table 33. Adverse Events of Special Interest (AEOSI) in KEYNOTE-059 and KEYNOTE-012	75
Table 34. Time to Onset of Adverse Events of Special Interest	77

Table of Figures

Figure 1. Molecular Subtypes of Gastric Cancer	17
Figure 2. Trial Design- KEYNOTE-059 (Cohort 1).....	29
Figure 3. Trial Design: KEYNOTE-012	41

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

On March 22, 2017 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck) submitted Supplement 24 to Biologics License Application (BLA) 125514, requesting marketing authorization for Keytruda (pembrolizumab) injection as a single agent, for the following indication:

For the treatment of patients with recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma (b) (4)

This reviewer concludes that the benefit risk assessment is favorable for pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma (b) (4)

therefore, recommend the approval of this request for accelerated approval in accordance with 21 CFR Part 601.41, subpart E, with modification of the Applicant's proposed indication as above, pending agreement regarding final labeling, and agreement regarding post-marketing commitments and requirements. The continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

The recommended dosage, based on the totality of the pharmacokinetic data for pembrolizumab is 200mg administered intravenously every 3 weeks until disease progression or unacceptable toxicity.

1.2 Risk Benefit Assessment

1.2.1. Disease Background

Although the incidence of gastric cancer has been declining over the past two decades, it is the fifth most common malignancy in the world after cancers of the lung, breast, colon/rectum and prostate. [1, 2] It occurs more commonly in men than in women, and its incidence varies across geographic regions with approximately half of all cases occurring in East Asia (mainly China), where the highest estimated mortality rates are observed (24 per 100,000 in men, 9.8 per 100,000 in women in East Asia compared to

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

2.8 in men and 1.5 in women in North America). In the United States (US), an estimated 28,000 patients will be diagnosed in 2017, and approximately 10,960 patients are expected to die from the disease. [3]

When diagnosed in the localized stages, gastric cancer is curable with a 5-year survival rate of approaching 70%. [4] Unfortunately, in the US where there are no widely performed gastric cancer screening programs, most patients are already symptomatic with advanced and often incurable disease at the time of presentation. In this setting, prognosis is poor with the 5-year survival rate of less than 10%. [5]

1.2.2. Unmet Need

Currently, cytotoxic, platinum-and fluoropyrimidine-based combination therapies are accepted worldwide, including in the US, as first-line regimens for the treatment of advanced gastric and gastroesophageal junction adenocarcinoma. Patients who receive first line treatment have a median survival ranging from 8 to 10 months. In the US, cisplatin-fluoropyrimidine regimens are preferred over three-drug regimens because of toxicity concerns.[6] Three-drug regimens are usually reserved for medically fit patients who may receive docetaxel, cisplatin, fluoropyrimidine (DCF) and its variants (oxaliplatin or carboplatin), ECF (epirubicin, cisplatin, fluoropyrimidine), irinotecan/fluoropyrimidine, paclitaxel/cisplatin/fluoropyrimidine, or docetaxel/cisplatin in the first-line setting. Of these regimens, only docetaxel in combination with cisplatin and fluorouracil is FDA-approved for the treatment of patients with advanced gastric and gastroesophageal junction adenocarcinoma, who have not received prior chemotherapy for advanced disease (See Taxotere USPI).

In addition to cytotoxic agents, patients whose tumors express HER-2 may receive trastuzumab in the first-line setting. Trastuzumab (Herceptin) in combination with cisplatin and capecitabine or 5-fluorouracil, is approved for the treatment of patients with HER-2 over expressing metastatic gastric or GEJ adenocarcinoma who have not received prior treatment for metastatic disease (See Herceptin USPI). This approval was based upon the demonstration of a median overall survival (OS) of 13.5 months (95% CI: 11.7, 15.7) in Herceptin-treated patients compared to 11 months (95% CI: 9.4, 12.5) in patients who only received chemotherapy.

After failure of first-line therapy, options for treatment are limited. Three randomized trials of single agent chemotherapy (irinotecan and docetaxel) have demonstrated improvement in overall survival and quality of life when compared with best supportive care (BSC). [7-9] In these trials, the median OS rates were 4 to 5 months long. Based on these studies, the National Comprehensive Cancer Network (NCCN) recommends these agents as options for patients.

In the US, ramucirumab in combination with paclitaxel or as monotherapy is approved for treatment following first-line therapy. These two approvals were based upon

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

improvements in median OS in patients who received ramucirumab monotherapy compared to patients who received placebo (5.2 months [95% CI 4.4, 5.7] versus 3.8 months [95% CI 2.8, 4.7]; HR 0.78, 95% CI: 0.60, 0.998; p-value 0.047) and in patients who received ramucirumab in combination with paclitaxel versus placebo plus paclitaxel (9.6 months [8.5, 10.8] versus 7.4 months [6.3, 8.4]; HR 0.81 [95% CI: 0.68, 0.96]; p-value 0.017 [Refer to Cyramza USPI]). The objective response (partial or complete responses) was higher in the ramucirumab plus paclitaxel arm (28%, 95% CI 23, 33) compared to the placebo plus paclitaxel arm (16%, 95% CI 13, 20) (p<0.001). The median duration of response was 4.4 months [interquartile range (IQR) 2.8–7.5] in the ramucirumab plus paclitaxel arm compared to 2.8 months [IQR 1.4–4.4] in the placebo plus paclitaxel arm.[10]

On May 23, 2017, during the review of this supplemental BLA, pembrolizumab received accelerated approval for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-high) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or metastatic, MSI-high or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. [Refer to Keytruda USPI] The approval was based upon data from single-arm studies (n=90), in which the observed ORR was 33% (95% CI 23.7%-44.1%). The median duration of response was not reached.

In conclusion, available data for treatment-naïve advanced gastric cancer indicate that the prognosis for patients with advanced gastric cancer is poor with 5-year survival rates of less than 10% and median OS of less than one year. Although there are limitations regarding the data describing the prognosis of patients who have progressed following two or more prior chemotherapy regimens, it is likely that prognosis for these patients is much worse. Patients with metastatic gastric cancer who have progressed following two or more prior chemotherapy regimens (and a HER 2 inhibitor if indicated) represent an unmet medical need as there are currently no national consensus guidelines for treatment of advanced gastric cancer beyond the second-line setting and no FDA-approved therapies that would, for the purposes of this application, be considered 'available therapy' per FDA guidance documents.

1.2.3. Benefit

The primary evidence that pembrolizumab may provide clinically meaningful benefit in this patient population is based upon the results of the KEYNOTE-059 study which evaluated the efficacy of single agent pembrolizumab 200 mg IV administered every 3 weeks (Q3W) in patients with gastric cancer irrespective of PD-L1 status. In this single-arm study, the objective response rate (ORR) per RECIST 1.1 per blinded independent central review (assessment is 11.6% (95% CI: 8.0, 16.1) in the overall population, with 6 patients (2%) who achieved complete responses. Among the subgroup of patients who had PD-L1 positive tumors and excluding microsatellite instability high (MSI-high) patients, the ORR is 13.3% (95% CI: 8.2, 20.0). When ORR for patients with PD-

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

L1 positive tumors is evaluated by treatment setting (i.e., 3rd line [3L] versus $\geq$ 4th line [4L+], the ORR is 20.5% (95% CI: 12.0, 31.6) and 5.7% (95% CI: 1.6, 14.0), respectively.

Patients who achieved partial or complete responses appeared to have sustained responses. In the overall population, the median duration of response (DoR) was 14.2 months (95% CI: 9.9, NR; range: 2.4, 19.4+) with 60% of patients maintaining their response for 6 months or more. Among the subgroup of patients who had PD-L1 positive tumors and excluding MSI-high patients, the median DoR was 14.2 months (95% CI: 8.2, 20.0; Range: 2.8+, 19.4+).

Given historical data which indicate that patient outcomes may vary by geographic region, the fact that a significant proportion of trial patients (48%) were enrolled in the US is a positive attribute of the study.

1.2.4. Risks

The primary safety concerns with pembrolizumab treatment are immune-related adverse events (irAEs). The small size of the study (KEYNOTE-059) that provides the primary evidence of safety for this supplemental BLA may be inadequate to observe any additional risks or risks that may occur with rare frequency in this refractory gastric cancer patient population. Overall, however, the results of the analyses of safety in KEYNOTE-059 were largely consistent with the known adverse reaction and laboratory abnormality profile of pembrolizumab and with the current labeling information. Similarly, the treatment discontinuation and interruption rates observed among patients who received pembrolizumab in KEYNOTE-059 were at or below those observed in other indications.

1.2.5. Uncertainties

Microsatellite Instability-High

The ascertainment of microsatellite instability (MSI) status was not prospectively specified in the KEYNOTE-059 protocol. The Applicant conducted a retrospective assessment of MSI status and observed that 7 patients out of the 174 for whom MSI was evaluated were MSI-high. However, given the proportion of patients for whom the MSI status is unknown (n=85; 33%), there is some uncertainty regarding the proportion of patients with unknown MSI status who were MSI-high. To address this uncertainty FDA conducted sensitivity analyses to mitigate the potential effects of a high MSI-high rate among the efficacy population, and ultimately decided to exclude patients known to be MSI-high (n=7) from the efficacy analysis.

Programmed Death Ligand (PDL) 1

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

The role of PD-L1 in determining the likelihood of response to treatment with pembrolizumab is limited by a poor understanding of PD-L1 expression in gastric tumors, and the relative contribution of MSI-high and Epstein Barr virus (EBV) status. Although greater efficacy in patients with PD-L1 tumors was expected (and observed) given the mechanism of action of a pembrolizumab, the small number of patients, the low rate of MSI-high patients, the high proportion of patients for whom microsatellite status is unknown (30%), and the absence of information regarding EBV status, did not permit an understanding regarding the relative roles that all these biomarkers may play with regards to response to PD-L1 inhibition. An additional consideration in this application was the reliability of PD-L1 test results among patients who were reported to have PD-L1 negative tumors, as these patients tended to have testing performed on archival tissue specimens, while patients with PD-L1 positive tumors were more likely to have testing performed on fresh tissue. The ORR among patients whose tumors were PD-L1 negative is 6.5% (95% CI: 2.7, 13.0). Among these 7 patients, none of whom are MSI-high, a total of 3 achieved complete responses and 4 maintained the radiologic response for 6 months or longer. Among the 7 patients with PD-L1 negative tumors who achieved responses, 6 had tumor specimens that were greater than 400 days old and among the 3 patients who achieved complete responses, the age of tumor specimens used for PDL-1 testing was greater than 900 days.

In the opinion of this reviewer, the information that was submitted in the BLA provides insufficient evidence to support the safety and efficacy of pembrolizumab in patients whose tumors are PD-L1 negative. This is due to the small number of patients with PD-L1 negative gastric cancer who achieved an objective response to pembrolizumab, and to concerns regarding the sensitivity of PD-L1 testing in archival tumor specimens.

1.2.6. Overall Risk Benefit Assessment

Compared to the response rate of 30-40% observed in patients with MSI-high/dMMR solid tumors (See pembrolizumab USPI), this reviewer acknowledges that the ORR observed among patients in the current supplemental BLA is modest and may not capture the potential full benefit of treatment with pembrolizumab. Given the durability of the responses that were observed, the observation of complete radiographic responses, and the fact that similarly modest response rates with other immune checkpoint inhibitors in other solid tumor indications have translated into clinical benefit (with improvements on either progression free survival (PFS) or OS) (Refer to USPI for nivolumab and atezolizumab), treatment with pembrolizumab may be reasonably likely to predict clinical benefit.

Therefore, despite the previously described uncertainties, considering the unmet need in the treatment of gastric cancer following two or more lines of systemic therapy, the poor prognosis in patients with the disease, and the efficacy and safety data supporting this supplemental BLA, this reviewer concludes that the benefit risk assessment is favorable in an identifiable subgroups of patients who were evaluated in KEYNOTE-059 and recommends approval for pembrolizumab for the treatment of patients with PD-L1

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

expressing recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER-2/neu targeted therapy.

While the benefit risk assessment appears favorable in patients whose tumors are PD-L1 positive, the benefit:risk assessment is less clear for patients whose tumors are PD-L1 negative given the uncertainty regarding the adequacy of archival specimens in detecting PD-L1 expression, and the small numbers of patients who achieved radiological responses.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Pembrolizumab is an approved agent (KEYTRUDA®) with an extensive safety database and a well-characterized safety profile. Additionally, pembrolizumab is administered by health care professionals with experience in managing immune-related toxicities associated with immune-modulating agents (e.g., pembrolizumab, atezolizumab, nivolumab, ipilimumab, durvalumab). No new safety signals that require Risk Evaluation and Mitigations Strategies (REMS) were identified in patients with gastric cancer. The USPI for pembrolizumab contains patient counseling information for prescribing physicians (oncologists) as well as a Patient Package Insert.

1.4 Recommendations for Postmarket Requirements and Commitments

This reviewer recommends that the Applicant conduct a post-marketing study as a post-marketing requirement (PMR) in order to demonstrate that pembrolizumab has a favorable and clinically meaningful effect on survival that will support the regular approval of pembrolizumab for the treatment of patients recurrent or metastatic gastric or GEJ adenocarcinoma whose tumors are PD-L1 positive.

The Applicant has previously proposed, and FDA has agreed that KEYNOTE-061, entitled “A Phase III, Randomized, Open-label Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel in Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-Line Therapy with Platinum and Fluoropyrimidine”, could provide evidence of pembrolizumab’s effect on the overall survival and support regular approval of pembrolizumab for the treatment of recurrent advanced gastric cancer. In KEYNOTE-061, patients are randomized 1:1 ratio to receive pembrolizumab or paclitaxel and stratified by geographic region, time to progression on first line therapy, and PD-L1 expression status. Overall survival and PFS are dual primary endpoints.

At the time of the submission of the current supplemental BLA, KEYNOTE-061 had been fully enrolled (July 2016) and is pending the final analysis of overall survival.

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)

Reviewer Comment: The pre-specified primary efficacy analysis in KEYNOTE-061 is based on the evaluation of OS and PFS in an all-comer population with respect to PD-L1 status, and microsatellite instability will be retrospectively assessed. Given the recent approval of pembrolizumab for MSI-high solid tumors and the results of KEYNOTE-059 which demonstrate a higher ORR in the subgroup of patients who have PD-L1 expressing tumors, the confirmatory trial(s) will need to demonstrate clinical benefit as measured by an improvement in OS in microsatellite stable patients whose tumors express PD-L1.

Proposed PMR language:

Conduct and submit the results of one or more randomized trials to verify and describe the clinical benefit of pembrolizumab over standard therapy based on a clinically meaningful improvement in overall survival in patients with PD-L1 positive, microsatellite stable/mismatch repair proficient metastatic gastric or gastro-esophageal junction adenocarcinoma.

Milestone dates:

- Study / trial completion – (b) (4)
- Final report submission – (b) (4)

Reviewer Comment: On August 22, 2017, the Applicant submitted an amendment to the supplemental BLA stating that either KEYNOTE-061 or (b) (4) could fulfill this PMR. The milestones above reflect the study completion of (b) (4) KEYNOTE-061.

FDA will also request that Merck fulfill a post-marketing commitment (PMC) by submitting the final report, including datasets, from patients with PD-L1 positive microsatellite stable or microsatellite instability (MSI)-unknown recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma enrolled in Cohort 1 of Study KEYNOTE 059. In order to further characterize the duration of response in patients who achieve a complete or partial response to pembrolizumab, FDA will request that responding patients be followed for at least 12 months from the onset of response and that duration of response be assessed by independent central review.

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, programmed death-ligand 1 (PD-L1) and PD-L2. Pembrolizumab is supplied as a lyophilized powder in single-use vials for reconstitution and as a 100 mg solution in single use vials.

2.2 Tables of Currently Available Treatments for Proposed Indications

2.2.1 Treatment of Advanced Gastric Cancer

In advanced gastric or gastroesophageal junction adenocarcinoma (gastric cancer), therapeutic decisions are made based upon several factors including the HER-2 neu status, the presence of medical co-morbidities and performance status, and patient preferences, among other things. Given that metastatic gastric cancer is an incurable disease with a 5-year survival rate of approximately 5%, the goal of treatment is to prolong life and/or improve quality of life. This may be achieved with the use of cytotoxic chemotherapy and targeted therapies and, in patients with poor performance status, with supportive treatment.

The treatment of advanced gastric cancer has evolved over the last five decades. Treatment approaches in the 1970 through the 1980's involved the use of single chemotherapeutic agents such as the FDA-approved drugs fluorouracil, doxorubicin, and mitomycin C, and the subsequent use of combinations of these agents (e.g., the FAM [5-fluorouracil, doxorubicin, mitomycin C], FAP [5-fluorouracil, doxorubicin, cisplatin] regimens). These approaches yielded modest clinical benefits characterized by tumor responses in in some patients, with no effects on the patient survival.[11-13]

Randomized trials of agents that have been evaluated in patients following fluoropyrimidine and platinum-containing chemotherapy are shown in Table 1.

Table 1. Agents Evaluated Following Fluoropyrimidine and Platinum-containing Chemotherapy in Randomized Trials

Study	Treatment	Size	mOS	mPFS	ORR	P value
1a	RAM vs PBO	355	5.2 vs 3.8 HR .776	2.1 vs 1.3	3% vs 3% mDoR 4.2 mos. vs 2.9)	0.047
2a	RAM + PTX vs PBO + PTX	665	9.6 vs 7.4 HR .807	4.4 vs 2.9 HR .635	28% vs 16%; pvalue <.0001	0.017
3a	PTX + VPA Vs PTX	66	8.7 vs 9.8 HR 1.19	3.0 vs 4.5 HR 1.29	N/A	0.51
4a	S-1 + IRI vs IRI	293	8.8 vs 9.5 HR .99	3.8 vs 3.4	7.6% vs 7.4%	0.92
5a ^{AA}	DTX + OXP Vs DTX	52	8.1 vs 7.2	4.9 vs 2.0	24.0% vs 14.8%	0.40
6a ^{BB}	Nimotuzumab + IRI vs IRI	83	-	2.4 vs 2.8 HR .860	-	0.5668
7a	DTX+ SXC vs SXC	168	5.2 vs 3.6 HR .67	-	7% mTTP=3 mos.	0.01
8a	PTX vs IRI	218	9.5 vs 8.4 HR 1.13	3.6 vs 2.3	20.9% vs 13.6; p=.24	.38
9a ^{AA}	PEP02 (MM- 398), vs IRI or DTX	132	7.3 vs 7.8 vs 7.7	2.7 vs 2.6 vs 2.7	13.6% vs 6.8% vs 15.9%	DoR n/a
10b	Everolimus +BSC vs PBO+BSC	656	5.4 vs 4.3 HR 1.08	1.7 vs 1.4	4.5% vs 2.1%	.124
11b	DTX/IRI vs BSC	202	5.3 vs 3.8 HR .657	-	11%/8%	.007
12c	Apatinib vs PBO	267	6.5 vs 4.4 HR .71	2.6 vs 1.8	2.84% vs 0	.0149

Source: Reviewer Table [7, 8, 14-22]. P-value for 1^o endpoint; VPA= valproic acid; RAM= ramucirumab; OXP=oxaliplatin; DTX= docetaxel; PTX- paclitaxel; IRI=irinotecan; PBO= placebo; BSC= best supportive care; SXC= symptom control; a=2L only; b= 2L & 3L; c= 3L+ only; AA=ORR 1^o endpoint; BB=PFS 1^o endpoint

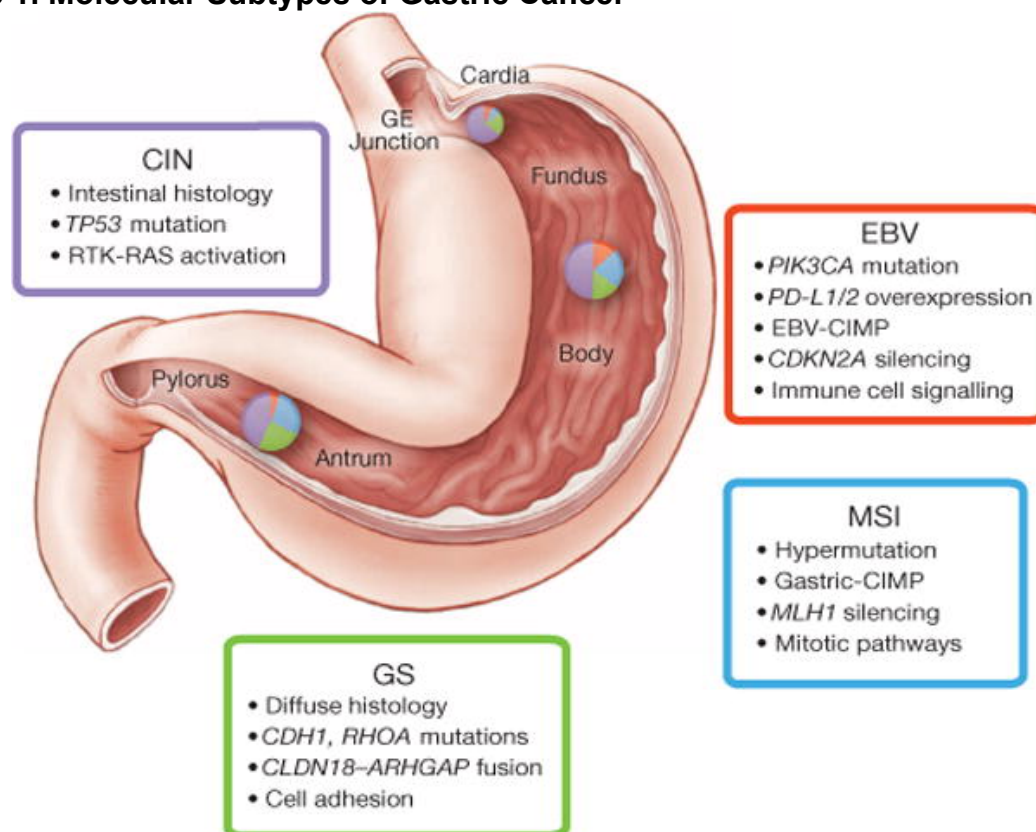
FDA- approved	2nd and 3 rd line	3 rd line only
------------------	---------------------------------	------------------------------

Refer to Section 1.2.2 for a summary of current treatment options for patients with advanced gastric cancer.

2.2.2. Microsatellite instability (MSI)- high/ mismatch repair deficient (dMMR) Gastric Cancer

The Cancer Genome Atlas (TCGA) analysis revealed gastric cancer as a molecularly heterogeneous disease. [23, 24] This analysis of 295 primary gastric adenocarcinomas classified gastric cancer according to four subtypes as shown in Figure 1 below.

Figure 1. Molecular Subtypes of Gastric Cancer



Source: *Nature*. September 11, 2014; 513 (7517): 202-209

Epstein-Barr virus (EBV) positive tumors displayed recurrent *PIK3CA* mutations, extreme DNA hypermethylation, and amplification of *JAK2*, *CD274* (also known as *PD-L1*) and *PDCD1LG2* (also known as *PD-L2*); these tumors comprised 9% of the samples. MSI-high tumors comprised 22% of the sample and these tumors showed elevated mutation rates, including mutations of genes that encode targetable oncogenic signaling proteins. Tumors that are genomically stable (20%) were enriched for the diffuse histological variant and mutations of *RHOA* or fusions involving RHO-family GTPase-activating proteins. The fourth molecular subtype consisted of tumors with chromosomal instability (50%) which showed marked aneuploidy and focal amplification of receptor tyrosine kinases (RTKs). Aberrant activation of RTKs through oncogene amplifications or mutations is prevalent in GEJ tumors, and it is likely that combinations of alterations in multiple oncogenic pathways drive their growth. [25, 26] Clinical

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

response of gastric tumors to checkpoint inhibitors may be modulated by several factors including MSI-high status, EBV status, and PD-L1.

2.3 Availability of Proposed Active Ingredient in the United States

At the time of the submission of this supplemental BLA, pembrolizumab was approved in the U.S. for the treatment of:

- patients with unresectable or metastatic melanoma
- patients with metastatic Non-Small Cell Lung Cancer (NSCLC) whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) $\geq 50\%$)] with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy
- patients with metastatic NSCLC whose tumors express PD-L1 (TPS $\geq 1\%$) with disease progression on or after platinum-containing chemotherapy
- patients with recurrent or metastatic head and neck squamous cell cancer with disease progression on or after platinum-containing chemotherapy.
- adult and pediatric patients with refractory classical Hodgkin lymphoma or who have relapsed after 3 or more prior lines of therapy.

During the review of this supplemental BLA, pembrolizumab received approval for the following additional indications:

- Non-Small Cell Lung Cancer (NSCLC)
 - in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic non-squamous NSCLC
- Urothelial carcinoma
 - for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.
 - 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-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.

2.4 Important Safety Issues With Consideration to Related Drugs

Pembrolizumab, like other approved products which target the PD-1 or PD-L1 pathway (e.g., nivolumab, avelumab, atezolizumab) or cytotoxic T-lymphocyte antigen (CTLA-4) (e.g., ipilimumab) have a well-characterized safety profile. In clinical trials evaluating

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)
these products, severe or serious immune-mediated adverse reactions and infusion-related reactions have been observed.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Clinical studies supporting the development of pembrolizumab for the treatment of patients with advanced gastric cancer has occurred under IND 110080 and IND 123482. The key regulatory activities relevant to this supplemental BLA submission are summarized below. Refer to Section 5.3.1 for a summary of key protocol amendments for KEYNOTE-059.

February 20, 2013

Applicant submitted new protocol for KEYNOTE-012 under IND 110080 to evaluate MK-3475 (pembrolizumab) in patients with advanced solid tumors.

August 14, 2013

Applicant amended KEYNOTE-012 protocol to evaluate pembrolizumab in a new cohort (Cohort D) of patients with advanced gastric cancer.

November 21, 2014

Applicant submitted original IND 123482 which included KEYNOTE-059, entitled “A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-059).”

December 15, 2014

Teleconference held at FDA’s request to discuss the need for an Investigational Device Exemption (IDE) for the PD-L1 immunohistochemistry assay to support KEYNOTE-059.

December 22, 2014

FDA issued the ‘may proceed’ letter for original IND 123482.

March 5, 2015

Type B End of Phase 1 (EOP1) meeting held to discuss the design of KEYNOTE-061 and KEYNOTE-062. During this meeting, the FDA agreed that KEYNOTE-061 could serve as the confirmatory trial for a potential accelerated approval based on data from KEYNOTE-059. FDA also stated that this meeting constituted an End-of-Phase 2 meeting.

April 27, 2015

Applicant submitted the Initial Pediatric Study Plan (iPSP) for gastric cancer which included a [REDACTED] (b) (4)

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

April 30, 2015

Applicant submitted a request for Orphan Drug Designation for pembrolizumab for gastric and gastro-esophageal junction adenocarcinoma.

June 16, 2015

Orphan Drug Designation granted to pembrolizumab for the treatment of gastric cancer, including gastroesophageal junction adenocarcinoma (#15-4817).

June 25, 2015

The Center for Devices and Radiological Health (CDRH) granted an IDE to Dako North America, Inc., for the Dako PDL1 IHC 22C3 pharmDx Kit used to assess PD-L1 expression in gastric cancer tissues in support of Merck clinical studies KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 (G140139/S002).

July 30, 2015

Applicant submitted the Agreed iPSP to FDA; FDA issues agreement with proposed Agreed iPSP on August 28, 2015.

January 31, 2017

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 recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma (b) (4)

based upon the results of KEYNOTE-059 (Cohort 1). During this meeting FDA agreed that a data cutoff date of January 16, 2017 would be acceptable for the BLA submission, and requested that the applicant submit the following:

- a proposal for submitting updated efficacy data to the sBLA;
- a sensitivity analysis based on the first 180 subjects enrolled and the first 210 patients enrolled compared with the overall patient population; and
- a minimum of 6 months of follow-up time for patients with confirmed responses.

March 7, 2017

Applicant requested agreement to submit updated proposed labeling revisions by April 7, 2017 for the supplemental BLA based upon anticipated action on an efficacy supplement for classic Hodgkin lymphoma which was under review at the time of Gastric efficacy supplement submission. FDA agreed to the Applicant's proposal on March 7, 2017.

March 8, 2017

Applicant proposed to submit an efficacy update based on a data cutoff of April 21, 2017, with the submission to occur within 3 months of sBLA submission. FDA agreed with this proposal on April 6, 2017.

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)
March 22, 2017

sBLA 125514/S-24 for treatment of patients [REDACTED] (b) (4)
[REDACTED] was submitted

The following additional regulatory activities occurred following the submission of the supplemental BLA:

April 18, 2017

sPMA for PD-L1 IHC assay for gastric cancer submitted.

April 26, 2017

Face to face application orientation meeting held.

June 21, 2017

Applicant submitted an amendment to the supplemental BLA to include updated efficacy data reflecting a data cutoff date of April 21, 2017, as previously agreed upon. This update included durability data. The Applicant also submitted a revised proposed USPI to reflect updates to the efficacy data.

2.6 Other Relevant Background Information

During the application orientation meeting, the Applicant provided an update on the enrollment of KEYNOTE-061, which was at the time of the meeting, intended to confirm and verify the clinical benefit of pembrolizumab in patients with gastric cancer. The Applicant states that the study was fully enrolled as of July 2016 and that results of the primary overall survival analysis were anticipated to be available by the 4th quarter of 2017.

During the review of this application, [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No data quality related issues were identified during the review process. All datasets were submitted in electronic common technical document (eCTD) standard format. The submission had all the requisite components of a supplemental application and was reviewable.

The Applicant reported a total of 73 protocol deviations in 53 patients as shown below in Table 2.

Table 2. Protocol Deviations in KEYNOTE-059

Deviation Type	No. Patients	Description
Entry criteria	7	Patients entered that did not satisfy the inclusion/exclusion criteria as stated in protocol
Safety assessment	28	Patients where Serious Adverse Events (SAE)/Adverse Events were not reported or not reported in timely manner
Clinical supplies	8	Pembrolizumab infusion time is outside window; Improper storage of study therapy that may affect efficacy and/or safety
Prohibited medications	3	Patients who took disallowed concomitant medications
Consent	19	Patients who did not give appropriate Informed Consent
Efficacy assessment	1 ^A	Failure to conduct major / significant protocol-specified efficacy and/or safety evaluations.
Discontinuation criteria ^D	2	Patients who developed withdrawal criteria but were not withdrawn from the study

Source: Reviewer table; CSR Section 16.2.2 ^DSUBJID=590097; 590162,- none were responders.

^A590034 was a responder.

Overall, patients who had protocol deviations pertaining to entry criteria or discontinuation criteria were not included among the subgroups of patients who achieved partial or complete responses; the following two patients were the exceptions:

- Patient **590034** had several protocol violations (i.e., efficacy assessment, informed consent form, and safety assessment) achieved a response.
- Patient **590184** was among the group of patients with consent form protocol deviations; this patient achieved a response.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

Based on the concern that the inclusion of these two patients in the efficacy evaluable population could potentially compromise the results of KEYNOTE-059, additional information was requested of the Applicant and is summarized below.

- Patient **590034**: the violations consisted of 1) an incorrect assessment of response by the investigator, 2) a delay in re-consenting the patient after a consent form update, and 3) a delay in reporting a Grade 2 adverse event.
- Patient **590184**: the violations consisted of 1) incomplete documentation of the re-consenting process, and 2) a delay in obtaining two CT scans, both of which occurred less than 7 days outside the pre-specified margin for obtaining the scans.

Reviewer Comment: Despite the possibility that the time to response and duration of response may have been affected by a few days for patient 590184, for each of the protocol violations identified among these two responders, this reviewer determined that the protocol violations did not likely impact the efficacy assessment of response or the overall results of the study given that the primary efficacy endpoint was ORR assessed by blinded independent central review.

Reviewer Comment: Given that the assessment of response was by central radiology review and no single clinical site had a large portion of responders, no specific site was identified. Additionally, (b) (4), the CRO that performed the central radiology review CRO had been reviewed several times within the last 3 years with no significant finding. Therefore, , a Bioresearch Monitoring inspection was not required. Overall, this clinical reviewer did not identify concerns with the quality of the data or potential significant financial conflicts of interest for any investigator.

3.2 Compliance with Good Clinical Practices

The Applicant included the following statement in the supplemental BLA submission: “The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice (GCP) standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.”

3.3 Financial Disclosures

In accordance with 21 CFR 54, the Applicant submitted a list of study clinical investigators and sub-investigators for KEYNOTE-059 (module 1.3.4, Table 1), Form FDA 3454, and the Due Diligence Form FDA 3455. According to Merck, the clinical investigators provided certification indicating that they held no financial interests or arrangements that required disclosure per the criteria described on Form 3454. The following cases were exceptions:

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

- One investigator in clinical site 0141 did not provide the certification despite due diligence (characterized as 3 attempts) on the Applicant's part to obtain this information.
- One investigator, in site (b) (6) held financial interest and/or arrangements (Type/Amount: Grant of \$1,487,485.00 in a contract with (b) (6)) that required disclosure per criteria described on Form 3455. The grant payment was made to the Institution for research with pembrolizumab for which the investigator was listed at the primary investigator.

Reviewer comment: In both cases above, no patients who achieved partial or complete responses after treatment with pembrolizumab were enrolled in the respective clinical sites.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to the FDA Chemistry Review in the original BLA submission. No safety or efficacy concerns were identified during this review that related to Chemistry, Manufacturing, and Controls (CMC).

4.2 Clinical Microbiology

Refer to the FDA Microbiology Review in the original BLA submission. No safety or efficacy concerns were identified during this review that related to product quality from a microbiology standpoint.

4.3 Preclinical Pharmacology/Toxicology

No Pharmacology/toxicology data were included in this submission. Refer to the FDA Pharmacology/Toxicology Review in the original BLA submission for details regarding the preclinical evaluation.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Pembrolizumab is a humanized monoclonal antibody of the IgG4k isotype designed to bind to PD-1 and directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little, if any, PD-L1, a variety of cancers were demonstrated to express abundant levels of PD-L1, which is thought to contribute to inhibition of active T-cell immune surveillance of tumors. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity.

4.4.2 Pharmacodynamics

Refer to the FDA Clinical Pharmacology Review in the original BLA submission.

4.4.3 Pharmacokinetics

The Applicant has evaluated the pharmacokinetics (PK) of pembrolizumab using a population approach characterized by pooling PK data from several trials conducted in patients with melanoma and non-small cell lung cancer (NSCLC). The Applicant has previously stated that the PK profile of pembrolizumab is consistent across the indications for which pembrolizumab was approved at the time of the supplemental BLA submission (i.e., melanoma, previously treated or untreated NSCLC, and head and neck squamous cell carcinoma [HNSCC]). Refer to the FDA Clinical Pharmacology Review for details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The evidence to support the safety and efficacy of pembrolizumab for the proposed indication in this efficacy supplement is primarily based upon data from KEYNOTE-059. Table 3 lists the clinical trials included in this supplemental BLA.

Table 3. Studies Providing Evidence of Safety and Efficacy in BLA

Trial ID/Title	Design	Regimen/Schedule/Route	Primary endpoint(s)	n	Countries
Study providing primary evidence of efficacy and safety					
KEYNOTE-059 ^A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma	Non-randomized, open-label, multi-cohort study (Cohort 1)	200 mg IV Q3W	ORR by IRR Safety	259	Australia, Canada, Chile, Colombia, Estonia, France, Israel, Italy, Japan, Lithuania, Peru, Portugal, Romania, Russia, South Korea, UK, USA
Study providing supportive evidence of efficacy and safety					
KEYNOTE- 012 ^B A Phase Ib Multi-Cohort Study of MK-3475 in Subjects with Advanced Tumors	Non-randomized, open-label, multi-cohort study including cohort with gastric cancer (Cohorts D)	10 mg/kg IV Q2W (Cohort D)	ORR by IRR Safety	39	Israel, Japan, Korea, Taiwan, USA

Source: Reviewer Table. ORR= objective response rate; IRR= independent radiology review;

^AData cut-off date of January 16, 2017 and efficacy update with data cutoff date of April 21, 2017. ^BData cut-off date of April 26, 2016.

Refer to Section 5.3 for a description of the key features of KEYNOTE-059 and an abbreviated description of key differences between KEYNOTE-059 and KEYNOTE-012.

5.2 Review Strategy

A single clinical trial, KEYNOTE-059, supports Merck's request for approval for pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma (b) (4)

under the provisions of 21 CFR 610.41,

Data from Study KEYNOTE-012 (Cohort D) that evaluated gastric cancer patients were considered supportive of the assessments of safety and efficacy in this application. Additionally, as appropriate, comparisons of the incidence and severity of adverse events in KEYNOTE-059 to the pembrolizumab Reference Safety Dataset were made to support the assessment of safety in the context of this supplemental BLA.

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)
5.2.1. Efficacy Review

The clinical review of efficacy included primary analyses using the clinical datasets to supplement and/or confirm the Applicant's results as reported in the Clinical Study Reports (CSR) for KEYNOTE-059 and KEYNOTE-012, the Integrated Summary of Efficacy (ISE), and the Summary of Clinical Efficacy (SCE) (data cut-off date : January 16, 2017). As agreed upon during the pre-BLA meeting, an efficacy update was submitted (data cut-off date: April 26, 2017) during the review of the submission and is the basis for the final analyses of duration of response to ensure a 6 months' or longer follow-up for patients who achieved responses.

The JMP statistical software was used to conduct analyses of the clinical datasets. The results of select analyses by the Biometrics reviewer using the SAS software were reviewed and included in the relevant sections of this review, as appropriate. Select results of the analyses conducted as part of the review of the Dako PDL1 IHC 22C3 pharmDx Kit companion diagnostic device were also included in this review.

Additionally, an extensive literature review was conducted using PubMed to assess current treatments for advanced gastric cancer.

5.2.2. Safety Review

As with efficacy, the review of clinical safety relies primarily upon data from KEYNOTE-059 based on a data cut-off date of January 16, 2017. The evaluation of safety is based upon incidence of adverse events (AEs) and laboratory values graded according to NCI CTCAE, version 4.0, and observed during treatment with pembrolizumab (i.e., from the first dose of pembrolizumab until treatment was stopped), and up to 30 days after last dose was administered (up to 90 days for serious adverse events). Primary analyses of the clinical safety datasets comprised the safety evaluation to supplement or confirm the Applicant's findings as reported in the CSR and SCS for KEYNOTE-059. As relevant, select patient narratives and case report forms (CRFs) were also reviewed. Adverse events were analyzed irrespective of attribution or relatedness to the investigational agent.

The results of the analyses of the data from KEYNOTE-059 data were compared to the safety findings of KEYNOTE-012, Cohort D (data cut-off date of April 26, 2016) which enrolled 39 patients with advanced gastric or gastroesophageal adenocarcinoma, or with the pembrolizumab Reference Safety Dataset which consists of pooled data from four clinical studies evaluating pembrolizumab for the treatment of melanoma and non-small cell lung cancer (NSCLC), and which comprised the first and second approved indications for pembrolizumab, respectively. According to Merck, this dataset reflects the established safety profile for pembrolizumab and it is consistent with the cumulative safety dataset for this product.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

All analyses of demographics, adverse events, vital signs, laboratory parameters, medical history, and concomitant medications excluded screen failures. The JMP statistical software was used to conduct analyses of the clinical datasets.

5.3 Discussion of Individual Studies/Clinical Trials

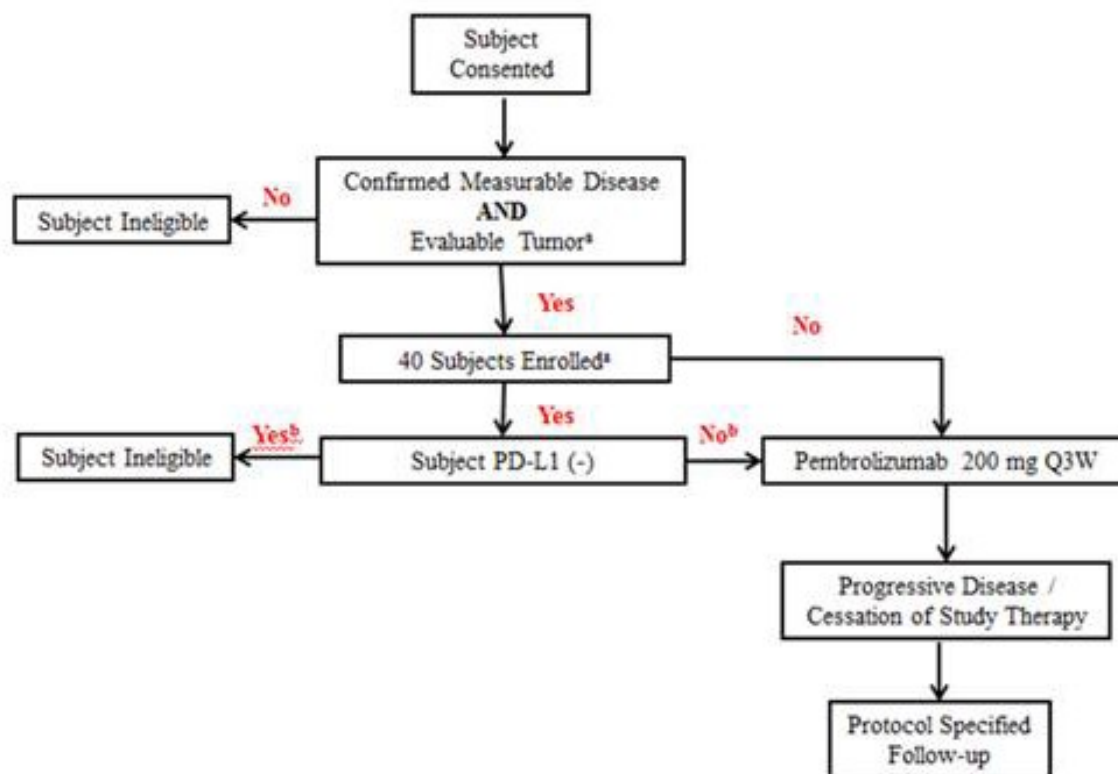
5.3.1 KEYNOTE- 059

Design:

KEYNOTE-059 is an ongoing open-label multi-center trial evaluating the safety and efficacy of pembrolizumab 200 mg administered intravenously once every three weeks in patients with gastric or gastroesophageal junction adenocarcinoma (gastric cancer). Patients are assigned in a non-random fashion to one of three cohorts to evaluate pembrolizumab as a monotherapy (Cohorts 1 and 3) or in combination with chemotherapy (Cisplatin plus Fluorouracil (5-FU) (Cohort 2). Cohort 1 (heretofore referred to as the 'study', or the 'trial') provides the data to support this supplemental BLA and will be described in detail in this section. The trial design schematic for Cohort 1 is shown Figure 2 below.

Initially, patients were enrolled irrespective of tumor PD-L1 status and the study team was blinded to this information until the time of a protocol- pre-specified interim analysis for futility of patients with PD-L1 negative tumors. During the interim analysis period, enrollment of patients with PD-L1- negative tumors was halted while enrollment of patients with PD-L1 positive tumors continued. Following the interim analysis, the study team was unblinded to information regarding PD-L1 status.

Clinical Review
 Lola Fashoyin-Aje
 BLA 125514 (Supplement 24)
 KEYTRUDA® (pembrolizumab/ MK- 3475)
Figure 2. Trial Design- KEYNOTE-059 (Cohort 1)



a. Subjects may be either PD-L1 positive or negative

b. If the response rate in PD-L1 negative subjects (from the first ~40 subjects enrolled) does not meet futility criterion, subjects that are PD-L1 negative may continue to be enrolled.

Source: Clinical Study Report (CSR) p86.

Study Population

The eligible patient population for Cohort 1 met the following key inclusion and exclusion criteria, modified for brevity:

Inclusion Criteria

1. Male/female with gastric or gastroesophageal junction adenocarcinoma of at least 18 years of age.
2. Presence of histologically or cytologically-confirmed recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma that is considered incurable by local therapies.
3. Evidence of disease progression on at least 2 prior chemotherapy regimens. Previous therapy regimens must have included a fluoropyrimidine and platinum

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

doublet (as part of either a line of therapy or adjuvant therapy) (Note: perioperative, neoadjuvant, adjuvant chemotherapy regimens were not considered prior regimens, unless the patients had progressed while receiving adjuvant therapy or within 6 months of receiving adjuvant treatment. In addition, the date of progression and how progression was determined must have been known with documentation available confirming progression on or after treatment).

4. Patient is HER-2/neu negative, or, if HER-2 positive, has previously received therapy with trastuzumab (Note: if HER-2/neu status was previously determined, that result was acceptable but documentation of status must have been available; patients with unknown status had their HER-2/neu status determined locally. Documentation of previous therapy with trastuzumab was provided).
5. Patient willingness to provide newly-obtained or archived tissue for PD-L1 biomarker analysis and, based on the adequacy of the tissue sample quality for assessment of PD-L1 status. Newly-obtained tissue will be from the stomach and/or gastroesophageal junction (endoscopic tumor biopsy) or a metastatic location IF obtained as part of normal clinical practice. Repeat samples may be required if adequate tissue is not provided.
6. Presence of adequate tissue for retrospective assessment of PD-L1 status was required.
7. Presence of measurable disease based on RECIST 1.1 as determined by central imaging vendor. (Note: previously irradiated lesions were considered measurable if progression has been demonstrated in such lesions).
8. Presence of ECOG performance status of 0 or 1.
9. Life expectancy of at least 3 months.
10. For female patients of childbearing potential, willingness to use 2 methods of birth control, abstinence from heterosexual activity for the course of the study through 120 or 180 days after the last dose of study medication, or presence of surgical sterilization. Duration of use will be determined when the subject is assigned to treatment. (Note: Patients of childbearing potential were defined as those patients who were not surgically sterilized or had not been free from menses for > 1 year).

For male patients, agreement to use an adequate method of contraception starting with the first dose of study therapy through 120 or 180 days after the last dose of study therapy. Duration will be determined when the patient is assigned to treatment.

Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)

11. Adequate organ function as defined by the following:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1,500$ /mcL
Platelets	$\geq 100,000$ / mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L without transfusion or EPO dependency
Renal	
Creatinine OR Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) OR ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN Cisplatin product label should be followed for acceptable creatinine clearance rates for subjects in Cohort 2 (combination treatment) <i>Notes: Creatinine clearance should be calculated per institutional</i>
Hepatic	
Total bilirubin	≤ 1.0 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Albumin	≥ 3.0 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy

Source: Copied from Clinical Study Report.

12. For female patients of childbearing potential, presence of a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or could not be confirmed as negative, a serum pregnancy test was required.

Exclusion Criteria

1. Weight loss > 10 % over 2 months prior to first dose of study therapy.
2. Clinical evidence of ascites by physical exam.
3. Current or prior receipt of study therapy or prior participation in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
4. Presence of active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) was not considered a form of systemic treatment.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

5. Presence of a diagnosis of immunodeficiency or use of systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids (prednisone 10 mg or equivalent) may be approved after consultation with the Sponsor.
6. Prior use of anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or unrecovered (i.e., presence of $\leq$ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
7. Prior use of chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or unrecovered (i.e., presence of $\leq$ Grade 1 or at baseline) from adverse events due to a previously administered agent
8. Presence of known additional malignancy that is progressing or requires active treatment, except basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
9. Presence of active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (i.e., without evidence of progression by imaging at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception did not include carcinomatous meningitis which was excluded regardless of clinical stability.
10. Known history of, or any evidence of active, non-infectious pneumonitis.
11. Presence of an active infection requiring systemic therapy.
12. History or current evidence of any condition (e.g. known deficiency of the enzyme dihydropyrimidine dehydrogenase), therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial (clinical or endoscopic evidence of tumor-related obstruction), or is not in the best interest of the subject to participate (e.g. any contraindication to the use of cisplatin, 5-FU, or capecitabine for patients in Japan, in the opinion of the treating investigator).
13. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Patient known to be pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 or 180 days after the last dose of trial treatment. Duration is determined by the cohort to whom the patient would be assigned.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

17. Has known chronic or acute Hepatitis B (e.g., HBsAg reactive) or Hepatitis C infection (e.g., HCV RNA [qualitative] is detected).

18. Has received a live vaccine within 30 days of planned start of study therapy.

Reviewer Comment: Of note, Amendment #7 was implemented to exclude patients who had >10% weight loss over 2 months prior to the first dose of trial treatment or if they had clinical evidence of ascites by physical examination as recommended by the external Scientific Advisory Committee to reflect the latest standards in oncology clinical trials.

Biomarker Assessment (PD-L1 Assessment and Microsatellite instability)

PD-L1 status was determined for the majority of patients using an investigational device exemption (IDE)-approved immunohistochemistry (IHC) assay. PD-L1 protein expression was determined by using the Combined Positive Score (CPS). The CPS method captures the sum of all PD-L1 membrane-stained cells at any intensity (tumor cells, macrophages, lymphocytes) in the tumor microenvironment over the total tumor cells present, expressed as a percentage. In KEYNOTE-059, a tumor sample was characterized as PD-L1 positive if the CPS expressed as a percentage was greater than 1%.

In response to an information request during the review of the application, Merck provided additional information regarding the protocol-specified process for evaluating tumor specimens for PD-L1 status, including requirements for processing times that may impact antigen stability. The FDA also requested that Merck provide patient-level data on tissue type used to ascertain PD-L1 status, tissue age, and slide cut time at the time of PD-L1 testing.

According to Merck's response, clinical sites submitted newly-obtained or archival specimens for PD-L1 immunohistochemistry testing. Information on specimen characteristics, including determination of whether a specimen was newly obtained or archival, was entered by each enrolling site and provided to the PD-L1 testing laboratory for entry into the database. A "newly-obtained" specimen is defined in the protocol's Subject Inclusion Criteria (Section 5.1.2) as follows:

Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1 (Cycle 1) and with no additional anti-cancer treatment having been given after the specimen was obtained. Newly obtained biopsy specimens are preferred to archived; however, subjects for whom newly-obtained tissue sample cannot be submitted (e.g. inaccessible or subject safety concern), an archived specimen may be submitted. Newly-obtained (FFPE block or tissue in formalin solution) or archived specimens are preferred to slides.

Microsatellite instability (MSI) testing was not conducted in a prospective fashion.

Clinical Review
 Lola Fashoyin-Aje
 BLA 125514 (Supplement 24)
 KEYTRUDA® (pembrolizumab/ MK- 3475)

Treatment

The protocol specified that for patients in Cohort 1, Pembrolizumab 200 mg was to be administered as a 30 minute intravenous infusion on Day 1 of every 3 week cycle. Patients received pembrolizumab until documented disease progression or for up to two years. Patients who achieved stable disease or better (i.e., complete or partial response) were eligible to receive up to one additional year of pembrolizumab if they experienced disease progression after completing the initial course, and had not received other therapies in the interim.

Reviewer Comment: According to the Merck, the dose of pembrolizumab that was evaluated in KEYNOTE-012 and which demonstrated preliminary evidence of anti-tumor activity was 10 mg/kg administered every 2 week (Q2W). More recent studies in other tumor types have indicated that the 10 mg/kg Q2W and 200 mg Q3W, which was evaluated in KEYNOTE-059, are comparable with regard to efficacy and tolerability. The 200 mg Q3W dose was selected as an appropriate dose for fixed dosing based upon simulations performed using the population PK model of pembrolizumab which indicate that the fixed dose of 200 mg Q3W provides exposures that 1) are consistent with those obtained with the 2 mg/kg dose Q3W, 2) maintain individual patient exposures in the exposure range established in melanoma to be associated with maximal efficacy response, and 3) maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

Dose Modifications and Supportive Care Guidelines

Dose reductions of pembrolizumab were not permitted. However, pembrolizumab could be withheld or discontinued for drug-related toxicities or severe or life-threatening adverse events. The protocol-specified guidelines for pembrolizumab-related adverse events are listed in Table 4 below.

Table 4. Dose Modification^A Guidelines for Drug-Related^B Adverse Events

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 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when subjects are clinically and metabolically stable.

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
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	2 ²	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	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 or recurrent Grade 2	Permanently discontinue	Permanently discontinue
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	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
Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event. ¹ For subjects 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 then subjects should be discontinued ² If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose ³ Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study treatment has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose			

Source: Adapted from final protocol (December 15, 2016) in CSR p.1038; ^APembrolizumab dose reductions were not permitted; ^BAttribution to pembrolizumab based on Investigator assessment.

The protocol also specified that an investigator could, at his/her discretion, implement dose modifications for intolerable Grade 2-3 toxicities that were not specified in the guidelines.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

Study Monitoring/Assessments

Clinical and laboratory assessments were conducted at protocol- specified times as shown in Table 5. These included physical examinations, vital signs assessments, assessment of Eastern Cooperative Oncology Group (ECOG) Performance Status.

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)

Table 5. Protocol-specified Schedule of Clinical Assessments

Trial Period:	Screening	Treatment Cycles ^a (3 weeks per cycle)						End of Treatment (last dose) or Discontinuation	Post-Treatment		
Treatment Cycle/Title:	Visit 1	1	2	3	4	To be repeated beyond 6 cycles			Safety Follow-up (30 days from last dose)	Follow Up Visits ^b	Survival Follow-up (Phone)
						5	6				
Scheduling Window (Days):	-28 to -1		± 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 Physical Examination	X							X			
Directed Physical Examination		X	X	X	X	X	X				
Ht (V1 only), Wt, & Vital Signs (T/P/RR/BP)	X	X	X	X	X	X	X	X			
ECOG Performance Status	X ^q		X	X	X	X	X	X			
Trial Treatment Administration ^p		X	X	X	X	X	X				
Post-study Anticancer Therapy Status										X	Q12 wks
Survival Status											Q12 wks
LOCAL Laboratory Assessments											
Pregnancy Test – Urine or Serum □-HCG ^d	X										
PT/INR and aPTT ^e	X										
Chemistry Panel ^{e,f}	X		X	X	X	X	X ^f	X	X		
CBC with Differential ^{e,g}	X		X	X	X	X	X ^g	X	X		
T3, FT4, and TSH ^{e,h}	X		X		X		X, then Q2 cycles		X		
Serum carcinoembryonic antigen (CEA) ^{e,i}	X			X		X	X	X			
Urinalysis ^e	X										
CENTRAL Laboratory Assessments											
Pharmacokinetics ^j & Anti-Drug Antibodies ^j		X	X		X	Q 4 cycles (8, 12, 16....)			X	X	
Blood for Future Biomedical Research ^c		X									
Blood for Proteomics and Genetics ^k		X									
Blood for RNA and DNA Analysis ^k		X	X	X				X			

Source: Copied (modified for brevity) from Final Protocol in CSR p. 1054

The safety of pembrolizumab was evaluated based upon reported adverse events that occurred, regardless of causality, from the time of treatment allocation through 30 (non-serious AEs) or up to 90 (for SAEs, events of clinical interest) days following cessation of pembrolizumab. Adverse event severity was assessed using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0).

Reviewer comment: The clinical assessment methods and time points described in the protocol of KEYNOTE-059 appear adequate to assess safety for the population, disease, and indication being investigated.

Efficacy Endpoint(s)/ Planned Analysis

The protocol specified that all patients in Cohort 1 who received at least one dose of pembrolizumab would be included in the efficacy and safety analysis population. The primary efficacy endpoint is objective response rate (ORR) per RECIST version 1.1., as assessed by central radiologic review.

The secondary efficacy endpoints were:

- Duration of response (DoR), defined as the time from first documented evidence of response until disease progression or death due to any cause, whichever occurs first among patients who achieve a CR or PR;
- Disease control rate (DCR) defined as the proportion of patients who achieved stable disease (SD), PR, or CR for 2 or more months;
- Progression free survival (PFS), defined as the time from the date of the first dose of study medication to the first documented disease progression or death; and,
- Overall survival (OS) defined as the time from the date of the first dose of study medication to death due to any cause, were additional secondary efficacy endpoints.

The assessment of response and disease progression was provided by an external independent imaging vendor, (b) (4)

The protocol specified that the ORR with a 95% confidence interval would be calculated using the Exact method based on binomial distribution; PFS and OS would be summarized using the Kaplan-Meier (KM) method; and KM curves and median estimates from these KM curves for duration of response would be calculated.

The study included one pre-specified interim analysis for futility of patients with PD-L1 negative tumors to be performed when approximately 40 patients were evaluable for a response assessment. The purpose of the interim analysis was to determine the futility of treatment of patients with PD-L1-negative tumors. The Applicant estimated that approximately 25 patients with PD-L1 negative tumors would be included in this interim

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

analysis. According to the protocol, the futility criterion would be met if the upper bound of the 95% confidence interval of ORR was less than 20% for patients with PD-L1 negative tumors (i.e., consisting of one or fewer responses out of 25 patients). If the futility criterion was met, then enrollment of patients with PD-L1 negative tumors would not be resumed.

The results of this analysis were to be reviewed by an external data monitoring committee, and provided by the external unblinded statistician to the Data Monitoring Committee (DMC). The protocol specified that the DMC would serve as the primary reviewer of the results of the interim analysis and would make recommendations regarding whether to resume enrollment of PD-L1 negative subjects in Cohort 1 to the Sponsor (Merck).

The final analysis was to be conducted when 80 or more patients (irrespective of tumor PD-L1 status) who met the post-interim analysis eligibility criteria had received a minimum of 6 months of pembrolizumab or discontinued pembrolizumab due to progression of disease. Refer to FDA Biometrics Review for additional details.

Tumor assessments occurred at Week 9 and then every 6 weeks for the first year, and every 9 weeks during the second year of treatment.

Summary of Key Protocol amendments (KEYNOTE-059) Relevant to Cohort 1

Amendment #2:

Changes to dose modifications and supportive care guidelines made to align with the current guidance in approved pembrolizumab product labeling.

Amendment #3

Protocol amended to remove the quality of life (QoL) assessments (i.e., EORTC QLQ-C30, EORTC QLQ-ST022) given the limitations of evaluating patient reported outcomes in this single-arm cohort study.

Amendment #7 (November 4, 2015):

Protocol amended for the following reasons:

- Inclusion/exclusion criteria were changed based on recommendation of external scientific advisory committee to update the eligibility criteria to 'reflect latest standards in oncology clinical trials and to ensure that patients could complete the study'. The eligibility criteria were revised as follows:
 - Include requirement for ECOG 0 or 1 performance status
 - Include requirement for albumin ≥ 3.0 g/dL
 - Include requirement for total bilirubin ≤ 1.0 ULN
 - Exclude patients with weight loss $> 10\%$ in the 2 months prior to first dose of study drug
 - Exclude patients with clinical evidence of ascites by physical exam

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

- Sample size was increased from 180 to approximately 210 to reflect the External Data Monitoring Committee's recommendation to resume enrolling patients irrespective of PD-L1 status after a pre-specified futility analysis for PD-L1 negative patients was not observed; The sample size determination was made to ensure that a minimum of 80 'all comer' patients meeting the revised eligibility criteria were enrolled.
- Modified the study's objective to remove statistical hypothesis testing and state that the objective of the study is estimation of response and the success of the study is determined by clinically meaningful ORR and durability of the response.
- Analysis of health related quality of life (HRQoL) was removed.
- Updated censoring rules for duration of response.

Reviewer comment: The final enrollment number (n = 259) was higher than the required sample size due to an extended one-month enrollment period to allow for a sufficient number of patients to be enrolled in Japan and due to higher than expected enrollment rates at other sites during the last 2 weeks of enrollment.

Reviewer comment: FDA requested a sensitivity analysis of the subgroups of the first 180 patients enrolled and the first 210 patients enrolled (the sensitivity analysis included 213 patients enrolled up to amendment 7 as there were three additional patients enrolled on the same date as the 210th patient) compared with the overall population of 259 patients.

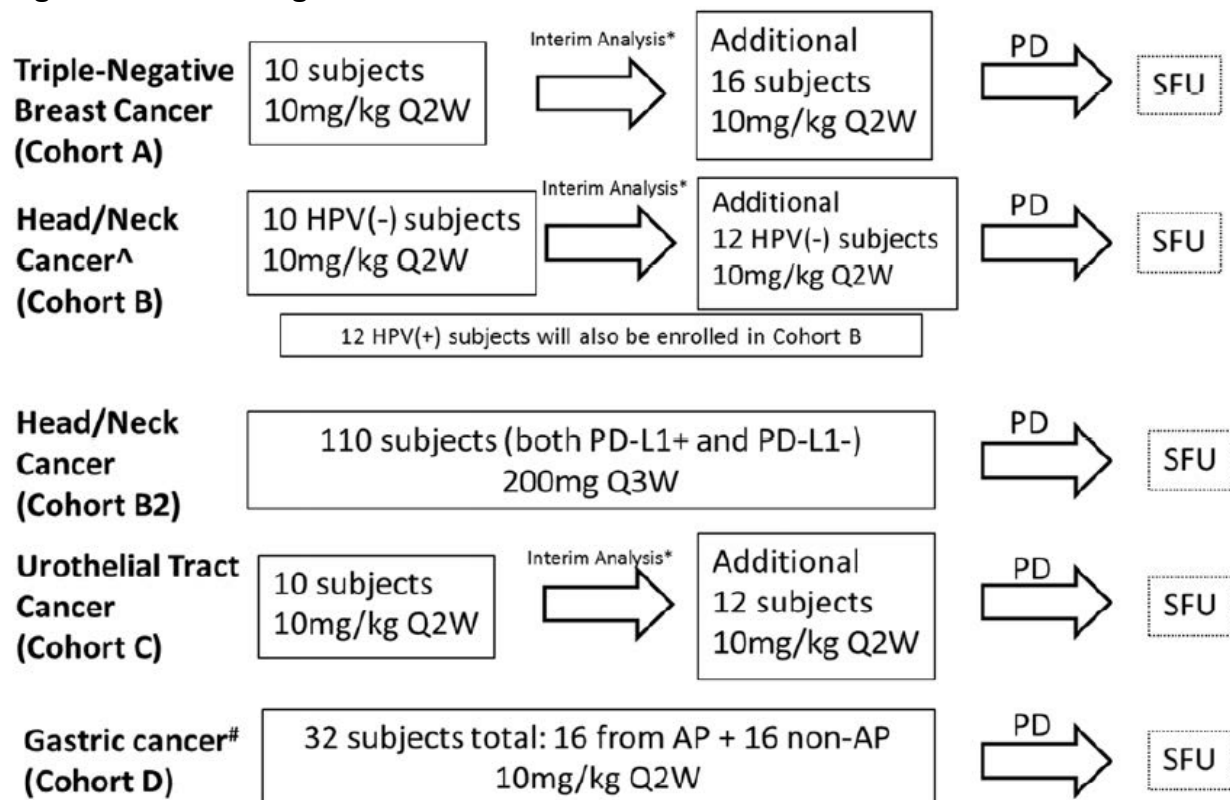
Amendment #9 (December 20, 2016)

Protocol amended to include recurrent Grade 2 pneumonitis as a reason for pembrolizumab discontinuation. This change was made to be consistent with the overall pembrolizumab program.

5.3.2 KEYNOTE-012

KEYNOTE-012 is a single-arm, open-label, multi-cohort, study of pembrolizumab monotherapy in patients with advanced solid tumors. The study was initially designed to assess the activity and safety of pembrolizumab 10 mg/kg administered every 2 weeks (Q2W) in 5 cohorts of patients with PD-L1-positive tumors: triple-negative breast cancer (Cohort A), head and neck squamous cell carcinoma (HNSCC) (Cohort B and Cohort B2), urothelial tract cancer (Cohort C), and Cohort D in patients with adenocarcinoma of the stomach or gastroesophageal junction whose tumors are PD-L1 positive. A schematic of the KEYNOTE-012 is shown below.

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)
Figure 3. Trial Design: KEYNOTE-012



*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

Source: Copied from Clinical Study Report, p31.

The primary objectives of KEYNOTE-012 relevant to the evaluation of patients with gastric cancer, were to determine the safety and tolerability of the 10 mg/kg Q2W dose of pembrolizumab in patients with PD-L1-positive advanced solid tumors enrolled in Cohorts A, B, C, and D, and to evaluate the anti-tumor activity of the 10 mg/kg Q2W dose of pembrolizumab in patients with PD-L1-positive advanced solid tumors enrolled in Cohorts A, B, C, and D based on the ORR per RECIST 1.1 assessed by independent central radiology review.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

Both KEYNOTE-012 (Cohort D) and KEYNOTE-059 (Cohort 1) enrolled patients with locally advanced or metastatic gastric cancer or GEJ adenocarcinoma. The key study design differences between these studies were:

- Prior therapies: KEYNOTE-059 (Cohort 1) enrolled only patients with at least two prior lines of systemic therapy (3L+). The patient population had approximately equal proportions of patients receiving third line (3L) treatment (51.7%) and those receiving four or more line (4L+) treatment (48.3%). KEYNOTE-012 (Cohort D) had no requirement specifying the number of prior therapy. As such, a total of 65.7% of the 39 patients enrolled had received 3 or more prior therapies (3L+) treatment while the remainder had received 0-2 prior therapies.
- PD-L1 status: KEYNOTE-059 (Cohort 1) did not require patients to have PD-L1 positive tumors as an eligibility criterion whereas KEYNOTE-012 did.
- Prior Her-2-neu treatment: KEYNOTE-059 (Cohort 1) required patients with HER-2 positive tumors (23.6%) to have previously received trastuzumab.

Patients who enrolled in KEYNOTE-012 Cohort D received pembrolizumab 10 mg/kg intravenously every 2 weeks while patients in KEYNOTE-059 Cohort 1 received pembrolizumab 200 mg intravenously every 3 weeks.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Merck's proposed indication in the current supplemental BLA is as follows:

"Pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma" (b) (4)

6.1.1 Methods

The primary evidence of efficacy in this application is based on data from the single-arm, multi-cohort, open-label, multi-center study KEYNOTE-059 (Cohort 1) which enrolled 259 patients with recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER-2/neu targeted therapy. Patients received pembrolizumab 200 mg every 3 weeks. The efficacy population includes all allocated patients who received at least one dose of pembrolizumab.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

The primary endpoints were the objective response rate (ORR) per RECIST 1.1 assessed by central imaging vendor for all patients and in patients with PD-L1 positive tumors. Patients in the efficacy population who did not have ORR data were counted as non-responders.

Reviewer Comment: Given the limitations inherent with the study's single arm design and small sample size, which limit the ability to reliably interpret time-to-event endpoints such as overall survival and progression-free survival, analyses of these secondary endpoints are not considered in the assessment of clinical benefit in this application. The objective response rate (ORR) and the durability of response will be the sole basis for the determination of pembrolizumab's efficacy for this supplemental BLA.

Given the recent approval of pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-high/dMMR solid tumors, some analyses were conducted excluding patients with MSI-high from the analysis population.

6.1.2 Demographics

Patients who were enrolled in KEYNOTE-059 (Cohort 1; n=259) were predominantly White (81%), male (76%), and less than 65 years of age (57%). A majority of patients (48%) were enrolled in the US, while the most common sites (>5%) for enrollment outside the US were Japan (13%), France (5%), Israel (5%), and Australia (5%).

Table 6. Demographics Characteristics (n=259)

Demographic Parameter	n	%
Age group		
<65	148	57
≥65	111	43
≥80	8	3
Age (years)		
Median	62	
Range	24-89	
Sex		
Female	61	24
Male	198	76
Race		
Asian	41	16
Black/African American	5	2
White	200	77
Missing	11	4
Multiple	2	<1
Ethnicity		
Hispanic/Latino	17	7
Not Hispanic/Latino	228	88
Not Reported/Missing/Unknown	14	5
Geographic Region		
United States	124	48
Ex-United States	135	52

Source: Reviewer Table; ADSL Data cut-off date January 16, 2017.

Reviewer Comment: Blacks or African American patients were not well represented (n=5). All five patients were enrolled in the US. Patients with Hispanic/Latino ethnicity were also not well-represented in the study, accounting for 17 (7%) of the total population enrolled. A total of 14 of these 17 were enrolled outside the US, mostly in Chile (n=10) while a total of 15 of the 17 patients reported race as 'White' while two patients who reported 'Hispanic/Latino' ethnicity were reported as RACE= 'Multiple.'

Table 7. Baseline Characteristics KEYNOTE-059 (n=259)

Baseline Parameter	n	%
ECOG		
0	107	41
1	151	58
2	1	<1

Clinical Review
 Lola Fashoyin-Aje
 BLA 125514 (Supplement 24)
 KEYTRUDA® (pembrolizumab/ MK- 3475)

Baseline Parameter	n	%
Locoregional vs distant metastases		
M0	16	6
M1	222	86
Mx	21	8
Brain metastases		
Yes	4	2
No	255	98
PD-L1 Status		
Positive	148	57
Negative	109	42
Unknown	2	<1
Microsatellite Status		
MSI-high	7	3
MSS	167	64
Missing	85	33
HER 2 status		
Positive	63	24
Negative	194	75
Intermediate	2	<1
Histology		
Tubular adenocarcinoma	243	94
Signet-ring cell carcinoma	7	3
Other poorly cohesive carcinoma	5	2
Mixed carcinoma	3	1
Prior surgery for gastric cancer		
Yes, total gastrectomy	49	19
Yes, partial gastrectomy	16	6
Yes, other	1	<1
No	193	75

Source: Reviewer Table; ADSL; Data cut-off date January 16, 2017.

The table below summarizes the specific prior treatments received by patients enrolled in KEYNOTE-059.

Table 8. Summary of Prior Treatments (n=259)

	n	%
Number of prior lines of therapy		
2	134	52
3	75	29
4	35	14
≥5	15	6
Prior 5 FU		
Yes	259	100

	n	%
Prior capecitabine		
Yes	123	47
No	136	53
Prior S1*		
Yes	28	11
No	231	89
Prior Platinum		
Yes	259	100
Prior Taxane		
Yes	217	84
No	42	16
Prior Irinotecan		
Yes	116	45
No	143	55
Prior Her 2 neu antibody		
Yes	61	24
No	198	76
Prior VEGF/VEGFR antibody		
Yes	107	41
No	152	59
Prior EGFR antibody		
Yes	5	2
No	254	98
Prior Anthracycline		
Yes	70	27
No	189	73
Prior MET antibody		
Yes	5	2
No	254	98
Prior Investigational Drug		
Yes	95	37
No	164	63
Prior other chemotherapy		
Yes	11	4
No	248	96

Source: Reviewer Table; ADSL; Data cut-off date January 16, 2017.

* S-1 is an oral fluoropyrimidine that is not FDA- approved.

Reviewer comment: The analysis of baseline characteristics by PD-L1 status and excluding patients who were MSI-high did not reveal any major differences compared to results shown in Table 7 and Table 8.

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)
6.1.3 Subject Disposition

KEYNOTE-059 was ongoing at the time of the supplemental BLA submission. Patients were enrolled from March 2, 2015 to May 26, 2016 from 52 clinical sites in North America, Europe, Australia, Asia, and South America. A total of 259 patients received at least one dose of study drug. As previously stated, patients were initially enrolled irrespective of their tumor PD-L1 status. During a protocol-specified interim analysis conducted for futility of patients with PD-L1 negative tumors, enrollment of patients with PD-L1 negative tumors was halted while enrollment continued for patients with PD-L1 positive tumors. According to the Applicant, during this interim analysis, a total of 33 patients with PD-L1 positive tumors were enrolled; two patients with PD-L1 negative tumors were also enrolled prior to a system update implemented to manage PD-L1 positive status eligibility requirements for Cohort 1. The DMC determined that the futility criteria were not met and enrollment of patients with PD-L1 negative tumors resumed on October 28, 2015.

The submission of the supplemental BLA was based on a data cut-off date of January 16, 2017. As agreed upon during the pre-BLA meeting, Merck Applicant submitted an efficacy update on June 21, 2017 reflecting a data cut of date of April 21, 2017. Study and treatment disposition is summarized in Table 9.

Table 9. Study and Treatment Disposition of Patients in KEYNOTE-059: (n=259)

Disposition Parameter	Original		Update	
	259	100%	N=259	100%
Reason for Study discontinuation	188	73	208	80
Death	153	59	182	70
Clinical progression	4	2	1	<1
Adverse event	12	5	10	4
Withdrawal by subject	14	5	11	4
Physician decision	3	1	3	1
Protocol violation	1	<1	1	<1
Progressive disease	1	<1	-	-
Reason for treatment discontinuation	231	89	235	91
Progressive disease	143	55	146	56
Death	26	10	28	11
Clinical progression	25	10	25	10
Adverse event	20	8	17	7
Withdrawal by subject	12	5	13	5
Physician decision	3	1	3	1
Protocol violation	2	1	2	1
Complete response	-	-	1	<1
Completed ^A	-	-	1	<1
Treatment ongoing	28	11	23	9

Source: Reviewer Table; ADSL- Efficacy (original submission data cut-off date January 16, 2017); ADSL- Efficacy Update data cut-off date is April 21, 2017. ^ACompleted 35 cycles of treatment and discontinuation visit.

A majority of patients discontinued treatment as a result of progressive disease (56%), clinical progression (10%), and death (11%). A total of 23 patients (9%) were still receiving pembrolizumab treatment at the time of the efficacy update.

6.1.4 Analysis of Primary Endpoint(s)

The protocol specified primary efficacy endpoint was the objective response rate (ORR) per RECIST 1.1 as assessed by the central imaging vendor for all patients and in patients with PD-L1 positive tumors. ORR was defined as the proportion of patients who received at least one dose of pembrolizumab and who achieved a partial or complete response by RECIST 1.1 as assessed by independent central radiology review.

In this application, the determination of response is based on patients who were identified as responders in the original submission of this supplemental application based on a data cut-off date of January 16, 2017 (*i.e.*, any 'new' responders or responders whose response category was updated from PR to CR based on the efficacy update are not included in the population of responders in the analysis of ORR).

Overall, the median follow-up duration of follow-up for patients enrolled in KEYNOTE-059 (Cohort 1) was 5.6 months (range: 0.5 to 24.7). Follow-up duration was defined as the time from first dose of pembrolizumab to the time of death or the data cutoff date, if the patient was still alive. The results of the analysis of the primary endpoint are shown in Table 10 below.

Table 10. Results of Response Evaluation: KEYNOTE-059 (n=259)

Parameter	All Patients	PD-L1 +	PD-L1 -
	N= 259*	N= 148	N= 109
	n(%)	n(%)	n(%)
ORR	30 (11.6)	23 (15.5)	7 (6.4)
95% CI	(8.0, 16.1)	(10.1, 22.4)	(2.6, 12.8)
CR	6 (2.3)	3 (2.0)	3 (2.8)
PR	24 (9.3)	20 (13.5)	4 (3.7)

Source: Reviewer Table. Data cut-off date of January 16, 2017; *Two patients with unknown PD-L1 status are included in total

A total of 148 patients (57%) had PD-L1 positive tumors, 109 patients (42%) had PD-L1 negative tumors, and 2 patients (1%) had unknown PD-L1 status. The ORR among patients with PD-L1 positive and PD-L1 negative tumors was 15.5% (95% CI: 10.1, 22.4) and 6.4% (95% CI: 2.6, 12.8), respectively. A total of 7 patients among the 259 patients achieve complete responses, including three patients among the subgroup of patients whose tumors tested negative for PD-L1.

Reviewer Comment: The observed estimate of the ORR is numerically higher in patients with PD-L1 positive tumors compared to patients with PD-L1 negative tumors.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

These results should be interpreted with caution given the small numbers of patients and the overlapping confidence intervals. Based upon the results of KEYNOTE-059, seven patients with PD-L1 negative tumors achieved responses including three who had complete responses. While it is recognized that there may be several drivers of response to checkpoint inhibitors beyond MSI-high and PD-L1 status, the observation of three patients with complete radiographic response among the subgroup of patients with PD-L1 negative tumors, may highlight uncertainty regarding falsely negative PD-L1 assessments among patients whose PD-L1 assessment is based upon the use of archival tissue.

An additional consideration for this application is the impact of MSI-high patients on the observed response rate. An analysis that excludes patients known to be MSI-high is shown below.

Table 11. Results of Response Evaluation: KEYNOTE-059 (n=252)

Parameter	ALL ^{A,B}	PD-L1 + ^B	PD-L1 - ^B
	N= 252	N= 143	N= 109
	0 (%)	n(%)	n(%)
ORR	26 (10.3)	19(13.3)	7(6.4)
95% CI	(6.9, 14.8)	(8.2, 20.0)	(2.7, 13.0)
CR	5 (2.0)	2 (1.4)	3 (2.8)
PR	21 (8.3)	17 (11.9)	4 (3.7)

Data cut-off date of January 16, 2017; ^ATwo patients with unknown PD-L1 status are included in total. ^BExcludes MSI-high patients.

Reviewer Comment: The analysis above did not exclude those patients in whom microsatellite instability was not tested (n= 85). However, given the low rate of MSI-high patients in KEYNOTE-059 among those patients who were retrospectively tested, it is not expected that a high proportion of patients with unknown MSI status were in fact MSI-high.

Reviewer Comment: Note that when patients with MSI-high are excluded from the ORR assessment, the lower bound of the 95% confidence interval is less than 10% which is lower than the ORR observed in the Kang et al study. However, the study enrolled a less heavily pre-treated patient population with 73% having received only 1 prior systemic regimen. [8]

6.1.5 Analysis of Secondary Endpoints(s)

Duration of Response (DoR)

The median follow-up duration among patients who achieve partial or complete responses (responders) was 13.9 months (range: 5.6 to 24.7). The analysis of DoR based on a data cut-off date of April 21, 2017 for the 30 patients identified as responders based on a data cut-off date of January 16, 2017, is shown in the table below.

Table 12. Duration of Response KEYNOTE-059 (n=259)

	All Patients N= 259*	PD-L1 + N=148	PD-L1- N= 109
Median Response Duration in months (range)	14.2 (2.4, 19.4+)	14.2 (2.8+, 19.4+)	NR (2.4, 10.3+)
Patients with DoR ≥ 6 months	18 (60%)	14 (61%)	4 (57%)
Patients with DoR ≥12 months	6 (20%)	6 (26%)	0

Note: Response duration based on data cut-off date of April 21, 2017. Median follow-up time was 13.9 months (range: 5.6 to 24.7). Includes *2 patients with unknown PD-L1 status.

A total of 13 (43%) of the responders were on study treatment at the time of data cut-off and none of these patients had evidence of progression at the last radiologic assessment as shown in the table below.

Table 13. Responder Disposition at Data Cut-off (n=30)

	n	%
On study treatment	13	43
Documented progression	12	40
Discontinued from study treatment	3	10
Death	1	<1
PD or death after ≥ 2 missed assessments	1	<1

Source: Reviewer Table; ADTTE Efficacy Update data cut off April 21, 2017

The results of the DoR analysis that excluded patients with MSI-high are shown below.

Table 14. Duration of Response KEYNOTE-059 (n=252)

	All Patients N= 252*	PD-L1+ N=143	PD-L1- N= 109
Median Response Duration in months (range)	14.2 (2.4, 19.4+)	14.2 (2.8+, 19.4+)	NR (2.4, NR)
Patients with DoR ≥ 6 months ^A	15 (58%)	11 (58%)	4 (57%)
Patients with DoR ≥12 months ^A	5 (19%)	5 (26%)	0

Source: Reviewer table. Response duration based on data cut-off date of April 21, 2017.

*Includes two patients with unknown PD-L1 status. ^ABased on numerical proportions.

6.1.6 Other Endpoints

ORR Based on Microsatellite status

Among the 259 patients enrolled in KEYNOTE-059 (Cohort 1), microsatellite expression was retrospectively tested in 174 patients who had matching tissue and blood samples available. A total of 7 patients (3%) were microsatellite instability (MSI) high, 167 (64%) were microsatellite stable (MSS). A total of 85 patients (33%) were not assessed (unknown) for microsatellite instability. Among the seven MSI-high patients, 4 achieved responses (57%). All 4 patients who achieved responses also had PD-L1 positive tumors.

Table 15. ORR by Microsatellite Status; KEYNOTE- 059- (n=259)

Subgroup	n	%	95% CI
MSI-high patients, n=7	4	57.1	(18.4, 90.1)
MSS + microsatellite Unknown, n= 252	26	10.3	(6.9, 14.8)
MSS, n= 167	15	9.0	(5.1, 14.4)
Microsatellite unknown, n= 85	11	12.9	(6.6, 22.0)

Source: Reviewer Table. Data cut-off date of January 16, 2017.

Reviewer Comment: Emerging evidence from other tumor types suggests that patients with tumors displaying high microsatellite instability (MSI-HIGH) may respond better to anti-PDL1 therapies than patients with non-MSI-HIGH tumors. Estimates of MSI-high or mismatch repair deficiency (dMMR) are as high 22% as reported in the TCGA analysis based upon treatment-naïve tumor samples, and appear to be lower in advanced disease compared to early disease (e.g., 47% in Stage 1b disease; 27% for Stage II disease, 20% for Stage III disease, and 12% for Stage IV disease). By any of these estimates, the incidence of MSI-high tumors in KEYNOTE 059 (4% (n=7/174) is lower than current reports in the literature.[23] The reason for this discrepancy is unknown.

Reviewer Comment: The post-hoc analyses of ORR among patients enrolled in KEYNOTE-059 (Cohort 1) appears to be heavily influenced by those patients who were MSI-high. In MSI-high patients, the data suggest that the selection of patients based on MSI-high expression be a better predictor of response to pembrolizumab than PD-L1 status in this patient population. However, given low incidence of MSI-high expression among patients enrolled in KEYNOTE-059, and the overlapping confidence intervals across the subgroups, the results of these findings should be interpreted with caution.

ORR by Line of Therapy: 3L versus 4L+

Among the 259 patients enrolled in KEYNOTE-059, 134 (52%) patients were receiving pembrolizumab in the 3rd line setting (3L) while 125 (48%) were receiving pembrolizumab in the 4th line or beyond (4L+). The results of the analysis of efficacy according to line of therapy are shown in Table 16 below.

Table 16. Results of Response Evaluation by Line of Therapy: KEYNOTE-059

Parameter	3L	3L*	4L+	4L+*
	N= 134	N= 131	N= 125	N= 121
	n(%)	n(%)	n(%)	n(%)
ORR	22 (16.4)	20 (15.3)	8 (6.4)	6 (5.0)
95% CI	(10.6, 23.8)	(9.6, 22.6)	(2.8, 12.2)	(1.8, 10.5)
CR	4 (3.0)	4 (3.1)	2 (1.6)	1 (<1)
PR	18 (13.4)	16 (12.2)	6 (4.8)	5 (4.1)

Source: Reviewer Table; data cut-off date of January 16, 2017.*Excludes 7 MSI-high patients.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

Overall, the majority of responders in KEYNOTE-059 were 3rd line patients. Of the 30 responders, 22 (73%) were receiving pembrolizumab in the 3rd line setting.

Reviewer Comment: This analysis of efficacy by line of therapy indicates higher response rates among patients who were receiving pembrolizumab in the 3rd line setting compared to patients receiving pembrolizumab in the 4th line and beyond. While the benefit of treatment with pembrolizumab appears to be highest in the less heavily pre-treated patients, 4L+ patients also appear to be achieving responses. These findings highlight the benefit of pembrolizumab in heavily pre-treated patients.

6.1.7 Subpopulations

Due to the limitations of a small sample size, and the absence of pre-specified subgroup analysis, the Applicant's analysis of efficacy by demographic and baseline characteristics was not verified by this reviewer.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

At the time of the submission and review of the current supplemental BLA, pembrolizumab had two approved dosing regimens: 2 mg/kg or 200 mg administered intravenously every 3 weeks (Q3W). KEYNOTE-059 (Cohort 1) evaluated pembrolizumab 200 mg Q3W while KEYNOTE-012 (Cohort D) evaluated the 10 mg/kg Q2W dosing regimen.

The Applicant evaluated the potential effect of dose on efficacy by comparing the ORR of patients enrolled in KEYNOTE-059 (Cohort 1) to that of patients enrolled in KEYNOTE-012 (Cohort D). This analysis was limited to patients with PD-L1 positive tumors and patients were matched according to number of prior lines of therapy. The results shown in Table 17 indicate a trend for higher ORR among patients who received pembrolizumab 10 mg/kg Q2W.

Table 17. ORR by Pembrolizumab Dose: KEYNOTE-059 vs KEYNOTE-012

	200 mg/Kg Q3W (KEYNOTE-059) N=148	10 mg/Kg Q2W (KEYNOTE-012) N=27
ORR % (95% CI) ^{A, B}	15.5 (10.1, 22.4)	18.5 (6.3, 38.1)

Source: Reviewer Table; ADORR, ADSL. ^APD-L1 positive tumors; ^BPatients who received 2 or more prior lines of therapy. ORR=objective response rate. CI= confidence interval.

For the cohort of patients that received 200 mg Q3W (n=148), ORR is 15.5%; 95% CI: 10.1%, 22.4%). For the cohort that received 10 mg/kg Q2W (n=27), the ORR is 18.5%; 95% CI: 6.3%, 38.1%). A similar analysis was not conducted for patients with PD-L1 negative tumors as KEYNOTE-012 only enrolled patients who had PD-L1 positive tumors. Refer to the clinical pharmacology review for more details.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

Reviewer Comment: While the ORR appears to be numerically higher for patients who received pembrolizumab 10 mg/kg Q2W compared to patients who received pembrolizumab 200 mg Q3W, this reviewer cautions against inferences of higher efficacy in the 10 mg/Kg group given that these studies were uncontrolled and the 95% confidence intervals between the two groups overlap.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The duration of the response among responders in KEYNOTE-059 and their disposition at time of data cut-off date is described in Section 6.1.5.

A discussion of tolerance effects is not applicable to this supplemental application review.

6.1.10 Additional Efficacy Issues/Analyses

PD-L1 Testing

During review of this application, FDA reviewers requested that Merck submit patient-level data regarding the characteristics of the tumor tissue used to assess PD-L1 tumor status. This request was made based upon the observation that there were 3 patients with complete responses among the patients who were categorized as having PD-L1 negative tumors.

Table 18 and

Table 19 below summarize the results of PD-L1 testing in archival versus newly obtained tumor tissue specimens and the overall response rate according to PD-L1 test results and specimen type (archival versus newly obtained).

Table 18. PD-L1 Positive Rate by Age of Tumor Specimen

Age of Tissue (days)	PD-L1 Positive* % (n/N)
≤ 42	73.3 (66/90)
60-900	52.9 (64/121)
>900	39.1 (18/46)

*Defined as CPS ≥1%

Table 19. PD-L1 Test Results by Specimen Type: Archival versus Newly Obtained

Specimen Type N=257 (%)	PD-L1 + n (%)	PD-L1+ Responders (n=23) n(%)	PD-L1 - n (%)	PD-L1- Responders(n=7) n(%)
Archival (>42 days) n=157 (65.0)	82 (49.9)	12 (52.2)	85 (47.7)	6 (85.7)
Newly Obtained (<42 days) n=90 (35.0)	66 (73.3)	11 (47.8)	24 (26.6)	1(14.2)

Note: these data exclude two specimens that were obtained but did not have a PD-L1 result returned. *specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1 (Cycle 1) and with no additional anti-cancer treatment having been given after the specimen was obtained.

- Rate of PD-L1 positivity was lower in archival tumor tissue compared to newly obtained tissue.
- The age of tumor specimens used for PD-L1 testing in all three PD-L1 negative patients who had a complete response to pembrolizumab therapy was >900 days.
- 39% of tumor tissue specimens that were > 900 days old at the time of testing were assessed as being PD-L1 positive, compared to 73% of newly obtained specimens.
- 6 of the 7 PD-L1 negative patients that had an objective response to pembrolizumab had tumor specimens that were > 400 days old.

Reviewer Comment: The data above suggest lower sensitivity in the detection of PD-L1 positive tumors when the PD-L1 assessment is based upon archival tumor specimens. This finding creates uncertainty regarding whether the observed response rate in patients whose tumors were classified as PD-L1 negative in this trial reliably characterizes the treatment effect of pembrolizumab in patients with PD-L1 negative gastric cancer (e.g. it is uncertain whether the three complete responders among the subgroups of patients who were classified as having “PD-L1 negative” tumors truly had PD-L1 negative tumors).

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)

KEYNOTE-012

The key efficacy findings of KEYNOTE-012 (Cohort D) are summarized in this section. These findings are based on a data cut-off date of April 26, 2016. Note that these findings were not verified by this reviewer. The median follow-up for patients enrolled in this trial is 11.4 months (range: 0.9- 29.9).

Table 20. Disposition of Patients Enrolled in KEYNOTE-012 (Cohort D)

	Gastric Cancer	
	n	(%)
Subjects in population	39	
Subject Study Medication Disposition		
Discontinued	37	(94.9)
Adverse Event	1	(2.6)
Progressive Disease	36	(92.3)
Two-year Treatment Completed	2	(5.1)
Each subject is counted once for Subject Study Medication Disposition based on the latest corresponding disposition record. (Database Cutoff Date: 26APR2016).		

Source: Copied from Clinical Study Report (CSR), p 51.

A total of 39 patients comprised the safety and efficacy population for Cohort D. The results of the primary efficacy endpoints are summarized in Table 21.

Table 21. Efficacy Summary: KEYNOTE-012 (Cohort D)

Efficacy Parameter	N= 39
Response (RECIST 1.1)	
ORR, n(%)	8 (20.5)
95% CI	(9.3, 36.5)
CR, n(%)	1 (2.6)
PR, n(%)	7 (17.9)
Response Duration	
Median in months, (range)	9.5 (5.6 - 22.1+)
Response ≥ 6 Months, n (%)	6 (75)
Response ≥ 12 Months, n (%)	2 (25)

Source: Reviewer Table based on CSR Table 11-2; p 58 and Table 11-3 p 61.

Reviewer comment: The ORR observed in KEYNOTE-012 is higher than that which was observed in KEYNOTE-059. This reviewer cautions against direct comparisons of these two studies beyond concluding that pembrolizumab is active in gastric cancer, as these two uncontrolled studies enrolled heterogeneous patient populations with variable numbers of prior treatments. Additionally, KEYNOTE-012 (Cohort D) is small in size and thus the ORR is subject to changes based on small numbers of responders. Finally, the 95% confidence intervals of the ORR in both studies are wide and overlap.

7 Review of Safety

Safety Summary

The review of safety relies primarily upon data from KEYNOTE-059 based on a data cut-off date of January 16, 2017. The evaluation of safety will be based upon incidence of adverse events (AEs) and laboratory values, graded according to NCI CTCAE, version 4.0, and observed during treatment with pembrolizumab (i.e., from the first dose of pembrolizumab until treatment was stopped), and up to 30 days after last dose was administered (up to 90 days for serious adverse events).

As appropriate, the results of the analyses of KEYNOTE-059 data are compared to the safety findings of KEYNOTE-012, Cohort D (data cut-off date of April 26, 2016) which enrolled 39 patients with advanced gastric or gastroesophageal adenocarcinoma and a heterogeneous experience with prior systemic therapy, or with the pembrolizumab reference safety dataset which consists of pooled data from four clinical studies evaluating pembrolizumab for the treatment of melanoma and non-small cell lung cancer (NSCL), which comprised the first and second approved indications for pembrolizumab, respectively. According to the Applicant, this reference safety dataset reflects the established safety profile for pembrolizumab and is consistent with the cumulative safety dataset for this product.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary data for the safety evaluation was based upon the results of KEYNOTE-059. The safety and tolerability of pembrolizumab in the study population were assessed by reviewing of all relevant safety parameters including adverse events (AEs), laboratory tests, and vital signs. Given the limited size of the study population in KEYNOTE-059, comparisons were made to the incidence and severity of AEs observed in the pembrolizumab reference safety dataset. The reference dataset comprises 2799 pembrolizumab-treated patients, of whom 41% were exposed to pembrolizumab for ≥ 6 months and 21% were exposed to pembrolizumab for ≥ 12 months. In previous supplemental applications, this reference dataset has been deemed 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.

7.1.2 Categorization of Adverse Events

In the protocol for KEYNOTE-059, an adverse event is defined as “as any untoward medical occurrence in a patient or clinical investigation subject administered a

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.” Progression of gastric cancer is not considered an adverse event.

A serious adverse event is defined as any adverse event occurring at any dose or during any use of pembrolizumab that results in death, is life-threatening, results in persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event.

Non-serious adverse events, regardless of causality that occurred from the time of treatment allocation through 30 following cessation of pembrolizumab, and serious adverse events and events of clinical interest, regardless of causality, that occurred from the time of treatment allocation through 90 days after the end of treatment or 30 days after the end of treatment if the patient initiated new anticancer therapy, whichever occurs first, were the basis for characterization of the pembrolizumab safety profile.

Overall, a total of 248 patients (96%) experienced one or more adverse events. Table 22 below shows the summary of AEs. A total of 159 patients (61%) experienced one or more AEs that were Grade ≥ 3 - 5 in severity. A total of 116 patients (45%) experienced one or more SAE.

Table 22. Overview of Safety: KEYNOTE-059 (n=259)

	KEYNOTE-059 N= 259		Reference Safety Dataset N= 2799	
Safety parameter	n	%	n	%
≥ 1 AEs	248	96	2727	97
Grade ≥ 3 AE	159	61	1273	46
≥ 1 SAE	116	45	1041	37
Discontinued due to AE	7	3	334	12

Source: Reviewer Table: Data cut-off date: Jan 17, 2017

Reviewer Comment: Overall, the rate of Grade 3 -5 AEs was numerically higher in KEYNOTE-059 compared to the pembrolizumab reference safety dataset. A review of the AEs with higher incidence KEYNOTE-059 suggests a higher incidence of investigator-reported laboratory abnormalities (anemia 12% vs 3%; hyponatremia 5% vs 2%; blood alkaline phosphatase increased 4% vs 1%, etc.). However, analysis of the laboratory data did not confirm these findings. Additionally, the non-laboratory based AEs are consistent with what would be expected in an advanced gastric cancer patient population.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

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

While some general comparisons of the incidence and severity of treatment emergent adverse events between study populations enrolled in KEYNOTE-059 Cohort 1 and those gastric cancer patients who were enrolled in KEYNOTE-012 (Cohort D), and the pooled patients in the reference safety dataset, this section is not applicable in this supplemental BLA given that the primary basis for the safety evaluation was a single trial.

7.2 Adequacy of Safety Assessments

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

Based upon a data cut-off date of January 16, 2017, the median number of months of pembrolizumab exposure in the safety analysis population (n=259) was 2.1 (range: 1 day to 21.4 months). Pembrolizumab treatment for 6 months or longer occurred in 19%; 9% of patients continued pembrolizumab treatment for 12 months or more. The summary of pembrolizumab exposure is shown below in Table 23.

Table 23. Duration of Pembrolizumab Exposure in KEYNOTE-059 (n=259)

Exposure (months)	n	%
< 1	78	30
≥ 1	181	70
≥ 3	84	32
≥ 6	48	19
≥ 12	23	9

Source: Reviewer Table. Data cut-off date January 16 2017

7.2.2 Explorations for Dose Response

Not applicable to this supplemental application, given the fixed dose of pembrolizumab. Refer to the clinical pharmacology reviews in the original and supplemental BLAs for a review of the data characterizing the dose response relationship of pembrolizumab.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this supplemental application. Please refer to the pharmacology and toxicology review in the original BLA submission.

7.2.4 Routine Clinical Testing

Physical examinations and laboratory assessments were performed with each cycle of pembrolizumab. Protocol-specified assessments of adverse events occurred up to 90

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

days following the last dose of pembrolizumab. Please refer to Table 5 for the schedule of clinical assessments in KEYNOTE-059.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable to this supplemental application.

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

The safety profile of pembrolizumab is well-characterized and consistent with that of other immune checkpoint inhibitors. Adverse events are primarily immune-mediated reactions and include colitis, hepatitis, hyperthyroidism, hypophysitis, hypothyroidism, nephritis, pneumonitis, rash, and renal failure. Please refer to Section 7.3.4 for the analysis of the incidence of these adverse events.

7.3 Major Safety Results

In this application, serious adverse events (SAEs) are defined as any adverse event (AE) that results in death, is life threatening, results in persistent or significant disability/incapacity, results in or prolongs an existing hospitalization. AEs that occurred up to 90 days after the last dose of study drug were included in the analysis.

Overall, a total of 211 serious adverse events were observed in 116 patients (45%) enrolled in Cohort 1. The most common SAEs were pleural effusion, anemia, intestinal obstruction, pulmonary embolism, nausea, vomiting, sepsis, dehydration, sepsis, back pain, and acute kidney injury.

7.3.1 Deaths

Excluding malignant neoplasm progression which was the cause of death in 17 patients, there were a total of 17 patients who experienced fatal adverse events.

The most common adverse events leading to death were acute kidney injury, pleural effusion, and pulmonary embolism; these occurred in 2 patients each. Other adverse events occurring in one patient each are shown in the table below. One patient (590003) experienced 2 fatal AEs (acute kidney injury and septic shock) and two patients, including one whose AE was reported as “death,” had unknown cause of death.

Table 24. Incidence of Fatal Serious Adverse Events (N=33)

Preferred Term	Number of patients
Abdominal pain	1
Acute kidney injury	2
Cardiac arrest	1
Death*	2
Gastrointestinal hemorrhage	1
Malignant neoplasm progression	17
Esophageal perforation	1
Pleural effusion	2
Pneumonia aspiration	1
Portal vein thrombosis	1
Pulmonary embolism	2
Respiratory failure	1
Sepsis	1
Septic shock	1
Sub-diaphragmatic abscess	1
Total	34

Source: Reviewer table (Dataset ADAE); *Cause of death unknown (590158). One patient who died not included in fatal AE listing (590191).

The deaths mostly occurred during the safety-follow-up (n=14) with only 3 occurring during the extended follow-up (respiratory failure [590068], sepsis [590172], portal vein thrombosis [590213]). Details of patients who experienced Grade 5 AEs are below.

Table 25. Deaths: Patient Narratives

Study Site /Subject ID	Preferred Term ^A	Summary
0021-590050	Esophageal perforation Day 356	62 yo M W diagnosed approx. 1 year prior to study. HER-2 neu positive. ECOG 0 & liver metastases at enrollment. Prior history included gastrointestinal AVM, gastritis, hematemesis, esophagitis, radiosurgery, chemotherapy, and radiation. Received 14 doses of pembrolizumab with last dose on Day 329. Pembrolizumab course interrupted following Cycle 1 for 4 weeks due to sepsis & supraventricular tachycardia, and for 4 weeks following Cycle 7 (Day 190) due to G3 colitis and <i>Clostridium difficile</i> infection. Pembrolizumab resumed on Day 206. On Day 344, experienced G2 esophageal pain. On Day 347, presented with fever, hiccups, abdominal and chest pain. Imaging (CT, esophagram) revealed esophageal perforation. EGD showed G3

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)

		esophageal ulcer. On Day 353 esophageal ulcer considered resolved and discharged from the hospital. On Day 356, died at home. Cause of death reported as due to G5 esophageal perforation due to disease progression.
0007-590031	Gastrointestinal Hemorrhage Day 27	77 yo M, W diagnosed approx. 1 year prior to study. HER 2 neu negative. Prior history of chemotherapy & esophageal stent. ECOG 0 & liver and adrenal gland metastases. Prior history of gastrointestinal hemorrhage, TIA, hemoptysis, dysphagia. Received 2 doses of pembrolizumab, with last on Day 22. Patient experienced Grade 5 hematemesis at home and became unresponsive; Comfort measures at hospital where experienced cardiac and respiratory arrest on Day 28. No autopsy.
0070-590240	Pleural effusion Day 211	67 yo M diagnosed approx. 1 year prior to enrollment. HER 2 neu negative. Prior history includes chemotherapy, radiation. ECOG 1 & bone, liver, and lymph node metastases at enrollment. Received 9 doses of pembrolizumab with last dose on Day 189. Course complicated by colitis considered related to study drug on Day 93. Pembrolizumab held; steroids administered. Colitis resolved and pembrolizumab resumed on Day 148. Hospitalized Day 228 for costal pain and cough which had onset Day 211; diagnosed with G2 pleural effusion. Received antibiotics, oxygen, and morphine. Effusion present on CXR on Day 230. Day 231 G3 delirium; Head CT scan unremarkable. On Day 239 died due to G5 pleural effusion. No autopsy. Of note, the CRF indicates that patient underwent aspiration of pleural fluid 20 days prior to death. The patient also was experiencing edema of lower limbs at time of pleural effusion and may have also had a <i>Streptococcus intermedius</i> infection.
0080-590078 ^A	Pleural effusion Day 17	44 yo F W diagnosed approx. 2 years prior to enrollment. HER 2 neu negative Prior history includes cough, stereotactic body radiation, total gastrectomy, celiac trunk lymphadenectomy, chemotherapy. ECOG 1 & bone and pleural cavity metastases at enrollment. Received 1 dose of pembrolizumab. On Day 17, admitted for dyspnea and diagnosed with G3 pleural effusion. Received

		thoracentesis. Dyspnea recurred on Day 21; readmitted, repeat thoracentesis. Laboratory results showed G3 anemia and thrombocytopenia. Received 2 units of RBCs. Day 24, died due to pleural effusion. No autopsy.
0101-590140	Pulmonary embolism Day 41	57 yo F, W diagnosed approx. 6 years prior to study. HER 2 neu negative. Prior esophagectomy, chemotherapy. ECOG 1 & bone and lung metastases at enrollment. Received 2 doses of pembrolizumab with last dose on Day 22. On Day 41, patient 'stopped breathing' and became unresponsive at home. He died 3 hours after transfer to hospital and resuscitative efforts including mechanical ventilation. Of note according to CRF, approximately 2 weeks prior to death, patient had previously experienced loss of consciousness and fall at home after feeling shorting of breath (he had had a gastric feeding tube inserted a day earlier). In ER, work up revealed tachycardia, hypoxia, but no signs of infection. CTA was negative for PE and ECG was unchanged from baseline. No treatment was administered and patient discharged home feeling better. No autopsy.
0112-590172	Sepsis Day 178	79 YO F diagnosed approx. 1 year prior to study. HER 2 neu positive. ECOG 0 and liver metastases. Prior chemotherapy. Received a total of 5 doses of pembrolizumab; last dose on Day 134. During treatment, experienced G2 anemia, G2 AST increased, and G1 performance status decrease; pembrolizumab dose delayed for each AE. On Day 178, presented to ER with refractory pain; hospitalized for treatment of G2 sepsis, severe hypoglycemia, and UTI. On Day 181, sepsis worsened to G5 and experienced multiple organ failure and died. No autopsy.
0118-590043	Acute kidney injury Day 21	79 yo M W diagnosed approx. 1 year prior to study. Her 2 neu negative. ECOG 1 and retroperitoneal and peritoneal metastases. Prior history of chemotherapy, peripheral edema and hypertension. Received a total of 1 dose of pembrolizumab. On Day 21, experienced G3 acute kidney injury. On Day 22, peripheral edema worsened on abdomen and legs and the patients was drowsy. Admitted to ICU. A urinary tract CT

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)

		was normal with no sign of obstruction. Condition continued to deteriorate despite treatment and patient died on Day 28. No autopsy.
0181-590158	Unknown Day 16	43 yo F W diagnosed approx. 1 year prior to study. Her-2 neu negative. ECOG 1 and stomach metastases at enrollment. Prior chemotherapy. Received a total of 1 dose of pembrolizumab. On Day 41, after several attempts to contact with no response, the site contacted the register office of the patient's town; informed that the patient died on Day 16. The cause of death was reported as unknown. No autopsy.
0181-590191	Unknown ^B Day 121	56 yo M W diagnosed approx. 4 years prior to study. HER-2 neu negative. ECOG 0 and lymph node metastases at enrollment. Prior total gastrectomy and chemotherapy. Received a total of 2 doses of pembrolizumab; last dose on Day 22. On day 43, G3 bilirubin increase. Treatment included biliary stent reposition and hospitalization. Discharged on Day 121 with recovery of G3 bilirubin increase. No follow-up after discharge and clinical site 'called the registry office, it was confirmed that on Day 121, the subject died due to an unknown cause.' No autopsy.
0200-590213	Portal vein thrombosis Day 211	73 yo M W diagnosed approx. 6 years prior to study. Her-2 neu negative. ECOG 1 & abdominal cavity and liver metastases at enrollment. Prior subtotal gastrectomy and chemotherapy. Received a total of 7 doses of pembrolizumab; last dose on Day 127. On Day 71 a scheduled CT scan revealed G2 mesenteric vein thrombosis. Treatment with nadroparin calcium initiated on Day 76. On Day 112, progressive disease, as reported by the investigator. On Day 148, discontinued study treatment and follow-up for G2 mesenteric vein thrombosis was ongoing. On Day 211 hospitalized for abdominal pain and fever. Blood culture positive for E. coli and P. vulgaris, and diagnosed with G4 sepsis and G3 portal vein thrombosis. On Day 212 CT confirmed portal vein thrombosis and progressive gastric cancer. Subsequent hospital course included

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)

		pneumonia, hypokalemia severe thrombocytopenia, pulmonary artery thrombosis, acute kidney injury, blood cultures positive for E. cloacae and E. faecum. Patient died on Day 226 with cause of death reported as due to portal vein thrombosis.
0210-590232	Abdominal pain Day 28	59 yo M W diagnosed approx. 1 year prior to study. Her-2 neu positive. ECOG 0 and liver and lung metastases at enrollment. Prior chemotherapy. Received a total of 1 dose of pembrolizumab. On Day 28 admitted to the hospice due to severe, worsening abdominal pain (G3), clinical disease progression, and general clinical deterioration. Died on Day 36 due to abdominal pain (G5) and malignant neoplasm progression. No autopsy.
0230-590099	Pneumonia aspiration Day 218	69 yo M W diagnosed approx. 1 year prior to study. HER 2 neu negative. ECOG 0 and liver and peritoneal metastases at enrollment. Prior chemotherapy and radiation. Received a total of 11 doses of pembrolizumab with last dose on Day 213. Hospitalized on Day 215 for acute onset left upper quadrant and left pleuritic pain and constipation. CT scan revealed known extensive tumor with the involvement of spleen and pancreas and infarct involving spleen suspected as cause of left-sided pain. On Day 217, condition deteriorated with increased oxygen requirement, tachycardia, infection, and 2 episodes of aspiration. On Day 218, diagnosed with G4 aspiration pneumonia. Following additional aspiration events, supportive measures and end-of-life care initiated. Died in hospital on Day 219.
0232-590155	Cardiac arrest Day 105	82 yo M W, diagnosed approx. 2 years prior to study. HER 2 neu negative. ECOG 1 and umbilical metastases at enrollment. Prior DVT, chemotherapy. Received a total of 5 doses of pembrolizumab with last on Day 97, following a delay on Day 38 (Cycle 3) due to G3 transient ischemic attack on Day 37 which resolved with sequelae and treatment resumed on Day 55. On Day 89, presented with a speech disturbance, confusion, and slow gait and CT revealed an extension of a previously diagnosed right middle

		cerebral artery stroke (G2). On Day 105, while still hospitalized for stroke, unwitnessed cardiac arrest during overnight hours, was discovered unresponsive in the early morning, to resuscitative efforts. No autopsy.
0015-590146	Pulmonary embolism Day 171	77 yo M W diagnosed approx.4 years prior to study. HER 2 neu positive. Prior history of coronary artery disease and coronary arterial stent, gastrectomy, and chemotherapy. ECOG 1 and metastases to liver, lymph nodes at enrollment. Received 8 doses of pembrolizumab with last dose on Day 144. On Day 157, admitted with fever, hypotension, and tachycardia. Head CT on Day 19 revealed no pathology. MRI on Day 161 revealed severe L2-4 spinal stenosis. On day 167, underwent L2-L4 Laminectomy. On Day 168 received enoxaparin to treat upper extremity DVT. Died unexpectedly on Day 170 while preparing for discharge due to G5 pulmonary embolism. No autopsy.
0021-590068	Respiratory failure Day 108	61 yo M W diagnosed approx.2 years prior to study. HER-2 neu negative. Prior history includes tobacco abuse, dysphagia, radiation, chemotherapy. ECOG 1 and liver metastases at enrollment. Received 2 doses of pembrolizumab with last dose delayed by 3 weeks due to G2 constipation, G3 thoracic vertebral fracture, G2 vertebral artery occlusion. Last dose received Day 42. Course (Day 62- 106) included diagnosis and recurrence of cervical spine osteomyelitis, pericardial effusion, progressive disease, dysphagia, C6-7 corpectomy with interbody arthrodesis and posterior/anterior arthrodesis C5-T1, and G3 respiratory failure requiring intubation. On Day 107, G3 respiratory failure was considered resolved. Discharged home. On Day 108, admitted with 'worsening neurological symptoms' and respiratory failure requiring re-intubation. Care withdrawn on Day 118 and died. No autopsy.
0100-590003	Septic shock Acute kidney injury Day 36	42 yo M W diagnosed approx. 1 year prior to study. HER 2 neu negative. ECOG 1 and abdominal cavity metastases at enrollment. Prior history included myocarditis, iron deficiency, ascites,& chemotherapy. Received a total of 2 doses of pembrolizumab with last dose on Day 20.

		On Day 28, received enoxaparin s for DVT. Patient reported a single episode of G2 hematemesis on Day 30. Gastroscopy was unrevealing. During procedure, patient aspirated, desaturated and required mechanical ventilation. Course significant for pneumonia, acute kidney injury, hypotension, and septic shock. Died on Day 36. No autopsy.
0007-590020	Sub-diaphragmatic abscess Day 13	58 yo M, W diagnosed approx.4 years prior to study. Her 2 neu positive. Prior radiation, esophagogastronomy, chemotherapy. ECOG 1 &metastases to abdominal lymph nodes, liver, adrenal gland, and mild abdominal pain at enrollment. Prior history of coronary artery disease and myocardial infarction. Received 1 dose of pembrolizumab. On Day 13presented with increased abdominal pain. Imaging revealed splenic infarct, gastric anastomosis site leak, free air below the diaphragm, left pleural effusion, and subdiaphragmatic abscess. CT-guided abscess drainage revealed streptococci bacteria. Received antibiotics, transitioned to inpatient hospice and died on Day 15. No autopsy.

Source: Reviewer table. ^ADeath considered ‘possibly related’ to pembrolizumab by investigator. ^BNot listed as an AE.

Based upon the review of the narratives for patients with these fatal adverse events, the clinical reviewer’s assessment is that two of the deaths (unknown) may be possibly related to treatment with pembrolizumab due to the absence of information regarding specific cause of death and that the other fatal adverse events are unlikely to be due to pembrolizumab In the case of the first patient with unknown cause of death, the patient was lost to follow-up after one dose of study drug and death was confirmed by the town register office. The second patient with unknown cause of death, the patient received 2 doses of pembrolizumab and was hospitalized for treatment of Grade 3 bilirubin increase which was attributed to biliary stent malfunction. The patient remained hospitalized from Day 43 to Day 121. The patient died under unknown circumstances on the same day of discharge. According to the submission, the death was also confirmed by the patient’s town registry. Autopsies were not conducted in either case.

Reviewer Comment: The review of the details regarding the deaths reported in this supplemental application did not raise any new safety concerns relative to the safety profile of pembrolizumab reflected in the current USPI.

Clinical Review
Lola Fashoyin-Aje
BLA 125514 (Supplement 24)
KEYTRUDA® (pembrolizumab/ MK- 3475)
7.3.2 Nonfatal Serious Adverse Events

A total of 194 non-fatal SAEs were observed to occur in 109 patients. Non-fatal SAEs most commonly occurred in the following SOC: gastrointestinal disorders (55), respiratory, thoracic and mediastinal disorders (20), infections and infestations, (19), general disorders and administration site conditions. The most common SAE were anemia, pleural effusion, nausea, vomiting, intestinal obstruction, dehydration, and back pain. A comprehensive list of SAEs is listed below.

Table 26. Non-Fatal Serious Adverse Events (≥1%)

System Organ Class and Preferred Term^a	Overall n
Blood and Lymphatic System Disorders n(%)	9 (3)
Anemia	7
Abdominal lymphadenopathy	1
Splenic infarction	1
Cardiac disorders n(%)	6 (2)
Supraventricular tachycardia	2
Pericardial effusion	1
Myocardial infarction	1
Cardiac tamponade	1
Atrial fibrillation	1
Congenital, familial and genetic disorders n(%)	1 (<1)
Trachea-esophageal fistula	1
Endocrine disorders n(%)	2 (1)
Thyroiditis	1
Hypothyroidism	1
Gastrointestinal disorders n(%)	51 (20)
Intestinal obstruction ^A	12
Nausea	5
Vomiting	5
Abdominal pain ^{\$}	5
Gastrointestinal hemorrhage	5
Dysphagia	4
Constipation	3
General disorders and administration site conditions n(%)	13 (5)
Asthenia	4
Pyrexia	4
Hepatobiliary disorders n(%)	9 (5)
Hepatic function abnormal	2
Infections and infestations n(%)	19 (7)
Pneumonia	4
Sepsis	4
Investigations n(%)	8 (3)

System Organ Class and Preferred Term ^a	Overall n
Blood creatinine increased	2
Aspartate aminotransferase increased	2
Metabolism and nutrition disorders n(%)	11 (4)
Dehydration	5
Musculoskeletal and connective tissue disorders n(%)	10 (4)
Back pain	5
Nervous system disorders n(%)	10 (4)
Transient ischemic attack	2
Renal and urinary disorders n(%)	5 (2)
Acute kidney injury	3
Respiratory, thoracic and mediastinal disorders n(%)	20 (8)
Pleural effusion	7
Pulmonary embolism	4
Dyspnea	3
Pneumonitis	2
Respiratory failure	1

Source: Reviewer table (Dataset ADAE);^aincludes grouped preferred terms.

\$= composite of abdominal pain, upper; A=composite of intestinal obstruction, small intestinal obstruction, ileus, large intestinal obstruction, obstruction gastric) gastrointestinal hemorrhage (diverticulum intestinal hemorrhagic, gastric hemorrhage, melena, gastrointestinal hemorrhage)

Reviewer comment: Overall, the proportion of patients who experienced one or more SAEs was higher in KEYNOTE-059 (Cohort 1) compared to the reference safety population (45% versus 37%). In general, the SAEs tended to be consistent with advanced gastric cancer.

7.3.3 Dropouts and/or Discontinuations

Consistent with the safety analysis, the analysis of treatment discontinuation was based upon a data cut-off date of January 17, 2017. The reasons for treatment discontinuation are shown in the table below. A total of 28 patients were still receiving treatment at the time of data cut-off date.

Table 27. Reasons for Treatment Discontinuation (n=259)

Reason for discontinuation of treatment	n	%
Progressive disease	143	62
Death	26	11
Clinical progression	25	11
Adverse event	20	9
Withdrawal by subject	12	5

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

Source: Reviewer table; ADAE, ADSL- Efficacy (original submission data cut-off date January 16, 2017).

A total of 7 experienced treatment discontinuation due to an adverse event. The reasons were: esophageal perforation, pleural effusion, gastrointestinal hemorrhage, hepatic failure, hepatic function abnormal, death (unknown cause), and bile duct stenosis. Two of the AEs leading to pembrolizumab discontinuation (bile duct stenosis and hepatic function abnormal) were considered drug-related as assessed by the Investigator and briefly described below. Three (esophageal perforation, pleural effusion, death) were fatal AEs and are described in Section 7.3.1.

SUBJID	Clinical summary	Reviewer comment
590170	At baseline, had two metastatic liver lesions and a lymph node near the liver. Hospitalized for G3 bile duct stenosis Day 41. Ultrasound of the revealed hepatomegaly and ultrasound signs of biliary hypertension. Underwent surgery for external drainage of the biliary ducts, which confirmed G3 bile duct stenosis. The 2 liver lesions and lymph node near the liver had also increased in size over a 3 month period during the study and disease progression was assessed at the last tumor assessment (Week 15). Patient reported to be alive approximately 4 months after commencing pembrolizumab, but was lost to follow-up thereafter.	The relatedness of this event to pembrolizumab may be confounded by the evidence of disease progression.
590263	Experienced fever, jaundice, pruritus, and increased liver enzymes (G4 hepatic function abnormal) on Day 70. Clinical course significant for G3 colitis on Day 22 (resolved), G1pneumonitis on Day 63 (ongoing at data cutoff). A CT scan did not reveal bile duct dilatation or parenchyma disorder. Liver biopsy on Day 84 indicated drug-induced cholestatic liver injury. Received steroids and immune suppressors. Pembrolizumab was permanently discontinued. Died of disease progression post-trial withdrawal (multiple new liver lesions, pleural effusion and peritoneal dissemination recorded at Week 26 visit).	Hepatic function abnormal possibly related to pembrolizumab given liver-biopsy proven drug-induced cholestatic liver injury and absence of other medications known to cause liver injury.

Consistent with the clinical development program for pembrolizumab, immune-mediated adverse events and infusion-related adverse events are identified as potential risks of treatment with pembrolizumab and are considered to be adverse events of special interest (AEOSI). The Applicant has identified a list of preferred terms (PTs) to assess the incidence of these AE in the pembrolizumab development program.

A total of 46 patients (18%) experienced one or more adverse events of special interest. None of these events were fatal. This rate is slightly lower than the rate observed in the reference safety dataset (21%). The AEs of special interest are summarized in Table 28 below.

Table 28. Adverse Events of Special Interest (AEOSI)

AEOSI	Total	Grade 1	Grade 2	Grade 3
	n(%)	n(%)	n(%)	n(%)
Hypothyroidism	23 (9)	11 (4)	11 (4)	1 (<1)
Hyperthyroidism	9 (3)	9 (3)	0 (0)	0 (0)
Colitis	6 (2)	0 (0)	3 (1)	3 (1)
Pneumonitis	5 (2)	2 (1)	1 (<1)	2 (1)
Infusion Reactions	4 (2)	1 (<1)	3 (1)	0 (0)
Severe Skin Reactions	4 (2)	0 (0)	0 (0)	4 (2)
Thyroiditis	4 (2)	2 (1)	1 (<1)	1 (<1)
Hepatitis	1 (<1)	0 (0)	0 (0)	1 (<1)
Myositis	1 (<1)	0 (0)	1 (<1)	0 (0)
Uveitis	1 (<1)	0 (0)	0 (0)	1 (<1)

Source: Reviewer Table: ADAE (Data cut-off January 17, 2017). Severe Skin Reactions: erythema multiforme (n=1); jaundice (n=1), rash (n=1), rash-maculopapular (n=1)

Among the 23 patients who experienced hypothyroidism, 18 had ongoing/persistent hypothyroidism at the time of data cut-off date.

Reviewer Comment: Overall, the incidence and severity of immune mediated adverse events observed in KEYNOTE-059 appears similar to the known incidence of these events for the approved indications.

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 248 patients (96%) experienced one or more adverse events (AEs). The most frequently reported (>20%) AEs by preferred term were fatigue (33.2 %, n=86), decreased appetite (27.8%, n=72), anemia (23.9%, n=62), nausea (23.6%, n=61), and constipation (20.8%, n=54). A total of 159 patients (61.4%) experienced one or more Grade 3-5 adverse events.

Table 29. Common Adverse Events^c (≥ 10%): Safety Population (n=259)

Preferred Terms ^a	Total (N=259)		3L (N= 134)		4+L (N= 125)	
	n	%	n	%	n	%
Fatigue	86	33	48	36	38	30
Decreased appetite	72	28	37	28	35	28
Nausea	61	24	31)	23	30	24
Constipation	54	21	36	27	18	14
Abdominal pain	50	19	25	19	25	20
Dyspnea	43	17	22	16	21	17
Diarrhea	41	16	27	20	14	11
Edema peripheral	41	16	22	16	19	15
Cough	39	15	24	18	15	12
Weight decreased	38	15	24	18	14	11
Vomiting	35	14	18	13	17	14
Dysphagia	32	12	18	13	14	11
Pruritus	32	12	20	15	12	10
Back pain	30	12	14	10	16	13
Rash	29	11	18	13	11	9
Pyrexia	27	10	10	7	17	14
Asthenia	26	10	12	9	14	11

Source: Reviewer Table: ADAE (Data cut off January 17, 2017); ^aExcludes laboratory terms.
^cRepresents all-causality adverse events during or within 30 days after last dose of pembrolizumab.

Reviewer comment: The AEs experienced in this population are consistent with either the established pembrolizumab safety profile or those observed in patients advanced gastric cancer. The observed incidence of AEs does not appear to be in excess of what would be expected in this clinical setting and likely related to underlying advanced gastric cancer.

Overall, there were no major differences in incidence of adverse events by line of therapy. Adverse events that occurred 5 or more percentage points in the ≥4th line (4L+)

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

patients compared to the 3rd line (3L) patients were pyrexia (3L= 7% , 4=L= 14%), hypothyroidism (3L= 6%, 4+L= 12%), and hyperglycemia (3L:7% vs 4+L:12%).

The most common Grade 3 to 4 AEs in KEYNOTE-059 (Cohort 1) ($\geq 2\%$) are listed in Table 30 below.

Table 30. Common ($\geq 2\%$) AE: Grade 3-4: Safety Population (n=259)

Preferred Term	n	%
Dyspnea	11	4
Fatigue	10	4
Abdominal pain	9	3
Dehydration	9	3
Dysphagia	8	3
Vomiting	7	3
Asthenia	7	3
Ascites	7	3
Nausea	6	2
Pleural effusion	6	2
Intestinal obstruction	6	2
Pulmonary embolism	5	2
Back pain	4	2
Sepsis	4	2
Tumor pain	4	2

Source: Reviewer Table: ADAE (Data cut off January 17, 2017); Excludes laboratory terms. Represents all-causality adverse events during or within 30 days after last dose of pembrolizumab.

Reviewer comment: With the exception of dyspnea and fatigue, these events were reported slightly more frequently in KEYNOTE-059 (Cohort 1) compared to the reference safety population. However, due to the small number of patients enrolled in KEYNOTE-059 compared to the reference safety population, the observed differences in the incidence of AEs may be attributable to small sample size.

7.4.2 Laboratory Findings

In general, the incidence of treatment-emergent laboratory abnormalities observed in KEYNOTE-059 was similar to or less than the observed incidence in the Reference Safety Dataset for pembrolizumab. The exceptions are summarized in Table 31 below. In most cases wherein the incidence of a laboratory abnormality was higher in KEYNOTE-059 compared to the referenced safety dataset, the difference was a 1-2 percentage point difference, based upon less than 10 patients, and of low severity (NCI CTCAE Grade 1 or 2).

Table 31. Laboratory Abnormalities Worsened^A from Baseline Higher in Incidence in KEYNOTE-059 Compared to Reference Safety Dataset.

Laboratory Abnormality	KEYNOTE-059 N= 259		Pooled Melanoma + NSCLC N= 2799	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
Hematology				
Hematocrit decreased	1.2	0.4	0	0
Chemistry				
Alanine aminotransferase, decrease	0.4	0	0	0
Blood urea nitrogen, increased	1.7	0.6	0	0
Carcinoembryonic antigen	2	0	0	0
Chloride, decreased	2.1	0	0	0
Creatinine decreased	0.4	0	0	0
Direct bilirubin increased	1.4	0.7	0	0
Phosphate increased	0.4	0	0	0
INR ^B increased	6.2	0	4.6	1.6
Prothrombin Time Increased	4.0	2.0	0	0
Thyrotropin decreased	3.0	0	0	0
Thyrotropin increased	2.6	0	0	0
Thyroxine, Free	2.2	0	0	0
Triiodothyronine	5.7	0	0	0
Urate decreased	0.4	0	0	0
Urate increased	2.2	0.9	0	0
Urea	4.6	1.1	0	0

Source: Reviewer Table. ADLB & ISS. *Note: For each laboratory abnormality the denominator is the number of patients who had baseline and post-baseline values for the test. Severity Grading is by NCI CTCAE. A= Based upon reporting of laboratory data up to 90 days after the end of treatment. B=Prothrombin International Normalized Ratio.*

7.4.3 Vital Signs

Vital signs were obtained at screening and during each follow up visit. No clinically meaningful vital sign changes were observed in the KEYNOTE-059 patient population based on mean change in vital sign measurements from baseline over time.

7.4.4 Electrocardiograms (ECGs)

Standard 12-lead ECGs were obtained once at screening in KEYNOTE-059; however, ECGs were not obtained as part of routine clinical testing during the conduct of the study, unless as clinically necessary.

No special safety studies/clinical trials conducted with pembrolizumab were submitted in this supplemental BLA.

7.4.6 Immunogenicity

According to the applicant, pre- and post-baseline serum samples from patients who have received pembrolizumab have been analyzed for anti-drug antibodies (ADA) as part of the clinical development program for pembrolizumab. In this supplemental BLA submission, the Applicant summarized the data on immunogenicity which comprised a pooled analysis totaling 2874 patients who received pembrolizumab 2 mg/kg, 10 mg/kg, or 200 mg flat dose across studies evaluating patients with melanoma, NSCLC, and HNSCC; of these 2874 patients, 1289 patients were evaluable. These data were reflected in the version of the USPI for pembrolizumab that was current at the time of this supplemental BLA submission, and which stated the following:

“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.”

Merck submitted a proposed update to the USPI with the current supplemental application which states

(b) (4)
27 (2.1%), of which 6 patients (0.5%) had neutralizing antibodies against pembrolizumab. Refer to the Clinical Pharmacology Review of the current sBLA submission for details.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the study providing the primary evidence of safety in this application, KEYNOTE-059, only one dose of pembrolizumab was evaluated. In KEYNOTE-012, Cohort D-(n=39) patients with gastric cancer received pembrolizumab 10 mg/Kg administered every 2 weeks. The table below provides a summary of adverse events in KEYNOTE-059 (Cohort 1) and KEYNOTE-012 (Cohort D).

Table 32. Summary* Adverse Events (AEs) in KEYNOTE-059 and KEYNOTE-012

AE Parameter	KEYNOTE-059 (Cohort 1) 200 mg Q3W (n=259)	KEYNOTE-012 (Cohort D) 10 mg/kg Q2W (n=39)
All grade AEs, n(%)	248 (96%)	39 (100)
Grade ≥3 AEs, n(%)	159 (61)	21 (54)
Serious AEs, n(%)	116 (45)	16 (41)
Deaths, n(%)	16 (6)	3 (8%)
Discontinued due to AE, n(%)	7 (3)	2 (5%)

*Source: Reviewer Table based upon incidence of AEs irrespective of assessment of 'relatedness' to pembrolizumab. *Limited to patients with gastric cancer*

Reviewer Comment: Overall the results of the exploratory analysis shown above do not appear to indicate dose dependency for adverse events. However, these results should be interpreted with caution given the small number of patients enrolled in KEYNOTE-012 and the differences in patients across both studies with regards to number of prior therapies.

A comparison of the incidence of AEOSI in KEYNOTE-059 and -012 is shown in Table 33 below.

Table 33. Adverse Events of Special Interest (AEOSI) in KEYNOTE-059 and KEYNOTE-012

AEOSI Parameter	KEYNOTE-059 (Cohort 1) 200 mg Q3W (n=259)		KEYNOTE-012 (Cohort D) 10 mg/kg Q2W (n=39)	
	n	%	n	%
Colitis	6	2	1	3
Hepatitis	1	<1	1	3
Hyperthyroidism	9	4	3	8
Hypothyroidism	23	9	5	13
Infusion Reactions	4	2	1	3
Myositis	1	<1	0	0
Pancreatitis	0	0	1	3
Pneumonitis	5	2	2	6
Skin	4	2	1	3
Uveitis	1	<1	0	0

Source: Reviewer Table: ADAE (Data cut off January 17, 2017). Represents all-causality adverse events during or within 30 days after last dose of pembrolizumab.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

Reviewer comment: External radiotherapy combined with concomitant chemotherapy is the standard of care treatment of locally advanced gastric and gastroesophageal adenocarcinoma. A consideration in the review of safety in this application was whether exposure to radiation in prior treatment regimens may have increased the risk of pneumonitis particularly among patients with GEJ cancers who may have some volume of lung exposed to radiation. Unfortunately, this analysis was not possible due to the low number of pneumonitis events observed in KEYNOTE-059 (n=5).

7.5.2 Time Dependency for Adverse Events

The time of onset of adverse events of special interest (AEOSI) was analyzed and the results are shown in Table 34 below. Overall, the data indicate that the onset of AEOSI's observed in the KEYNOTE-059 Cohort 1 study population is consistent with the previously observed finding that potentially immune mediated AEs can occur early and late during the course of treatment with pembrolizumab.

Table 34. Time to Onset of Adverse Events of Special Interest

Time to Onset, days	KEYNOTE-059 (n=259)	Pooled melanoma + NSCLC population (n=2799)
Colitis , n (%)	6 (2)	49 (2)
Mean (Std)	86 (63)	129 (99)
Median (range)	81 (22- 190)	107 (9- 494)
Hepatitis , n (%)	1(<1)	19 (1)
Mean (Std)	153	97 (147)
Median (range)	153 (153- 153)	40 (8-651)
Hyperthyroidism , n (%)	9 (4)	96 (3)
Mean (Std)	57 (42)	70 (88)
Median (range)	46 (21- 149)	44 (1- 665)
Hypothyroidism , n (%)	23 (9)	217 (9)
Mean (Std)	75 (43)	124 (89)
Median (range)	69 (21- 157)	106 (1- 576)
Infusion Reactions , n (%)	4 (2)	70 (3)
Mean (Std)	26 (20)	101 (121)
Median (range)	26 (1- 50)	43 (1- 521)
Myositis , n (%)	1 (<1)	11 (<1)
Mean (Std)	143	156 (140)
Median (range)	143- 143	101 (4- 459)
Pneumonitis , n (%)	5 (2)	94 (3)
Mean (Std)	146 (109)	131 (1141)
Median (range)	152 (41- 317)	100 (2- 588)
Skin , n (%)	4 (2)	46 (2)
Mean (Std)	120 (112)	146 (154)
Median (range)	87 (31- 273)	107 (4- 653)
Uveitis , n (%)	1 (<1)	14 (1)
Mean (Std)	381	122 (125)
Median (range)	381- 381	63 (13- 400)

Source: Reviewer table. (Data cut off January 17, 2017)

Reviewer Comment: Given the small numbers of events, the results of the above analysis should be interpreted with caution and conclusions regarding time dependency of adverse events may not be possible.

7.5.3 Drug-Demographic Interactions

Analyses were conducted to evaluate the incidence of treatment emergent adverse events according to key demographic factors including race and ethnicity, sex, age, and geographic region (US versus Ex-US). In general, no major differences were observed with regards to the incidence of adverse events by demographic factors. While some differences were observed in the proportion of patients who experienced some types of

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

adverse events, these differences did not demonstrate a pattern that suggests that any demographic factors independently impact the safety profile of pembrolizumab.

7.5.4 Drug-Disease Interactions

The incidence and severity of adverse events was compared according to ECOG performance status at enrollment. In general, there were no major differences in the incidence of AEs by ECOG performance status (i.e., ECOG 0 versus 1). However, compared to patients with ECOG 0 (n=107), patients with ECOG 1 (n= 151) experienced a higher incidence of serious adverse events (52% vs 36%) and Grade 3-5 adverse events (67% vs 54%).

7.5.5 Drug-Drug Interactions

Given that pembrolizumab is an immunoglobulin G4 (IgG4) antibody that is administered parentally and cleared by catabolism, drug-drug interactions (DDI) are not expected to affect its exposure. No dedicated DDI studies have been performed. Refer to the Clinical Pharmacology review for pembrolizumab in the original BLA submission.

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

Refer to the current USPI for pembrolizumab for information regarding human reproductive and pregnancy risks.

7.6.3 Pediatrics and Assessment of Effects on Growth

Refer to the current USPI for pembrolizumab regarding the safety of pembrolizumab in pediatric patients. Overall, however, such data are of limited relevance for this supplemental BLA, as gastric cancer is extremely rare in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the KEYNOTE-059 trial, pembrolizumab overdose was defined as any dose equal to or greater than 1,000 mg (i.e., ≥ 5 times the indicated dose). No patients In KEYNOTE-059 were reported to have been exposed to a pembrolizumab overdose and no experience with overdose with pembrolizumab is available.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

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

A total of 13 Periodic Adverse Drug Experience Reports (PADER) for pembrolizumab have been generated since the drug was first approved and confirmed that all serious adverse reactions identified in this reports have been previously included in product labeling under earlier supplements. The most recent PADER included information regarding Steven Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), myocarditis, encephalitis, sarcoidosis, myasthenic syndrome, and solid organ transplant rejection. The Applicant's (b) (4)

. The following actions were taken based on this review:

- (b) (4)
- (b) (4)
- (b) (4)
- Thyroiditis added to the existing "thyroid disorders" paragraph in the Warnings and Precautions section of the prescribing information
- Information regarding immune-mediated skin adverse reactions in the Warnings and Precautions section of the prescribing information was updated.
- A "Dear Health Care Provider" letter was issued to inform prescribers regarding the observation of 10 cases (including 3 fatal cases) of Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) have been reported in patients who were treated with KEYTRUDA.

9 Appendices

9.1 Literature Review/References

1. Stomach Cancer: Estimated Incidence, Mortality and Prevalence Worldwide in 2012. <http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp>. Accessed on June 22, 2017.
2. Terry MB, Gaudet MM, Gammon MD. The Epidemiology of Gastric Cancer. *Seminars in Radiation Oncology*. 2002; Vol 12(2): 111-127
3. Siegel, R. L., Miller, K. D. and Jemal, A. (2017), *Cancer statistics, 2017*. CA: A Cancer Journal for Clinicians, 67: 7–30.
4. Cancer Facts and Figures: 2017. American Cancer Society. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf>. Accessed on June 22, 2017.
5. Power DG1, Kelsen DP, Shah MA. Advanced gastric cancer--slow but steady progress. *Cancer Treat Rev*. 2010 Aug;36(5):384-92
6. NCCN Clinical Practice Guidelines: Gastric cancer (Version 2.2017).
7. Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014;15(1):78–86.
8. Kang JH, Lee SI, Lim do H, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012; 30(13):1513–1518.
9. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer*. 2011 Oct;47(15):2306-14
10. Wilke H1, 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 Oct;15(11):1224-35.
11. Macdonald JS1, Gohmann JJ. Chemotherapy of advanced gastric cancer: present status, future prospects. *Semin Oncol*. 1988 Jun;15(3 Suppl 4):42-9.
12. Schnall S1, Macdonald JS. Mitomycin therapy in gastric cancer. *Oncology*. 1993 Apr;50 Suppl 1:70-7.
13. Kim NK1, Park YS, Heo DS, et al. A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. *Cancer*. 1993 Jun 15;71(12):3813-8.

Clinical Review

Lola Fashoyin-Aje

BLA 125514 (Supplement 24)

KEYTRUDA® (pembrolizumab/ MK- 3475)

14. Fushida S, et al. Paclitaxel plus valproic acid versus paclitaxel alone as second- or third-line therapy for advanced gastric cancer: a randomized Phase II trial. *Drug Des Devel Ther.* 2016 Jul 25;10:2353-8
15. Li J, et al. Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction. *J Clin Oncol.* 2016 May 1;34(13):1448-54
16. Tanabe K et al. Phase II/III study of second-line chemotherapy comparing irinotecan-alone with S-1 plus irinotecan in advanced gastric cancer refractory to first-line treatment with S-1 (JACCRO GC-05). *Ann Oncol.* 2015 Sep;26(9):1916-22
17. Lim JY et al. Multi-center Randomized Phase II Study of Weekly Docetaxel Versus Weekly Docetaxel-plus-Oxaliplatin as a Second-line Chemotherapy for Patients with Advanced Gastric Cancer. *Anticancer Res.* 2015 Jun;35(6):3531-6.
18. Satoh T et al. Randomized phase II trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer. *Gastric Cancer.* 2015 Oct;18(4):824-32
19. 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 Jan 4;383(9911):31-9.
20. Ohtsu A, Ajani JA, Bai YX, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol.* 2013 Nov 1;31(31):3935-43.
21. Roy AC, Park SR, Cunningham D, et al. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. *Ann Oncol.* 2013 Jun;24(6):1567-73.
22. Comprehensive molecular characterization of gastric adenocarcinoma. *Cancer Genome Atlas Research Network. Nature.* 2014 Sep 11;513(7517):202-9.
23. Cristescu R, Lee J, Nebozhyn M, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med.* 2015;21:449–456.
24. Bass AJ, Thorsson V, Shmulevich I, et al. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014;513: 202–209.
25. Ooi CH, Ivanova T, Wu J, et al. Oncogenic pathway combinations predict clinical prognosis in gastric cancer. *PLoS Genet.* 2009 Oct; 5(10):e1000676.
26. Wadhwa R, Song S, Lee JS, et al. Gastric cancer-molecular and clinical dimensions. *Nat Rev Clin Oncol* 2013;10(11):643–655.

9.2 Labeling Recommendations

Labeling was ongoing at the time of this review. FDA proposed the following changes to Merck's proposal for product labeling relevant to this indication:

- (b) (4)

However, given the modest effect of pembrolizumab demonstrated in KEYNOTE-059, outside expertise was sought to provide input regarding the magnitude of benefit conferred by this treatment. This effort was ongoing at the time of this report.

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

/s/

IBILOLA A FASHOYIN-AJE
09/19/2017

MARTHA B DONOGHUE
09/19/2017