APPLICATION NUMBER:

125514Orig1s024

SUMMARY REVIEW
<table>
<thead>
<tr>
<th>Date</th>
<th>September 22, 2017</th>
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</thead>
<tbody>
<tr>
<td>From</td>
<td>Martha Donoghue, MD</td>
</tr>
<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
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<tr>
<td>BLA #</td>
<td>Supplement 24, BLA 125514</td>
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<tr>
<td>Applicant</td>
<td>Merck &amp; Co. (Merck)</td>
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<tr>
<td>Date of Submission</td>
<td>March 22, 2017</td>
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<td>PDUFA Goal Date</td>
<td>September 22, 2017</td>
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<tr>
<td>Proprietary Name / Established Name</td>
<td>Keytruda/pembrolizumab</td>
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<tr>
<td>Proposed Dosing Regimen</td>
<td>200 mg intravenously every three weeks</td>
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</table>

**Applicant Proposed Indication(s)/Population(s):**

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma.

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

**Recommended Regulatory Action:**

*Accelerated approval*

**Recommended Indication(s)/Population(s):**

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy.

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

On March 22, 2017 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck) submitted Supplement 24 to Biologics License Application (BLA) 125514, seeking approval under the provisions for 21 CFR 601.41 (accelerated approval) for pembrolizumab (Keytruda) for the following proposed indication:

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

Pembrolizumab, a humanized, programmed death receptor-1 (PD-1)-blocking monoclonal antibody, was first approved on September 4, 2014, for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600-mutation positive, a BRAF inhibitor. Following this approval, approved pembrolizumab for the treatment of the following cancers:

- unresectable or metastatic melanoma
- PD-L1-positive, non-small cell lung cancer;
- recurrent or metastatic head and neck squamous cell carcinoma;
- classical Hodgkin lymphoma (cHL) that is refractory or relapsed after 3 or more prior lines of therapy; and locally advanced or metastatic urothelial carcinoma in patients who are not eligible for cisplatin-containing chemotherapy or with disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- Unresectable or metastatic Microsatellite instability-High or mismatch repair deficient cancers
  - That have progressed following prior treatment and have no satisfactory alternative treatment options
  - Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

2. Background

Indicated Population and Available Therapy

Although the incidence of gastric cancer has been declining over the past 2 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 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%. 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%.

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 (GEJ) 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. 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 adenocarcinoma, including adenocarcinoma of the gastroesophageal junction (GEJ), who have not received prior chemotherapy for advanced disease (See Taxotere USPI).

In addition to cytotoxic agents, patients whose tumors express HER2 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). In these trials, the median OS rates were 4-5 months. 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 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 ramucirumab USPI]). A greater proportion of patients achieved responses (partial or complete responses) 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 [1.4–4.4] in the placebo plus paclitaxel arm.
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 HER2 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.

Pre-Submission Regulatory History
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 pre-submission regulatory activities relevant to this supplemental BLA are summarized below.

February 20, 2013
Merck submitted new protocol for KEYNOTE-012 under IND 110080 to evaluate MK-3475 in patients with advanced solid tumors.

August 14, 2013
Merck amended KEYNOTE-012 protocol to evaluate pembrolizumab in a new cohort (Cohort D) of patients with advanced gastric cancer.

November 21, 2014
Merck 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
Merck submitted the Initial Pediatric Study Plan (iPSP) for gastric cancer which included...

April 30, 2015
Merck 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
Merck submitted the Agreed iPSP to FDA; FDA issued an iPSP Agreement letter for the 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, 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
Merck 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
Merck 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.

Submission Regulatory History

March 22, 2017
sBLA 125514/S-24 for treatment of patients was submitted

April 18, 2017
sPMA for the Dako PD-L1 IHC assay for gastric cancer submitted.

April 26, 2017
Face to face application orientation meeting held.

May 23, 2017
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 pembrolizumab 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.

June 21, 2017
Merck 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 response durability data. The Applicant also submitted a revised proposed USPI to reflect updates to the efficacy data.

August 23, 2017
In response to FDA’s request for information pertaining to the April 29, 2016, the external Data Monitoring Committee (eDMC) recommendation that Merck halt enrollment of patients with PD-L1 negative tumors in the trial, embargoed information related to interim results of the KEYNOTE-061 trial and relevant communications between the eDMC and the Executive Oversight Committee (EOC) were submitted via email. This information was submitted to the BLA in CD-ROM format on September 13, 2017.

September 15, 2017
Merck submitted agreed upon language and milestone dates for postmarketing requirement to verify and confirm the clinical benefit of pembrolizumab in patients with PD-L1 gastric cancer
and a postmarketing commitment to further characterize the duration of response in patients with PD-L1 positive gastric cancer in the KEYNOTE-059 trial.

3. Product Quality

There are no outstanding product quality issues that preclude approval.

This sBLA included submission of data to support a new assay for the detection and confirmation of antibodies for pembrolizumab (MK-3475) in human serum, and data supporting a new immunogenicity assay for the detection of neutralizing antibodies to pembrolizumab (MK-3475) in human serum. The Office of Biotechnology Products (OBP) reviewers concluded that the qualification of new negative and positive controls for the screening/confirmatory assay to detect anti-drug-antibodies and validation of the new, more sensitive assay to detect neutralizing antibodies against were acceptable.

This sBLA also included a request for categorical exclusion from the environmental assessment, which was accepted by OPB and the quality reviewer determined that appropriate pembrolizumab drug product supplies were used in these studies.

4. Nonclinical Pharmacology/Toxicology

Not applicable to this efficacy supplement.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval. This supplement contained the following clinical pharmacology information:

- An update immunogenicity report

- Results of an updated population pharmacokinetic (popPK) analysis pooling data from gastric cancer patients in Studies KEYNOTE-059 and KEYNOTE-012 into the existing dataset.

This sBLA did not include immunogenicity results in patients with gastric cancer or gastroesophageal junction adenocarcinoma from KEYNOTE-059 and KEYNOTE-012; however, it included an updated immunogenicity report with data from multiple studies enrolling nearly 3000 patients with melanoma, NSCLC or head and neck squamous cell carcinoma (HNSCC) evaluating the incidence of anti-drug antibody (ADA) positive samples utilizing the latest generation of ADA and neutralizing anti-drug antibody (Nab) assays. The updated immunogenicity rate among the 1289 evaluable patients was similar to that previously described in product labeling. The observed incidence of treatment emergent ADA in 1289 evaluable patients based on a pooled analysis of melanoma, NSCLC and HNSCC patients was 2.1% (27 out of 1289). The remainder of the 1289 evaluable patients included 12 with non-treatment
emergent positive ADA (0.9%) and 1250 (97%) with negative ADA immunogenicity status. Among the 27 patients with treatment emergent ADA, 6 patients had antibodies with neutralizing capacity, for an overall incidence of 0.5% (6 out of 1289) neutralizing ADA. Merck also included additional analyses to determine the potential effect of treatment emergent ADA on exposure, safety and efficacy. For all of the 27 patients with treatment-emergent ADA, the exposure of pembrolizumab was similar to that for other patients treated with the same regimen. Furthermore, patients with treatment-emergent ADAs did not appear to have an increased risk of adverse events associated with neutralizing antibodies (e.g. anaphylaxis, urticaria, angioedema) or injection site reactions. There was no observable relationship between tumor size and the presence or absence of treatment-emergent neutralizing antibodies. Given the low incidence rate (2.1%) of ADA formation and the lack of effect of ADAs on the exposure, safety and efficacy of pembrolizumab, the clinical pharmacology review team considered it acceptable to not test immunogenicity in patients with gastric or gastroesophageal junction adenocarcinoma and concluded that the available immunogenicity data from the 2874 evaluable pembrolizumab-treated patients across multiple tumor types support the use of pembrolizumab in patients with gastric cancer or gastroesophageal junction adenocarcinoma.

In this submission, Merck also provided data from an extension of the population pharmacokinetics (popPK) analysis of pembrolizumab to gastric cancer population. An existing time-dependent population PK model in patients with melanoma or non-small cell lung cancer (NSCLC) was used as the starting point of the present analysis. Data from gastric cancer patients in studies KN059 and KN012 were added to the existing popPK dataset and the parameters from the existing model were re-estimated. Results of this analysis showed comparable estimated PK parameters between gastric cancer and other types of tumors. In addition, comparison of observed data also suggested that pembrolizumab exposure in patients with gastric cancer and NSCLC following 200 mg Q3W pembrolizumab doses were comparable. Therefore, the clinical pharmacology reviewers concluded that the PK of pembrolizumab is similar in gastric cancer patients and patients with other types of tumors.

The clinical pharmacology review team concluded that a postmarketing requirement (PMR) or postmarketing commitment (PMC) clinical pharmacology study was not needed to support approval of this sBLA.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

7.1. Source of Efficacy Data

Merck submitted data from KEYNOTE-059 to support this supplemental application. Key features of KEYNOTE-059 will be described in this section.

Design: KEYNOTE-059, an ongoing open-label, multi-center, multiple disease-specific cohort trial, evaluating the safety and efficacy of pembrolizumab 200 mg administered intravenously once every three weeks in patients with gastric or gastroesophageal junction adenocarcinoma
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 efficacy data supporting Merck’s current request for a new indication for the treatment of patients (gastric cancer).

**Study Population:** The eligible patient population for Cohort 1 met the following key inclusion and exclusion criteria:

**Inclusion Criteria:**

1. Male/female 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 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. Tumor is HER2/neu negative, or, if HER2 positive, has previously received therapy with trastuzumab (Note: if HER2/neu status was previously determined, that result was acceptable but documentation of status must have been available; patients with unknown status had their HER2/neu status determined locally. Documentation of previous therapy with trastuzumab was provided).
5. Presence of adequate tissue for retrospective assessment of PD-L1 status of was required.
6. 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).
7. Presence of ECOG performance status of 0 or 1.
8. Life expectancy of at least 3 months.

**Exclusion Criteria:**

1. Weight loss > 10 % over 2 months prior to first dose of study therapy.
2. 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.

Reference ID: 4156909
replacement therapy for adrenal or pituitary insufficiency, etc.) was not considered a form of systemic treatment.

5. Known history of, or any evidence of active, non-infectious pneumonitis.
6. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

**Treatment:** Patients received pembrolizumab 200 mg administered as a 30 minute IV infusion on Day 1 of every 3 week cycle, 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 one additional year of treatment if they experienced disease progression after completing the initial course, and had no received other therapies in the interim.

**Biomarker Assessment (PD-L1 and Microsatellite instability):** A tumor sample was characterized as PD-L1 positive if the immunohistochemistry staining was $\geq 1\%$ based on the combined positive score (CPS). The CPS method captured 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. Clinical sites submitted newly-obtained or archival specimens for PD-L1 immunohistochemistry testing. Microsatellite instability (MSI) testing was not conducted in a prospective fashion.

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

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 final analysis was to be conducted when 80 or more patients had been enrolled irrespective of tumor PD-L1 status and received a minimum of 6 months of pembrolizumab or had discontinued pembrolizumab due to progression of disease.
7.2. Summary of Efficacy Results

The protocol-defined dual primary efficacy endpoints were the overall response rate (ORR) per RECIST 1.1 assessed by blinded independent central review committee in all patients who received at least one dose of pembrolizumab and in patients with PD-L1 positive tumors.

Refer to the clinical and biometrics reviews for the results of analyses of demographics and baseline factors. A total of 148 patients (57%) were reported as having PD-L1 positive tumors, 109 patients (42%) had PD-L1 negative tumors, and PD-L1 assessment was not performed for 2 patients’ cancers.

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.

The results of the ORR analyses in the overall population and by PD-L1 expression status are shown in Table 1.

Table 1. Results of Response Evaluation: KEYNOTE-059 (n=259)

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

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

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.

Among the 7 MSI-high patients, 4 achieved responses (57%). All 4 patients who achieved responses also had PD-L1 positive tumors. The analysis of ORR by microsatellite expression status is shown below in Table 2.
Table 2. ORR by Microsatellite Status; KEYNOTE-059- (n=259)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>MSI-high patients, n=7</td>
<td>4</td>
<td>57.1</td>
<td>(18.4, 90.1)</td>
</tr>
<tr>
<td>MSS + microsatellite unknown, n= 252</td>
<td>26</td>
<td>10.3</td>
<td>(6.9, 14.8)</td>
</tr>
<tr>
<td>MSS, n= 167</td>
<td>15</td>
<td>9.0</td>
<td>(5.1, 14.4)</td>
</tr>
<tr>
<td>Microsatellite unknown, n= 85</td>
<td>11</td>
<td>12.9</td>
<td>(6.6, 22.0)</td>
</tr>
</tbody>
</table>

Note: Data cut-off date of January 16, 2017.

The median follow-up for response duration among patients who achieved partial or complete responses (responders) was 13.9 months (range: 5.6 to 24.7). The results of the analysis of duration of response (DoR) are shown Table 3.

Table 3. Duration of Response KEYNOTE-059 (n=259)

<table>
<thead>
<tr>
<th>All Patients N= 259*</th>
<th>PD-L1 + N=148</th>
<th>PD-L1- N= 109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Response Duration in months (range)</td>
<td>14.2 (2.4, 19.4+)</td>
<td>14.2 (2.8+, 19.4+)</td>
</tr>
<tr>
<td>Patients with DoR ≥ 6 months</td>
<td>18 (60%)</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>Patients with DoR ≥12 months</td>
<td>6 (20%)</td>
<td>6 (26%)</td>
</tr>
</tbody>
</table>

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.

The review team decided to base the assessment of the effectiveness of pembrolizumab for this application on the overall response rate and duration of response in the subpopulation of patients with gastric or gastroesophageal adenocarcinoma that were not known to be MSI-H and who had PD-L1 positive tumors. This decision was based on the following factors:

1. Pembrolizumab is already approved for the treatment of patients with MSI-H tumors (including MSI-H gastric cancer).
2. 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 (See Section 7.3 below for details).
3. Emerging data from the KEYNOTE-61 trial suggesting that patients with PD-L1 negative gastric cancer are unlikely to derive a survival benefit from pembrolizumab.

Among the 259 patients treated with pembrolizumab, 55% (n = 143) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than 1 and microsatellite stable (MSS) tumor status or no determination of MSI or deficient mismatch repair (dMMR) status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. CPS is the number of PD-L1 positive cells (tumor cells, macrophages, lymphocytes) divided by total number of tumor cells, expressed as a percentage.
The baseline characteristics of these 143 patients were: median age 64 years (47% age 65 or older); 77% male; 82% White, 11% Asian; and ECOG PS of 0 (43%) and 1 (57%). Eighty-five percent had M1 disease and 7% had M0 disease. Fifty-one percent had two and 49% had three or more prior lines of therapy in the recurrent or metastatic setting. The results of the analysis of the ORR based on PD-L1 status and excluding patients who were known to be MSI-H are shown below.

Table 4. Results of Response Evaluation: KEYNOTE-059 (n=252)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ALL A,B</th>
<th>PD-L1 + B</th>
<th>PD-L1 - B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR 0 (%)</td>
<td>26 (10.3)</td>
<td>19 (13.3)</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(6.9, 14.8)</td>
<td>(8.2, 20.0)</td>
<td>(2.7, 13.0)</td>
</tr>
<tr>
<td>CR</td>
<td>5 (2.0)</td>
<td>2 (1.4)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>PR</td>
<td>21 (8.3)</td>
<td>17 (11.9)</td>
<td>4 (3.7)</td>
</tr>
</tbody>
</table>

Note: Data cut-off date of January 16, 2017; A Two patients with unknown PD-L1 status are included in total. B Excludes MSI-high patients.

For the 143 patients, the ORR was 13.3% (95% CI: 8.2, 20.0); 1.4% had a complete response and 11.9% had a partial response. Among the 19 responding patients, the duration of response ranged from 2.8+ to 19.4+ months, with 11 patients (58%) having responses of 6 months or longer and 5 patients (26%) having responses of 12 months or longer. The results are shown in below.

Table 5. Duration of Response KEYNOTE-059 (n=252)

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

Note: Response duration based on data cut-off date of April 21, 2017. *Includes two patients with unknown PD-L1 status. A Based on numerical proportions.

7.3 PD-L1 Testing and Tumor Specimen Age
Merck submitted patient-level data regarding the characteristics of the tumor tissue used to assess PD-L1 tumor status. These data were submitted per FDA’s request based upon the observation that there were 3 patients who achieved complete responses among the subgroup of patients who were categorized as having PD-L1 negative tumors; these patients were not MSI-H. Table 6 Table 6 and Table 7 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).

Reference ID: 4156909
Table 6. PD-L1 Positive Rate by Age of Tumor Specimen

<table>
<thead>
<tr>
<th>Age of Tissue (days)</th>
<th>PD-L1 Positive* % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤42</td>
<td>73.3 (66/90)</td>
</tr>
<tr>
<td>43-900</td>
<td>52.9 (64/121)</td>
</tr>
<tr>
<td>&gt;900</td>
<td>39.1 (18/46)</td>
</tr>
</tbody>
</table>

*Defined as CPS ≥1%

Table 7. PD-L1 Test Results by Specimen Type: Archival versus Newly Obtained

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>PD-L1+ n (%)</th>
<th>PD-L1+ Responders (n=23) n(%)</th>
<th>PD-L1- n (%)</th>
<th>PD-L1– Responders(n=7) n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Archival (&gt;42 days) n=157 (65.0)</td>
<td>82 (49.9)</td>
<td>12 (52.2)</td>
<td>85 (47.7)</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td>Newly Obtained (&lt;42 days) n=90 (35.0)</td>
<td>66 (73.3)</td>
<td>11 (47.8)</td>
<td>24 (26.6)</td>
<td>1 (14.2)</td>
</tr>
</tbody>
</table>

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.

Overall, the rate of PD-L1 positivity was lower in archival tumor tissue compared to newly obtained tissue. Among the tumor tissue specimens that were > 900 days old at the time of testing, 39% were assessed as being PD-L1 positive compared to 73% of newly obtained specimens. 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, and 6 of the 7 PD-L1 negative patients that had an objective response to pembrolizumab had tumor specimens that were > 400 days old. Given the differences in PD-L1 expression detected in archival versus newly obtained gastric cancer tissue and the older age of specimens in patients with PD-L1 negative tumors who exhibited a response to pembrolizumab, FDA concluded that there is uncertainty regarding whether the response rate in the PD-L1 negative population in KEYNOTE-059 was representative of the effect of pembrolizumab in PD-L1 non-expressing gastric cancers.

7.4 Patient Quality of Life

No clinical outcomes assessment data (COA) were included in this application. With Amendment 3 to the KEYNOTE-059 protocol, Merck removed the quality of life assessments due to concerns regarding the difficulties with interpreting COA data derived from a single arm trial.
8. Safety

Analyses of safety data in this supplemental application were limited by the lack of a control arm and by the relatively small number of patients enrolled in KEYNOTE-059 (n=259). Nevertheless, the clinical reviewer found that the safety profile of pembrolizumab in this application was consistent with the known safety profile of pembrolizumab described in product labeling. The observed incidence of adverse events (AEs) did not appear to be in excess of what would be expected in this clinical setting and likely related to underlying advanced gastric cancer.

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. A total of 46 patients (18%) experienced one or more adverse events of special interest. None of these events were fatal. 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. Refer to the clinical review for a detailed description of safety.

9. Advisory Committee Meeting

This efficacy supplement was not referred to the Oncologic Drugs Advisory Committee since the safety profile is acceptable for the indicated patient population and durable overall response rate has been used as a primary endpoint to support accelerated approval of multiple drugs and biologics for the treatment of refractory cancers. Given the relatively modest overall response rate in this application, the Division decided to enlist the advice of three Special Government Employees (SGEs) with expertise in the treatment of patients with gastric cancer and one patient representative who is a gastric cancer survivor. Following clearance by the Division of the Advisory Committee and Consultant Management staff, the Division provided a briefing document summarizing the data included in the sBLA to each SGE and held four separate teleconferences (one with each SGE) to discuss the overall risk:benefit assessment of the application and seek advice regarding draft labeling for Keytruda.

The SGEs were unanimous in their opinion that the data provided in the sBLA supported a favorable benefit:risk assessment for use of pembrolizumab in patients with PD-L1 positive gastric cancer with disease progression following two or more prior therapies. The SGEs acknowledged that the overall response rate was relatively modest, but were impressed with the long duration of responses observed in the patients who exhibited a response to treatment with pembrolizumab. Each also expressed an opinion that pembrolizumab provides a much needed treatment option for patients with advanced gastric cancer. None of the SGEs had particular concerns with the overall safety profile of pembrolizumab for use in patients with gastric cancer. Two SGEs stressed the importance of including a recommendation in product labeling for consideration of obtaining a fresh biopsy for patients with tumors that were determined to not express PD-L1 based on testing of an archival tumor specimen given the concern regarding differences in assay sensitivity in older tumor specimens.
10. **Pediatrics**

This application is exempt from the requirements under the Pediatric Research Equity Act because pembrolizumab received orphan designation for the treatment of patients with gastric cancer including gastroesophageal junction adenocarcinoma on June 16, 2015.

11. **Other Relevant Regulatory Issues**

The Applicant included the following statement in the sBLA 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.

The clinical review team, in conjunction with the Office of Scientific Investigations, determined that site inspections were not necessary because the Applicant and the independent radiology review contractor ( ) have undergone recent site inspections that did not uncover significant findings and subgroup analyses of study results by clinical site did not identify any data trends that would warrant inspection of any particular site.

In accordance with 21 CFR 54, the Applicant submitted a list of study clinical investigators and sub-investigators for KEYNOTE-059, 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, with the following two exceptions:

- 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) held financial interest and/or arrangements (Type/Amount: Grant of $1,487,485.00 in a contract with 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.

The clinical reviewer concluded that these financial interests were unlikely to influence the study results because no patents enrolled in these clinical sites achieved a partial or complete response to pembrolizumab.
12. Labeling

This section of the review will focus on high-level issues regarding the labeling submitted by Merck.

Indications and Usage: DOP2 revised the indication to reflect

The agreed upon indication statement is listed below.

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Dosage and Administration: DOP2 concurred with proposed recommended dosage of 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression unacceptable toxicity, or up to 24 months in patients without disease progression. FDA also recommended inclusion of information in the Patient Selection subsection regarding use of an FDA-approved test to identify patients with PD-L1 expressing gastric cancer, and a recommendation to evaluate the feasibility of obtaining a fresh tumor biopsy if results based on archival tissue showed lack of PD-L1 expression.

Warnings and Precautions: There were no new safety signals identified in KEYNOTE-059. Given the large safety database already evaluated for serious adverse reactions of pembrolizumab, risks of pembrolizumab have been adequately characterized and this section was not updated to include the results from KEYNOTE-059 which would not have altered the current description of serious adverse events in a meaningful way.

Adverse Reactions: Because the safety profile of pembrolizumab was generally similar to the safety profile observed for other pembrolizumab indications, abbreviated information was incorporated into the Gastric Cancer subsection of product labeling. Information regarding pembrolizumab exposure in patients with gastric cancer was added, along with a statement indicating that the toxicity profile in patients with gastric cancer was similar to the toxicity profile observed in patients with non-small cell lung cancer or melanoma. The Immunogenicity subsection was updated to incorporate data from multiple studies in patients with melanoma, non-small cell lung cancer or head and neck squamous cell carcinoma evaluating anti-drug antibody (ADA) positive samples using the latest ADA and neutralizing anti-drug antibody assays.
Clinical Pharmacology: Section 12.3 was updated to incorporate the results of population PK modeling that incorporated gastric cancer data from KEYNOTE-012 and KEYNOTE-059.

Clinical Studies Section: In the gastric cancer subsection, extensive revisions were made to Merck’s proposed labeling. Information regarding responses in patients with MSI-H gastric cancer was also added. was omitted.

Medication Guide: This section was revised in conjunction with the Patient Labeling Team to provide information about the gastric cancer indication. Minor additional editorial/formatting revisions were also incorporated.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

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.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMR
In accordance with 21 CFR 601.41 Subpart E (accelerated approval), to confirm the clinical benefit of treatment with pembrolizumab, Merck agreed to 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 (MMR) proficient metastatic gastric or gastroesophageal junction adenocarcinoma.

Note: There is an existing PMR for Merck to submit the results of trials conducted to verify and describe the clinical benefit of pembrolizumab in patients with MSI-H or mismatch repair deficient tumors in at least 300 patients with non-colorectal cancers (PMR 3213-1). This PMR is intended to verify the clinical benefit of pembrolizumab in patients with MSI-H cancers, including MSI-H gastric cancers.

PMC
In order to obtain a more precise estimate of the duration of response in patients with refractory gastric cancer Merck agreed to submit the final study report from patients with PD-L1 positive
Cross Discipline Team Leader Review

Microsatellite stable or microsatellite-instability (MSI)-unknown gastric cancer enrolled in Cohort 1 of KEYNOTE-059 as a post-marketing commitment (PMC), ensuring a minimum follow-up of 12 months and assessment of duration of response by independent central review.

14. Recommended Action and Benefit:Risk Assessment

Recommended Regulatory Action

I recommend accelerated approval of pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy.

Risk:Benefit Assessment.

Locally advanced or metastatic gastric/gastroesophageal junction (GEJ) adenocarcinoma is a serious and life threatening disease. 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 an estimated 5-year survival rate of less than 10%. [5]. 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) have 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.

In this supplemental BLA, the efficacy of pembrolizumab is based upon data from Study KEYNOTE-059, a multicenter, non-randomized, open-label multi-cohort trial that enrolled 259 patients with gastric or GEJ adenocarcinoma who progressed on at least 2 prior systemic treatments for advanced disease. Previous treatment must have included a fluoropyrimidine and platinum doublet and patients with HER2/neu positive tumors must have previously received an approved HER2/neu-targeted therapy. Patients received pembrolizumab 200 mg every 3 weeks until occurrence of unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Assessment of tumor status was performed every 6 to 9 weeks. The major efficacy outcome measures were overall response rate (ORR) according to RECIST 1.1, as assessed by blinded independent central review (BICR), and duration of response (DOR).
Two major issues addressed by the FDA review team during evaluation of this supplemental application related to identification of the efficacy population and whether to base the assessment of the effectiveness of pembrolizumab for this application on the ORR and DOR in the subpopulation of patients with PD-L1 positive gastric or gastroesophageal adenocarcinoma that were not documented to be MSI-H (n=143). This decision was based on multiple factors.

First, pembrolizumab is already approved for the treatment of patients with MSI-H tumors (including MSI-H gastric cancer) based on demonstration of clinically meaningful and durable overall responses. Although a substantial minority (33%) of patients had with tumors unknown MSI status, the review team decided to include these patients in the efficacy population because among the patients with known MSI status, incidence of MSI-H gastric cancer was low (4%) and therefore it is unlikely that a high proportion of patients with undetermined MSI status were MSI-H.

The review team concluded that data from the KEYNOTE-059 trial did not provide sufficient evidence that pembrolizumab was effective in patients with PD-L1 negative gastric/GEJ cancer. The ORR in patients with microsatellite stable (MSS) or undetermined microsatellite instability (MSI) PD-L1 negative gastric/GEJ cancer enrolled in KEYNOTE-059 was lower (6.4%) than the observed ORR in patients with MSS or MSI-unknown PD-L1 positive gastric/GEJ cancer (13%) (see Table 4 in section 7.3.1 of this review). Furthermore, there is uncertainty regarding whether the ORR 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/GEJ cancer due to decreased assay sensitivity in archival tumor specimens resulting in an overestimation of the true treatment effect by possible inclusion of patients with false negative PD-L1 results (Tables 6 and 7 in Section 7.3.2 of this review). Finally, FDA reviewed embargoed data from the KEYNOTE-61 trial (an ongoing trial randomizing patients with gastric cancer that has progressed following first line treatment to either pembrolizumab or capecitabine) that was reviewed by the external data monitoring committee prior to institution of a protocol amendment discontinuing enrollment of patients with PD-L1 negative tumors. These data suggest that patients with PD-L1 negative gastric cancer are unlikely to derive a benefit from treatment with pembrolizumab.

Among the 259 patients enrolled in KEYNOTE-59, 55% (n = 143) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. The baseline characteristics of these 143 patients were: median age 64 years (47% age 65 or older); 77% male; 82% White, 11% Asian; and ECOG PS of 0 (43%) and 1 (57%). Eighty-five percent had M1 disease and 7% had M0 disease. Fifty-one percent had two and 49% had three or more prior lines of therapy in the recurrent or metastatic setting.

For the 143 patients with PD-L1 positive tumors and MSS or undetermined MSI tumor status, the BIRC-assessed ORR according to RECIST was 13.3% (95% CI: 8.2, 20.0); 1.4% had a complete response and 11.9% had a partial response. Patients who achieved partial or complete responses appeared to have sustained responses. Among the 19 responding patients, the duration of response ranged from 2.8+ to 19.4+ months, with 11 patients (58%) having responses of 6 months or longer and 5 patients (26%) having responses of 12 months or longer.
The review team determined that the efficacy data provided in the sBLA satisfied the criteria for accelerated approval of pembrolizumab in patients with gastric/GEJ cancer whose tumors express PD-L1 with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy. This determination was primarily based on the observed response rate and, in particular, the magnitude of the duration of response, indicating that pembrolizumab treatment is likely to provide a meaningful clinical benefit to patients. Although the observed ORR is relatively modest, for patients who achieved responses, the duration of responses is striking; with 58% of responders having a duration of response of more than 6 months and 26% of responders having a response of more than 12 months. For patients with refractory gastric/GEJ cancer, this duration of response is clinically meaningful given the dismal prognosis of patients with refractory disease and likely to predict the clinical benefit (improved survival) of pembrolizumab.

The toxicity of pembrolizumab is related to its mechanism of action, which can result in development of autoimmune disease. As with prior approvals in other tumor types, the risks of immune-mediated adverse reactions are acceptable for patients with a life-threatening disease such as gastric cancer given the ability to manage those risks, in most cases, with discontinuation of pembrolizumab and medical intervention (e.g., administration of corticosteroids).

Among the 259 patients with gastric cancer enrolled in Study KEYNOTE-059, the median duration of exposure to pembrolizumab was 2.1 months (range: 1 day to 21.4 months). Adverse reactions occurring in patients with gastric cancer were similar to those occurring in patients with melanoma or non-small cell lung cancer (NSCLC). As with other approved indications, the adverse reaction profile of pembrolizumab appears manageable in patients with gastric cancer, with only 3% of patients in the KEYNOTE-059 trial discontinuing pembrolizumab due to an adverse event.

Based on these considerations and taking into account the totality of the data and outcomes with currently available treatments, I agree with the clinical and statistical review teams’ conclusion that the benefit-risk profile for pembrolizumab is favorable in patients with gastric or GEJ adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu targeted therapy.

Concurrent with the approval of pembrolizumab for this indication sBLA, the Center for Diagnostics and Radiological Health will approve the Premarket Approval Application (PMA) supplement (P150013/S006) for the Dako PD-L1 IHC-22c3 pharmDx assay for the identification of patients with gastric cancer that expresses PD-L1, for whom treatment with pembrolizumab has been shown to be safe and effective.
15. References

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

/s/

MARTHA B DONOGHUE
09/22/2017

PATRICIA KEEGAN
09/22/2017
I concur with this review.