Review Memo

Application Type	Supplemental Biologics License Application(s)
Application Number(s)	125514
Priority or Standard	Standard
Submit Date(s)	• April 13, 2020: complete submission of Merck's response to the CR letter to Supplements 59, 60, 61, 62, 63, 64, 69 • April 14, 2020: Supplements 76, 77, 78, 79, 80 • April 15, 2020: Supplements 81, 82 • April 20, 2020: Supplement 83
Received Date(s)	Same as above
PDUFA Goal Date	October 13, 2020 (for Merck's response to the CR letter)
Division/Office	DO3/OOD
Established/Proper Name	pembrolizumab
Trade Name	Keytruda
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Dosage form	Injection, for intravenous use
Applicant proposed Dosing Regimen	400 mg every six weeks
Applicant Proposed Indication(s)/Population(s)	New 400 mg every six weeks dosing regimen for all approved indications
Recommendation on Regulatory Action	Accelerated approval

Regulatory Background

For regulatory background prior to the submission of the original efficacy supplements (59, 60, 61, 62, 63, 64, and 69) refer to my review dated February 18, 2020. Also refer to the February 18, 2020, review for information on prior regulatory approaches to support the approval of PK-based changes in dosing for nivolumab and atezolizumab.

On April 18, 2019, Merck submitted an efficacy supplement (59) to support the addition of an alternative dosing regimen of 400 mg every 6 weeks to the "Dosage and Administration" section of the pembrolizumab USPI for the treatment of melanoma.

On April 23, 2019, Merck submitted efficacy supplements to support the addition of the alternative dosing regimen of 400 mg every 6 weeks for the following additional indications:

- Classical Hodgkin lymphoma (60)
- Primary mediastinal large B-cell lymphoma (61)
- Hepatocellular carcinoma (62)
- Merkel cell carcinoma (63)
- Gastric or gastroesophageal junction adenocarcinoma (64)
- Non-small cell lung cancer (69)

In these supplemental applications, Merck proposed to use a pharmacokinetics and exposure-response-based strategy to bridge the proposed 400 mg every six weeks regimen to the approved dosing regimens of 200 mg every three weeks or 2 mg/kg every three weeks by leveraging clinical data and models developed based on clinical trial data of pembrolizumab in studies in melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, urothelial cancer, gastric cancer, microsatellite high/mismatch repair deficient (MSI-H/dMMR) cancers, primary mediastinal large B-cell lymphoma, hepatocellular cancer, and cervical cancer. Merck did not submit new clinical or preclinical data in the submissions.

On February 18, 2020, FDA issued a Complete Response letter for the applications. The CR letter included the following two items:

1. The supplements, supported by pharmacokinetic modeling, contained insufficient information to determine that the proposed 400 mg every six weeks dose is safe and effective for the treatment of patients with melanoma, cHL, PMBCL, HCC, MCC, gastric cancer, and NSCLC.

   The safety and effectiveness of pembrolizumab in ipilimumab-refractory melanoma, previously-treated NSCLC, and MCC were established in trials that evaluated a dosing regimen of 2 mg/kg every three weeks whereas the safety and effectiveness of pembrolizumab in the adjuvant treatment of melanoma, first-line NSCLC as a single agent or in combination with chemotherapy, cHL, PMBCL, HCC, and gastric cancer (and other indications) were established in trials that evaluated a flat pembrolizumab dose of 200 mg every three weeks.

   Although the predicted C_{trough} (based on modeling) for the pembrolizumab dosing regimen of 400 mg every six weeks was within 20% of the measured C_{trough} of patients exposed to the 2 mg/kg every three weeks regimen, the predicted C_{trough} of the 400 mg every six weeks dose was outside of 20% of the measured C_{trough} of patients exposed to the 200 mg every three weeks regimen. Therefore, based on an assessment of C_{trough} alone, the potential exists that efficacy may be reduced in patients with different malignancies.

   In addition to the scientific concerns described above, if information could be provided in amended supplements to support the approval of the proposed dosing regimen only in ipilimumab-refractory melanoma, previously-treated NSCLC, and MCC, we would need to understand how labeling would be sufficient to communicate the recommended dose in each of the indications. As a practical matter, pembrolizumab is generally not administered in patients with ipilimumab-refractory melanoma and patients with NSCLC frequently receive pembrolizumab in the first-line setting. Use of pembrolizumab in the treatment of patients with MCC is uncommon due to the rarity of this tumor. Therefore, the vast use of pembrolizumab is expected to be in indications where the safety and effectiveness of pembrolizumab were assessed in clinical trials

using the 200 mg every three weeks regimen. Therefore, from a public health perspective, ensuring a safe and effective regimen of pembrolizumab across each indication will be important.

To address these concerns, provide adequate clinical outcomes data from one or more clinical trials in at least one condition of use along with pharmacokinetics (PK) data sufficient to demonstrate the safety and effectiveness of the alternate pembrolizumab dosing schedule. If you propose to limit the proposed regimen to certain indications, you will need to provide adequate labeling and justification to address the safe and effective use of pembrolizumab only in the proposed indications.

2. Among patients with hematologic malignancies, there have been differences in safety compared to that in patients with solid tumors, including early deaths, which led to a limitation of use for the PMBCL indication. Therefore, a prospective clinical assessment of safety and efficacy in patients with hematological malignancies is warranted.

During the review of the original applications, given the lower predicted C_{trough} associated with the 400 mg dosing regimen (compared with the 200 mg every three weeks regimen), multiple discussions were held with OCP, Division management across the five Divisions within OOD, and OOD/OCE management. Considerations in favor of approving the 400 mg dosing regimen across all indications were made based on additional sensitivity analyses that included worst case simulations using data from clinical trials of pembrolizumab in NSCLC (based on these analyses, if the assumptions are valid, it would be unlikely that the efficacy of pembrolizumab would be compromised when using the 400 mg every six weeks regimen).

There were also considerations against approving the 400 mg dose across all indications. One was that the efficacy of pembrolizumab was established using the 200 mg every three weeks dose and not the 2 mg/kg every three weeks dose for indications where pembrolizumab has had the most profound impact, including durable complete responses in MSI-H/dMMR tumors, cHL, and primary mediastinal large B-cell lymphoma, and curative intent treatment (adjuvant melanoma). The predicted C_{trough} of the 400 mg regimen for these indications was outside of the 20% criterion originally set by OCP (and OOD [formally OHOP]) to support approval based on a modeling approach.

In addition to general concerns, specific concerns related to hematological malignancies were also voiced, where clearance of pembrolizumab may be reduced, and early all-cause mortality was observed in the single arm trial investigating the effects of pembrolizumab in patients with primary mediastinal large B-cell lymphoma. Although, this early mortality may have been disease-related, the potential for increased toxicity was also considered with the higher dose (400 mg every six weeks).

Overall, outside of the potential safety concern in hematological malignancies, efficacy was the primary concern with the proposed new dosing regimen. This is because Merck had previously

investigated doses of pembrolizumab as high as 10 mg/kg and determined this dose to be tolerable in large clinical trials (e.g., in lung cancer or as a first-line treatment of melanoma).

Complete Response:
To address the complete response letter, Merck provided the following information on (or prior to) April 13, 2020:

1. Data and information from Study KN555 to support the use of the proposed every six weeks dosing regimen. The data included anti-tumor efficacy data (on ORR), PK data, and safety data

2. Reiteration of the previously submitted modeling and simulation-based rationale supporting the proposed dosing regimen

3. Merck's justification regarding the safety of pembrolizumab in patients with hematological malignancies

New Efficacy Supplements
In addition to Merck's submissions to address the CR letter; Merck also submitted new efficacy supplements on April 14, 2020, (76-80), April 15, 2020, (81-82), and April 20, 2020 (83), to extend the 400 mg every six weeks dosing regimen to the following additional indications.

- Renal cell carcinoma (76)
- Endometrial carcinoma (77)
- Cervical carcinoma (78)
- Urothelial carcinoma (79)
- Head and neck squamous cell carcinoma (80)
- Small cell lung cancer (81)
- Esophageal cancer (82)
- Microsatellite instability high cancer (83)

Introduction
Merck submitted a Type A meeting on March 26, 2020, to discuss with FDA their proposal to address the items in the February 18, 2020, complete response letter.

When the applications were originally submitted, the primary rationale for changing the dosing regimen from once every three weeks to once every six weeks was one of convenience. Given current public health considerations, however, there is a different risk-benefit calculus that favors reduced interaction in the health care setting.

In light of this risk-benefit calculus, after notification of the Type A meeting request, FDA held a teleconference with Merck on the same day (March 26, 2020) at 4:00 pm. During the telephone conference, Merck stated that they have preliminary clinical data from Study KN555 in patients

with melanoma to address item #1 of the CR letter as well as additional PK data and summary safety data of pembrolizumab 10 mg/kg in patients with hematological malignancies (this is a higher dose than the proposed 400 mg dose).

FDA encouraged Merck to submit this information as soon as possible, and FDA stated that Merck could submit the CR in parts to facilitate the Agency's review of the submission. FDA and Merck held a subsequent teleconference on March 30, to further discuss the timing of the submission of components of the submission.

Merck submitted the following to address the Complete Response letter:

April 1, 2020
- Tables, Listings, and Figures (TLF) package in PDF form for KN555 (efficacy, safety)
- Datasets for KN555
- PDF of dataset specifications

April 3, 2020
- USPI in all approved indications
- PK report (In lieu of Module 2.7.2)
- PK datasets
- March 30, 2020, teleconference sponsor meeting minutes

April 6, 2020
- KN555 protocol
- KN555 (cohort B) interim statistical report
- ADaM datasets
- PDF of ADaM specifications

April 8, 2020
- KN555 CIOMS and narratives
- KN555 financial disclosures
- Hematologic safety report

April 8, 2020
- Response to an information request (related to source of data from KN001, KN006, and KN252)

April 10, 2020
- Response to information requests that provided information on dataset variables and clarification regarding adverse events

April 13, 2020
- SDTM 3.1.3 datasets in XPT format; Define files

- Regulatory history
- Clinical overview and summaries

April 15, 2020
- Response to an information request pertaining to the ADRS dataset

April 23, 2020
- Merck provided a revised annotated label and labeling in SPL format

Review of Submission

KN555
KN555 is entitled, "A Phase 1 Randomized Clinical Study of Pembrolizumab (MK-3475) to Evaluate the Relative Bioavailability of Subcutaneous Injection Versus Intravenous Infusion in Participants with Advanced Melanoma." The protocol describes two cohorts of patients. The primary objectives of Cohort A are to (1) characterize the pharmacokinetic (PK) profile, including the absorption phase, of pembrolizumab following subcutaneous (SC) injection (285 mg: 165 mg/mL and 130 mg/mL) and (2) estimate the relative bioavailability of pembrolizumab via SC injection (285 mg: 165 mg/mL and 130 mg/mL) versus intravenous (IV) infusion (200 mg: 25 mg/mL). Because Cohort A is not relevant to this application, further discussion of this protocol will be limited to Cohort B.

Cohort B was added to KN555 in Amendment 01 and provided for the enrollment of 100 patients with advanced melanoma who would receive 400 mg IV pembrolizumab every six weeks. The rationale of this cohort was to collect PK, efficacy, and safety data from participants receiving a 400 mg IV dose of pembrolizumab every six weeks. Merck primarily assessed efficacy based on objective response rate (ORR) based on blinded independent central review (BICR). ORR was assessed using RECIST version 1.1 with a modification to allow a maximum of 10 target lesions and 5 per organ (Merck has employed this modification in other clinical trials of pembrolizumab). Although the study collected data on other endpoints (e.g., survival, PFS, response duration), the review of KN555 for these applications will primarily focus on ORR and pharmacokinetics.

For sample size considerations, the KN555 protocol stated that the ORR for the 400 mg every six weeks dose is expected to be similar to that seen with pembrolizumab 200 mg every three weeks. Therefore, if the observed ORR for the 100 subjects is 35%, a 95% CI for the true ORR based on the method of Clopper and Pearson (1934) would be (25.7%, 45.2%).

During the meeting on March 26, 2020, FDA agreed that Merck could submit data from KN555 from patients who were followed long enough to be assessed for response. Therefore, Merck confirmed that they could provide response data from 44 patients who were enrolled in the study and would have been eligible for both Week 9 and Week 21 scans. Merck confirmed that they would provide data using ITT principles (e.g., if a patient discontinued prior to Week 21, but would have been eligible, they would be considered a non-responder).

Comment: Although the proposed 44 patient analysis is not a pre-specified analysis, FDA agreed to consider the data given the public health impact and due to the fact that these data are largely supportive of the PK analyses. Furthermore, the data come from a single arm trial and are largely descriptive.

Merck provided financial disclosure information for KN555 which stated that none of the 52 investigators or sub-investigators held financial interests or arrangements that required disclosure.

KN555 Results

Cohort B of KN555 initiated enrollment in May of 2019 and completed enrollment of 101 patients in January of 2020. Merck's interim analysis of KN555 (Cohort B) using a February 6, 2020, data cut-off date includes data from 44 subjects who were enrolled in the study and would have been eligible for imaging at both Week 9 and Week 21.

Most patients in KN555 were enrolled in South Africa (82%) with the remainder enrolled in Spain or Australia. Sixteen (36%) of the 44 patients had discontinued pembrolizumab by data cut-off with 15 of the 16 discontinuing due to clinical or radiographic disease progression and one patient discontinuing due to patient decision. Demographics of the 44 patients are described in the table below.

Table 1: Demographic or disease characteristics

Parameter		Result
Gender	Male (%)	59%
	Female (%)	41%
Age in years	Median (range)	64 (32 to 88)
Race	White (%)	89%
	Non-White or Other (%)	11%
ECOG	0 (%)	54.5%
	1 (%)	45.5%
LDH	≤ ULN (%)	57%

The confirmed ORR (per BICR) from the 44 patient cohort was 38.6% (95% CI: 24.4, 54.5) with 9.1% CRs and 29.5% PRs. The data were too immature to adequately describe duration of response.

Comment: Although not based on a formal statistical comparison, the point estimate for the ORR in KN555 is consistent with the historical response rates observed across various dosing

regimens in patients with (ipilimumab-naïve) metastatic melanoma (see below) who received different dosing regimens of pembrolizumab. These data provide support for the PK analyses and justification that administration of 400 mg every six weeks is unlikely to result in important clinical differences compared with the administration of 200 mg every three weeks.

Table 2: Response rates of melanoma in pembrolizumab clinical trials in melanoma

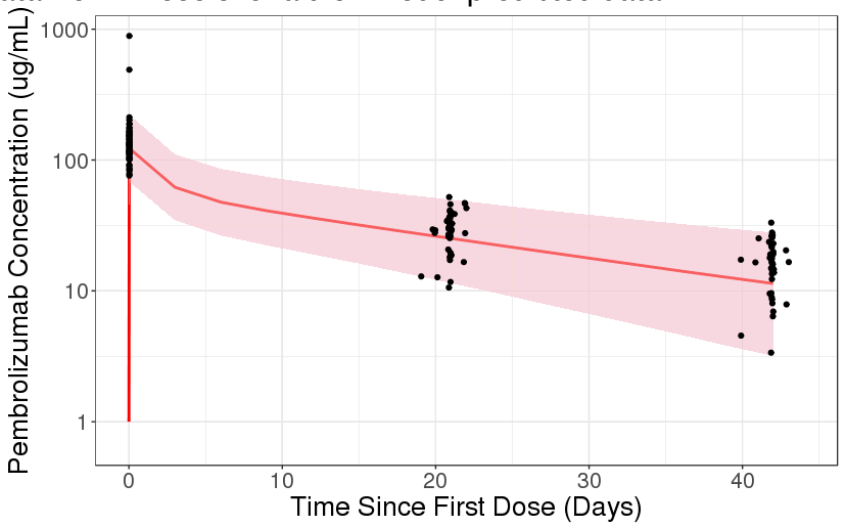
Study	Number of Subjects	Objective Response Rate
KN555 (pembrolizumab 400 mg Q6W)	44	38.6%
KN001 (pembrolizumab monotherapy: Cohorts IPI-naïve, 2 mg/kg Q3W)	73	35.6%
KN001 (pembrolizumab monotherapy: IPI-naïve, 10 mg/kg Q3W)	141	34.8%
KN001 (pembrolizumab monotherapy: IPI-naïve, 10 mg/kg Q2W)	99	40.4%
KN001 (pembrolizumab monotherapy: IPI-naïve, all subjects)	313	36.7%
KN006 (randomized pembrolizumab monotherapy; 10 mg/kg Q3W or Q2W)	556	36.5%
KN252 (randomized pembrolizumab plus placebo; 200 mg Q3W)	352	31.5%

The above table is based on data submitted by Merck that may have different data cut-off dates than data described in the literature (e.g., Kang et al., Ann Oncol 2017). For example, the KN001 data in the table above is based on a single data cut-off date of October 18, 2014. Additionally, the data in the table includes the *all patients as treated* population (similar to the KN555 data). The results for KN006 are consistent with data published in Schachter et al., Lancet, 2017. These represent an updated data cut-off date as compared to the original NEJM report by Robert et al., 2015, and what is described in labeling (ORR for 10 mg/kg every three weeks was 33%, and ORR for 10 mg/kg every two weeks was 30%).

KN555 Pharmacokinetics Data

I agreed with Merck's conclusion that the *observed* PK data from KN555 appeared generally consistent with their models' predictions (and the observed comparisons of C_{trough} were favorable as compared with the models' predictions). The data in the Figure below (copied from Merck's submission) show the actual observed PK results (black dots) compared with the median PK profile (and 90% prediction interval) from a predicted model of 2993 subjects treated with a 400 mg every six weeks dosing regimen.

Figure 1: PK Data from KN555 overlaid on model-predicted data



The *observed* C_{trough} in KN555 at six weeks for pembrolizumab 400 mg administered every six weeks was within 18% of that when compared to 200 mg administered every three weeks. Furthermore, the GM of C_{trough} in KN555 at six weeks for 400 mg administered every six weeks was actually about 10% *higher* than that at 2 mg/kg every 3 weeks. Furthermore, as predicted, the GM of the observed C_{max} at six weeks was lower for the 400 mg Q6W regimen as compared to previously studied 10 mg/kg regimens (providing support for Merck's justification supporting the safety of the 400 mg every six weeks dose). The tables below show the PK results in terms of exposure and % difference between the dosing regimens.

Table 3: PK Exposure Metrics for the different dosing regimens (including observed and model-predicted for 400 mg Q6W)

PK exposure metric, GM (95% CI)	2 mg/kg Q3W	200 mg Q3W	10 mg Q2W	400 mg Q6 model-predicted	400 mg Q6 observed[#]
Week 6 (early cycle)					
C_{min} (µg/mL)	13.5 (13.3, 13.6)	18.1 (17.8, 18.3)	119 (117.1, 120.6)	10.6 (10.4, 10.8)	14.9 (14.4, 15.4)
C_{max} (µg/mL)	44.1 (43.7, 44.5)	59.1 (58.5, 59.7)	220.3 (217.8, 222.7)	123.0 (121.6, 124.3)	136.0 (135.6, 136.4)

[#]GM of C_{min} from 41 subjects and GM of C_{max} from 56 subjects in KN-555 Cohort B

Table 4: Comparison of PK parameters between KN555 and those observed following administration of different doses of pembrolizumab

PK parameter, 400 mg every six weeks	Compared with 200 mg every three weeks		Compared with 2 mg/kg every three weeks		Compared with 10 mg/kg every other week	
Week 6 (early cycle)						
	Observed KN555	Model-predicted	Observed KN555	Model-predicted	Observed KN555	Model-predicted
% difference in geometric mean of $C_{min\ wk6}$	-18	-41	10	-21	---	
% difference in GM of $C_{max,\ wk6}$	130	108	208	179	-38	-44

KN555 Adverse Event Profile

In general, the toxicity profile of pembrolizumab administered at 400 mg IV every six weeks was consistent with the toxicity profile of pembrolizumab administered using other dosing regimens. Follow-up is limited, however, compared to the historical pembrolizumab database (accordingly the time at risk for AEs is substantially lower for KN555 compared to the results of the historical studies). Approximately 16% of patients experienced an immune-mediated event or infusion related reaction. None were Grade 3 or greater. Hypothyroidism and hyperthyroidism were each reported in 4.5% of patients . Cases of limbic encephalitis (Grade 2) and colitis (Grade 2) were reported.

Table 5: Adverse event summary for KN555

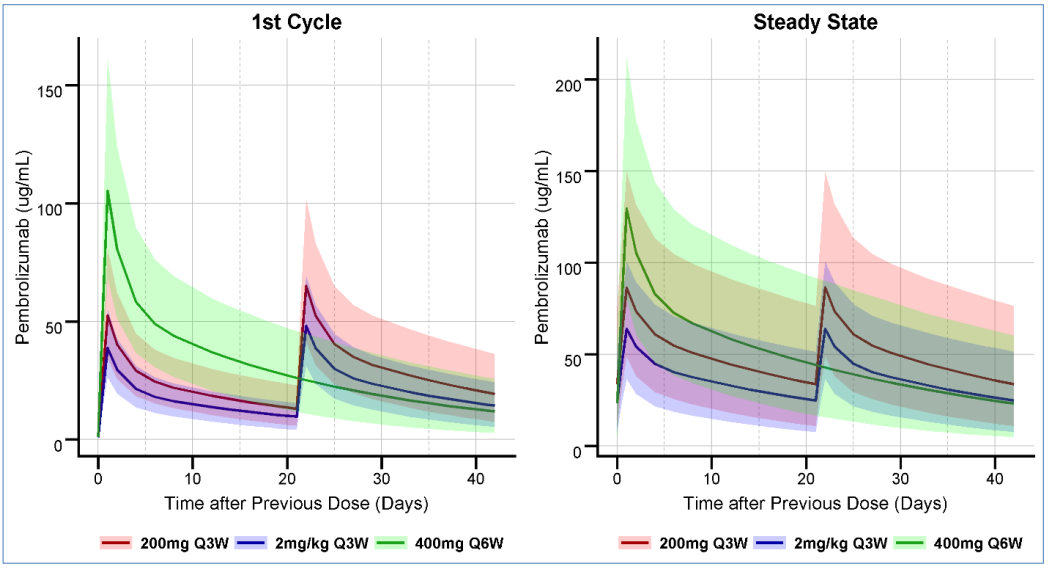
	Pembrolizumab 400 mg Q6W	
	n	%
Subjects	44	
Grade 3 to 5 AEs	11	25%
SAEs	7	15.9%
Deaths	0	0
IMaRs or IRRs	7	15.9%

Modeling and Simulation Analyses

Efficacy

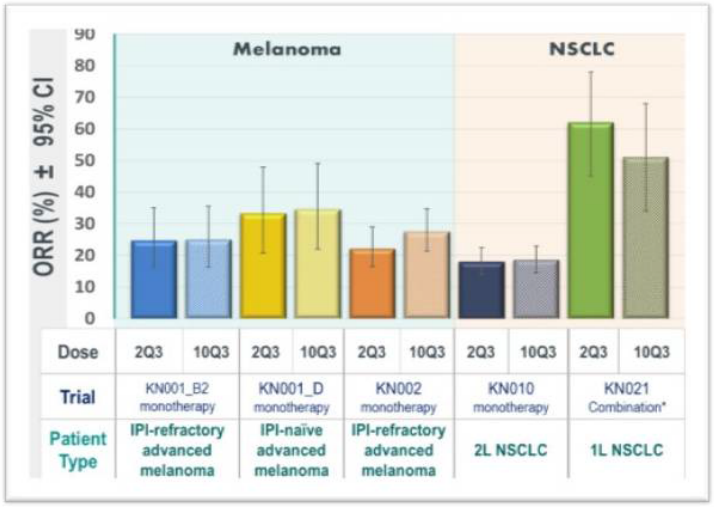
In the original submission(s), Merck provided a modeling and simulation approach to justify approval of the 400 mg every six weeks dosing regimen. The OCP review found that based on population PK (popPK) simulations, the expected geometric mean (GM) of steady-state C_{avg} was 36.9% higher and C_{trough} was 8.9% lower at 400 mg every six weeks compared to 2 mg/kg every three weeks. The C_{trough} within 20% of predicted (with a higher overall C_{ave}) was not expected by OCP to result in any clinically meaningful effect on efficacy. The figure below, copied from the OCP review, shows the predicted PK profiles by dosing regimen.

Figure 2: Predicted PK profiles by dosing regimen



The expected geometric mean (in the simulations) of steady-state C_{avg} was approximately equal and the C_{trough} was 33% lower with 400 mg every six weeks when compared to 200 mg every three weeks. Although the predicted C_{trough} was 33% lower, OCP concluded that available exposure-response data and sensitivity analyses suggested that the expected efficacy difference between 400 every six weeks and 200 mg every three weeks was unlikely to be clinically meaningful. The rationale for this conclusion included consistent flat dose/exposure-response relationships for overall response rate (ORR) across approved indications (see Figure below and also see Figures in the Appendices of the OCP review) and across a dose range from 2 mg/kg or 200 mg every three weeks to 10 mg/kg every two weeks. OCP also found that under a *worst case* scenario sensitivity analysis (in NSCLC), the potential efficacy loss with the 400 every six weeks dosing regimen (relative to the 200 mg every three weeks) was projected to be 4.7% and unlikely to be detectable in a feasible clinical trial.

Figure 3: ORR by dosing regimen in melanoma and NSCLC



In addition, Merck also provided further rationale as to the comparison of the expected efficacy for the 400 mg every six weeks dosing regimen and the 200 mg every three weeks dosing regimen. Merck found that in indications where the 200 mg every three weeks dose was studied, patients with a body weight ≥ 100 kg (comparable to a dose of 2 mg/kg or less) had similar efficacy compared to patients with a body weight under 100 kg (comparable to >2 mg/kg). A similar finding was also observed in KEYNOTE-054, a study that assessed pembrolizumab in the adjuvant setting in melanoma.

In addition to these analyses based on weight, Merck stated that predicted target saturation (based on target-mediated drug disposition) is expected to be maintained in patients as target saturation is predicted at doses at or above 0.1 mg/kg to 0.3 mg/kg, and that because the target is on immune cells and not tumor cells, that differences in exposure/dose-response are not expected across tumor types. This apparent lack of difference was assessed via AUC_{0-6} and C_{trough} as the exposure metrics and best response as the response criterion across tumors. The lack of effect on best response was observed in multiple tumors including solid tumors and in classical Hodgkin lymphoma and PMBCL. Merck also stated that based on models and simulations, that the approved doses achieve target saturation in tumor tissue, even in the most conservative scenarios considering patients with extreme tumor conditions. Furthermore, Merck stated that target saturation is expected to be maintained even in the few participants (~0.5%) who may experience a transient reduction in C_{min} below the observed clinical experience with the 2 mg/kg dosing regimen.

Safety

Safety of the 400 mg every six weeks dosing regimen is primarily supported by safety data obtained with dosing regimens that provided higher exposure to pembrolizumab (10 mg/kg every two or three weeks). In Merck's pooled analyses (KN001, 002, 006, and 010), the incidence of Grade 3 to 5 adverse events and SAEs was similar, irrespective of whether a patient received 2 mg/kg every three weeks, 10 mg/kg every three weeks, or 10 mg/kg every two weeks. Furthermore, even though few patients have received 10 mg/kg dosing regimens in combination with chemotherapy, the less than half-log change in C_{max} between 200 mg and 400 mg would not be expected to result in a large difference in adverse events between the two regimens.

Table 6: Comparative assessment of safety of different dosing regimens of pembrolizumab (across KN001, 002, 006, and 010)

	2 mg/kg Q3W	10 mg/kg Q3W	10 mg/kg Q2 W	Total
Grade 3 to 5 AEs	47%	47%	46%	46%
SAEs	39%	37%	37%	37%
Deaths	5%	4%	3%	4%
Discontinued for AE	11%	12%	13%	12%

Hematological indications
The CR letter for the 400 mg every six weeks efficacy supplements indicated that among patients with hematologic malignancies, there have been differences in safety compared to that observed in patients with solid tumors, including early deaths, which led to a limitation of use for the PMBCL indication. Therefore, a prospective clinical assessment of safety and efficacy in patients with hematological malignancies is warranted

To address this deficiency, in addition to the PK and efficacy data from KN555 (in melanoma), Merck provided a hematological safety statistical report with further justification regarding the safety of pembrolizumab in patients with hematological malignancies. The report described the safety of pembrolizumab for both the 200 mg every three weeks and 10 mg/kg dosing regimens in patients with hematological malignancies, compared to the reference safety database.

Relapsed or refractory classical Hodgkin disease
Overall the safety of the pembrolizumab 10 mg/kg every other week cohort (n=31) appeared consistent with the data from the reference safety dataset. Although there were differences in severe or serious AEs between the 200 mg and 10 mg/kg dosing regimens, it is difficult to ascertain whether the differences were drug- or disease-related as the number of patients who discontinued due to an AE were similar between groups (as were the number of deaths).

Merck indicated that the biggest difference in immune-related adverse reactions (IMaRs) in patients with rrcHD (treated at all doses) versus the reference safety database was for hypothyroidism. Merck postulated that this difference may have been related to prior neck radiation among patients with rrcHD. Although Merck provided tables that listed specific adverse events and IMaRs, interpretation of specific events was limited by the number of patients who received the 10 mg/kg dosing regimen.

Table 7: rrCHD

	KN087 200 mg Q3W	KN013- cohort 3 10 mg/kg Q2W	Reference Safety Database
Number of patients	210	31	2799
Grade 3 to 5 AEs	33%	42%	46%
SAEs	23%	39%	37%
Deaths	2%	0%	4%
Discontinued for AE	9%	10%	12%
IMaRs / IRRs G3 to 5	4%	10%	6%
Discontinued for IMaR / IRR	7%	10%	3%

Primary Mediastinal B-cell Lymphoma (PBMCL)
The number of patients was limited for PBMCL although patients, in different trials (with somewhat different populations), received both the 200 mg Q3W regimen and the 10 mg/kg Q2W regimen. Although the safety data generally appeared favorable among patients who

received the 10 mg/kg dosing regimen, there were too few patients treated at this dose level to make meaningful conclusions.

Table 8: Cross-study safety comparison of different dosing regimens of pembrolizumab in PBMCL

	KN170 200 mg Q3W	KN013 - C4A 200 mg Q3W	KN013 – C4A 10 mg/kg Q2 W	Reference Safety Database
Number of patients	53	11	10	2799
Grade 3 to 5 AEs	59%	55%	20%	46%
SAEs	26%	55%	20%	37%
Deaths	6%	0	0	4%
Discontinued for AE	8%	9%	0	12%
IMaRs / IRRs G3 to 5	2%	0	10%	6%
Discontinued for IMaR / IRR	0	0	0	3%

Merck stated in the application that they believed that early deaths following treatment with pembrolizumab in patients with rrPBMCL were generally related to the rapid pace of disease in non-responding patients. As such, the limitation of use in labeling for the PBMCL indication states that KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Hematologic Conclusions (also See Below)
Due to limited numbers of patients, it is difficult to assess whether a higher dose of pembrolizumab will result in a different adverse event profile in patients with hematological malignancies. The safety experience of the 10 mg/kg dosing regimen did not appear worse than that of the reference safety database; however, there was a modestly higher incidence of adverse events in patients who received the higher dose regimen in patients with rrcHD. It is difficult to make conclusions regarding this observation due to the cross-study comparison and limited number of patients treated with the 10 mg/kg dose.

Approval Considerations and Risk-Benefit Assessment
I am recommending Accelerated Approval, per 21 CFR part 601, subpart E, of Merck's efficacy supplements that will provide for a dosing regimen of 400 mg every six weeks in addition to 200 mg every three weeks for all adult indications. This decision comes after considering the reviews of the applications by FDA review staff as well as internal discussion within OCP, OOD, and OCE management.

FDA's Expedited Programs Guidance describes the following criteria for Accelerated Approval. Considerations pertaining to these efficacy supplements will follow:

1. A drug that treats a serious condition: I agree that pembrolizumab is approved for cancers that are life-threatening in the absence of treatment.

2. The drug generally provides a meaningful advantage over available therapies: In general, in oncology, FDA has considered granting Accelerated Approval for products in situations where the drug has an improved outcome over available therapy, or the drug has an effect on a surrogate or intermediate endpoint in situations where there is no available therapy. This generally has been the case in oncology because efficacy is so important (e.g., a "safer" drug without efficacy would not benefit patients with cancer).

   Nevertheless, FDA's Guidance states that (among other reasons) when available therapy exists for a condition, a new treatment generally would be considered to address an unmet medical need if the treatment

   - Provides efficacy comparable to those of available therapy, while (1) avoiding serious toxicity that occurs with available therapy, (2) avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious condition, or (3) reducing the potential for harmful drug interactions

   - Provides safety and efficacy comparable to those of available therapy but has a documented benefit, such as improved compliance, that is expected to lead to an improvement in serious outcomes

   - Addresses an emerging or anticipated public health need, such as a drug shortage.

   Importantly, the 400 mg Q6W regimen is believed, based on *both* PK and clinical data, to be comparable to the 200 mg Q3W regimen. This appears to represent a unique situation for an AA determination where thousands of patients have benefited from pembrolizumab in clinical trials or in the commercial setting and the drug is being compared to itself.

   Although the risks and benefits of the 400 mg/kg Q6W dosing regimen will be described in more detail below, except in indications where pembrolizumab has received Accelerated Approval, pembrolizumab would be considered an available therapy. It is against such therapy that the 400 mg Q6W dosing regimen is being compared. As the first two bullets indicate, this application would provide for a therapy that is comparable to an available therapy (i.e., pembrolizumab 200 mg Q3W) or in addition to a therapy approved under Accelerated Approval (i.e., pembrolizumab 200 mg Q3W) but would provide for additional benefit given emerging public health considerations. Specifically, the Q6W dosing regimen will allow patients to spend less time at infusion centers or health care settings (compared to the Q3W dosing regimens), reducing the chance of patients (or providers) contracting emerging community or other nosocomial (serious) infections. This consideration is especially important for patients with cancer who are at increased risk of complications or mortality due to serious community acquired infections (and addresses a current public health need).

Previously, FDA has granted regular approval for dosing regimen changes for other PD-(L)1 inhibitors (for nivolumab and atezolizumab). For these drugs, FDA accepted predicted C_{trough} levels within 20% as supporting approval. In the modeling approach (in the initial efficacy supplements), pembrolizumab was outside of this threshold for some of the studied indications; therefore, Merck provided additional data and information to support the approval (and in part why these applications will receive Accelerated Approval rather than regular approval).

3. The demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint):

   The approval of these efficacy supplements are based on the totality of data that includes modeled PK data for the 400 mg Q6W regimen compared to the 200 mg Q3W regimen; observed PK data from a subset of patients who received 400 mg Q6W in KN555; observed BICR-assessed (confirmed) ORR from a subset of patients enrolled in KN555; and additional safety analyses in patients with hematological malignancies who received pembrolizumab.

   As stated above, in the analyses based on modeling, the predicted pembrolizumab C_{trough} when administered at 400 mg every six weeks was within 20% of the exposure when pembrolizumab was administered at a dose of 2 mg/kg every three weeks. The predicted C_{ave} was also expected to be higher for the 400 mg every six weeks regimen. Based on these exposure considerations supported by safety data from the 10 mg/kg regimen, 400 mg every six weeks is believed to provide comparable clinical effects when compared to the 2 mg/kg every three weeks regimen.

   Although the 400 mg/kg regimen was considered comparable to the 2 mg/kg Q3W regimen, the predicted C_{trough} of the 400 mg/kg Q6W regimen was outside of the 20% threshold when compared to the PK results of the 200 mg Q3W regimen (although the C_{aves} were comparable). Therefore, to support approval of the 400 mg Q6W regimen, Merck provided additional data and analyses, including results from KN555.

   Although the predicted C_{trough} of the 400 mg Q6W dosing regimen was outside of the 20% threshold when compared to the PK results of the 200 mg Q3W regimen, the *observed* PK results for C_{trough} were within this threshold in the subset of patients from KN555 with available PK data. Furthermore, the observed confirmed response rate in KN555 in patients with available data was consistent with the ORR in patients with melanoma (without prior exposure to ipilimumab). Although this data from KN555 is reassuring, analyses of ORR (an intermediate endpoint) and PK should be considered preliminary as they are from the subset of patients with available data. Additional data from the entire cohort of ~100 patients will be requested to verify and describe the effect on ORR and durability of

response in KN555. Importantly, clinical benefit of pembrolizumab has been observed in melanoma with similar response rates in prior randomized clinical trials (e.g., KN006).

In addition to the data from KN555, Merck provided additional E-R analyses to support their contention that the 400 mg Q6W dosing regimen is expected to be comparable to 200 mg Q3W. These include E-R analyses of pembrolizumab by patient weight as well as exploratory analyses based on predicted target saturation. Furthermore, FDA's OCP found that under a worst case scenario sensitivity analysis (in NSCLC), the potential efficacy loss with the 400 every six weeks dosing regimen (relative to the 200 mg every three weeks) was projected to be 4.7% and unlikely to be detectable in a feasible clinical trial (e.g., a non-inferiority or equivalence trial would have to be prohibitively large to assess for the absence of such a small difference).

Although the 400 mg dose is higher than 200 mg, safety is expected to be similar between the two doses. This conclusion is based on the totality of data with 10 mg/kg Q2 or Q3 week dosing regimens in patients with solid tumors. Although patients with hematological malignancies have also received 10 mg/kg dosing regimens, fewer patients overall have received the higher dose regimens. Because there is more uncertainty regarding the effects of pembrolizumab in patients with hematological malignancies (e.g., both hematological regimens have received Accelerated Approval), the DMH2 requested that Merck assess the effects of the 400 mg Q6W dose in patients with hematological malignancies (to further assess benefit-risk). This data in addition to KN555 will provide data to further verify and describe the effects of pembrolizumab when administered every six weeks.

In summary, based on all the considerations described above, in the clinical review, and in the OCP review, the 400 mg Q6W dosing regimen is expected to provide for a favorable risk-benefit profile in different disease settings and a risk-benefit profile comparable to 2 mg/kg or 200 mg every 3W regimens. Extending the dosing regimen to every six weeks will also address a public health need by decreasing the number of visits to infusion centers and reducing the chance that a patient with cancer will interact with someone carrying a serious community acquired or nosocomial infection.

4. Confirmatory trials may be required to verify and describe the anticipated effect on IMM or other clinical benefit: Although clinically meaningful differences in safety and effectiveness are not expected based on the considerations described above (in #3), data from KN555 were considered preliminary; and therefore, Merck will provide final data from KN555 to verify and describe the effects on PK, ORR, safety, and duration of response in patients with melanoma who receive pembrolizumab 400 mg every six weeks (to inform labeling across solid tumor indications). As stated above, effects of a comparable magnitude on ORR have been observed to correlate with improvements in PFS and OS in KN006. Merck will also provide additional efficacy and safety data from patients with hematological malignancies to support conversion to regular approval (of the dosing change in the hematological indications). Ultimately, an assessment of the totality of the data will be used to determine that the PMRs are fulfilled. As indicated in this review, this will include

modeling and observed PK data for the 400 mg Q6W regimen as well as assessments of Merck's ER analyses.

Importantly, conversion of an indication that, to date, has received Accelerated Approval should depend upon the original post-marketing requirements (PMRs), and not on the PMRs for these dose-regimen-modifying applications. AA indications include small cell lung cancer; classical Hodgkin lymphoma; PMBCL; locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status; MSI-H CRC and MSI-H solid tumors; gastric cancer; cervical cancer; hepatocellular cancer; Merkel cell carcinoma; and endometrial cancer. For these indications, continued marketing will be subject to the original approval PMRs (and not to the results of the dose-regimen-modifying PMRs).

As a hypothetical example, if confirmatory trials show that pembrolizumab is not safe and effective for indication X; however, the confirmatory PMRs are fulfilled for the 400 mg Q6W supplements, labeling could be updated to remove indication X while keeping the 400 mg Q6W regimen for the remainder of the regimens. Conversely, if confirmatory trials of pembrolizumab in indication X demonstrate that pembrolizumab is safe and effective for indication X but PMRs for the 400 mg Q6W are not supportive of this dosing regimen, the labeling could be amended to modify the dosage and administration section while keeping for example, the 200 mg every three weeks dosing regimen for indication X.

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/s/

STEVEN J LEMERY
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