CENTER FOR DRUG EVALUATION AND RESEARCH

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Reviewer Name(s)	Naomi Redd, Pharm.D.
Team Leader	Doris Auth, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 21, 2017
Subject	Evaluation of Need for a REMS
Established Name	Avelumab
Trade Name	Bavencio
Name of Applicant	EMD Serono, Inc.
Therapeutic Class	Anti-programmed death ligand-1 (PD-L 1) monoclonal human IgG1 antibody
Dosage Form and Administration	Intravenous injection 200 mg/10ml single dose vial ; 10 mg/kg IV over 60 minutes every 2 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Bavencio (avelumab) is necessary to ensure the benefits outweigh its risks. EMD Serono Inc., submitted a Biologic Licensing Application (BLA) 761049 for avelumab with the proposed indication for the treatment of metastatic Merkel Cell Carcinoma (mMCC) with disease progression following at least one prior systemic chemotherapy regimen. The serious risks associated with avelumab include immune-related adverse events (irAEs) of pneumonitis, hepatitis, colitis, endocrinopathies, and nephritis. The applicant did not submit a proposed REMS, but submitted a European Risk Management Plan (EU RMP) which proposes to mitigate these risks with labeling and routine pharmacovigilance.

DRISK and the Division of Oncology Products 2 (DOP-2) agree that a REMS is not necessary to ensure the benefits of avelumab outweigh its risks for the following reasons:

- MMC is a rare disease with no approved therapies. The benefit of avelumab in the treatment of mMCC was demonstrated in the Applicant's registrational trial (approximately one-third of patients met the primary endpoint of overall response to treatment, and of these patients, the majority (86%) had DOR rates more than 6 months, and 45% with a DOR of more than 12 months).
- The risks associated with avelumab are in part due to its inhibitory effects of PD-L1. The PD-L1 molecule can cause immune-related adverse events (irAEs) once inhibited, due to restoration of the immune system. If approved, Avelumab will belong to a class with 3 other drugs (nivolumab, pembrolizumab and atezolizumab) in which irAEs are communicated through the label in Warnings and Precautions.
- Patients must be given avelumab every 2 weeks, which gives the opportunity for AEs to be evaluated at minimum, at or during these treatment intervals.
- Prescribers are likely to be aware of the risks of irAEs, and the management thereof, with other drugs in this class.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Bavencio (avelumab) is necessary to ensure the benefits outweigh its risks. EMD Serono, Inc., submitted a Biologic Licensing Application (BLA 761049) for avelumab with the proposed indication for the treatment of metastatic Merkel Cell Carcinoma (mMCC). BLA 761049 is under review in DOP-2. (b) (4) The applicant did not submit a REMS with this application but submitted a EU RMP, in which they proposed to manage the risks of avelumab in

labeling and perform routine pharmacovigilance activities. The Applicant's proposed label did not include a Boxed Warning, but did propose labeling irAEs in Warnings and Precautions.

2 Background

2.1 PRODUCT INFORMATION

Avelumab is a programmed death ligand-1 (PD-L1) blocking monoclonal antibody indicated for the treatment of patients with mMCC.[1] The PD-L1 molecule is expressed on several cells of the body, in particular epithelial and vascular endothelial cells. Over-expression of this molecule results in immunosuppression and rapid tumor growth, which often leads to poor prognosis, especially in tumor types in epithelial environments.[2] Avelumab binds to PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This interaction releases the inhibitory effects of PD-L1 on the immune system resulting in the restoration of immune responses as well as providing anti-tumor activity.[1]

The terminal half-life of avelumab is 6.1 days in patients receiving 10 mg/kg. Other than body weight, there have been no clinically meaningful differences in the pharmacokinetics of avelumab based on age, sex, race, PD-L1 status, tumor burden or renal impairment. There is limited data on the pharmacokinetics of avelumab in patients with mild to moderate hepatic impairment, and the effect of severe hepatic impairment in patients taking avelumab is unknown.[1]

Avelumab is supplied as a 200 mg/10ml solution in a single dose vial, to be given at a dose of 10 mg/kg infused over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.[a] The intended setting in which avelumab is likely to be administered is in an inpatient setting, or an outpatient infusion center. Avelumab is an NME[b] and is not part of a drug class that currently has a Boxed Warning or REMS. This drug has been granted orphan, fast track, and breakthrough therapy designation. The indication for mMCC will be approved under accelerated approval based on tumor response and duration of response. (b) (4)

2.2 REGULATORY HISTORY

The following are relevant regulatory actions pertinent to this BLA:

- 03/04/2014: New Investigational New Drug (IND) application 119134 submitted for Study EMR 100070-003; a single-arm multi-center study of avelumab in 88 patients with MCC who have received at least one line of previous chemotherapy.
- 04/02/2014: FDA granted "safe to proceed letter" for IND 119134
- 09/21/2015: Orphan designation granted for the treatment of mMCC
- 10/01/2015: Fast Track designation granted

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

- 11/17/2015: Breakthrough Therapy designation granted
- 04/28/2016: Tradename “Bavencio” conditionally accepted
- 06/16/2016: Multi-disciplinary Pre-BLA meeting; rolling review granted
- 09/23/2016: BLA 761049 received
- 11/22/2016: BLA 761049 filed
- 01/05/2017: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for avelumab.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Merkel Cell Carcinoma (MCC) is a rare and aggressive neuroendocrine tumor of the skin, commonly in sun-exposed areas, that usually appears as a single pink, red, or purple bump. These bumps are often painless, and sometimes may break open or bleed. MCC tumors often spread quickly as new lumps surrounding the skin, and can also invade nearby lymph nodes that can be felt under the skin, commonly in the neck or armpits.[3] Approximately 1,600 cases of MCC are diagnosed in the United States each year, and 5 year mortality rates average between 40-46% percent. The majority of MCC cases present with local disease (66%), however nearly one-third of patients will develop distant metastasis.[3,c,d]

MCC is most commonly seen in Caucasian males older than 70 years of age. In addition to age, other risk factors for MCC include excessive sun exposure and immunocompromised disease states, with approximately 80% of MCC cases being linked to Merkel cell polyomavirus.[4] In patients who have had solid organ transplantation, the risk of MCC is increased by 10-fold, by 13-fold in patients with HIV, and by 12-fold in patients with chronic lymphocytic leukemia.[5] Although currently termed an orphan disease, the incidence of MCC is rising, partly due to patients living longer, but also because there is increased awareness overall in regards to skin cancer and the importance of testing, as well as improved diagnostic techniques.[5,d] Since MCC can present as a painless disease lacking striking characteristic features, diagnosis is often made after a tumor is biopsied.[6] Prognosis can be poor, especially in metastatic disease, with a median survival time of approximately 9 months from the time of diagnosis.[4]

3.2 Description of Current Treatment Options

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

There is currently an unmet medical need for treatment of patients diagnosed with mMCC. At this time, there are no FDA approved options indicated for the treatment of mMCC, nor are there any treatments in literature that demonstrate substantial survival benefit. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for MCC recommend enrolling the patient in a clinical trial as the first option if available. If chemotherapy is used as an option, NCCN guidelines recommend cisplatin or carboplatin, with or without etopside, as well as other chemotherapy regimens that may be used for the treatment of small cell lung cancer.[6] However, the NCCN guidelines, as well as other literature note that chemotherapy regimen options for MCC are not durable, with survival rates of no more than 3-9 months, and exhibit high toxicity in elderly patients.[4]

4 Benefit Assessment

The efficacy of avelumab was demonstrated in the Applicant's registrational trial, Study 1, which was an open-label, single-arm, multi-center study conducted in 88 patients with histologically confirmed mMCC whose disease had progressed on or after chemotherapy administered for distant metastatic disease.[1] Patients with autoimmune disease, medical conditions requiring systemic immunosuppression such as organ or allogeneic stem cell transplantation, as well as infection with HIV, and hepatitis B or C were excluded from the trial. Patients were also excluded if they received previous treatment with anti-PD-1, anti-PD-L1 or CTLA-4 antibodies, or had central nervous system metastases.[1]

The median age of patients enrolled in Study 1 was 73 years old (range 33 to 88 years old), 74% were male, and 92% were White. Sixty-five percent of patients had at least 1 prior therapy for mMCC, and 35% had been exposed to 2 or more prior therapies. Over half of the study population (53%) had visceral metastases.[1]

Patients received a dose of 10 mg/kg as an IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Tumor response assessments were done every 6 weeks. The primary efficacy endpoint was a confirmed overall response rate (ORR). Efficacy analyses were conducted when the last patient enrolled completed 12 months of follow-up. Secondary endpoints of the study included duration of response (DOR), progression free survival (PFS), and overall survival (OS).[7]

The efficacy results are outlined in Table 1 below. Of the 88 patients evaluated in Study 1, 29 patients responded, and the median duration of response had not been reached (range from 2.8+ to 23.3+ months). The clinical reviewers recommend approval based on ORR and the secondary endpoint of DOR.[e]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Table 1: Efficacy Results of Study 1[1]

Efficacy Endpoints	Results (N = 88)
Confirmed Best Overall Response (BOR)	
Complete Response (CR), n (%)	10 (11.4%)
Partial Response (PR), n (%)	19 (21.6%)
Overall response rate, n (%)	29 (33.0%)
(95% CI)	(23.3, 43.8)
Duration of Response (DOR)	N=29
Patients with DOR ≥ 6 months, n (%)	25 (86%)
Patients with DOR ≥ 12 months, n (%)	13 (45%)

5 Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for avelumab. These safety data are pooled from the Applicant's dose finding study (n=1650) and in the single-arm efficacy study (n=88) for a combined total of 1738 patients exposed to avelumab.[1] Adverse events highlighted by the review division were immune related adverse events (irAE), which are a result of the mechanism of action of avelumab. Categories of irAEs included: pneumonitis, colitis, hepatitis, endocrinopathies (thyroid disorders, adrenal sufficiency, Type 1 Diabetes Mellitus), nephritis and renal dysfunction.[1,7] The sponsor included the following irAE in the proposed Warnings and Precautions section of the label.[f]

5.1 IMMUNE-MEDIATED PNEUMONITIS

(b) (4)

5.2 IMMUNE-MEDIATED HEPATITIS

(b) (4)

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

(b) (4)

5.3 IMMUNE-MEDIATED COLITIS

(b) (4)

5.4 IMMUNE-MEDIATED ENDOCRINOPATHIES

(b) (4)

5.5 IMMUNE-MEDIATED NEPHRITIS AND RENAL DYSFUNCTION

Immune-mediated nephritis was documented in 1 patient (0.1%), which led to permanent discontinuation. Recommendations are to administer corticosteroids for events Grade 2 or greater.

5.5.1 Safe-Use Conditions

The adverse events described in section 5.1 above are directly related to the immune modulating and inhibiting events of blockade of the PD-L1 signaling cascades by avelumab. Proper monitoring and administration of corticosteroids when necessary are included as recommendations in the product label.

In the irAEs outlined above, many of the cases resolved on their own, and some patients had to permanently discontinue avelumab.

6 Expected Postmarket Use

Avelumab is expected to be used in an inpatient setting or infusion center, based on the recommended administration of 10 mg/kg to be given over a period of 60 minutes every 2 weeks. Although avelumab is being evaluated for treatment of other tumor types, off label use in other disease states, or the probability of this drug being dispensed by healthcare practitioners other than oncologists or practitioners that specialize in oncology treatment is not expected. Patients must be given avelumab every 2 weeks, which gives the opportunity for AEs to be evaluated at minimum, at or during these intervals.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for avelumab beyond routine pharmacovigilance, and their proposed labeling did not include Boxed Warnings.

8 Discussion of Need for a REMS

When evaluating the need for a REMS, DRISK considers factors from Section 505-1 (a) of the Food Drug &Cosmetic Act (i.e., FDAAA factors) to assess the benefit:risk profile for all NME's. These factors include the estimated size of the population, seriousness of disease, the expected benefit, the expected duration of treatment, and the serious of known or potential adverse events. The following is an assessment of these factors as it relates to avelumab.

This BLA for avelumab is a NME under review for the treatment of mMCC, a rare and aggressive neuroendocrine skin cancer that affects approximately 1600 patients in the United States annually. Patients who are afflicted with MCC are often elderly, and/or may have concomitant immunocompromising conditions, hence making this a fragile patient population, and one of the most difficult to treat cancer populations.[4] Less than half of patients do not live beyond 5 years, and the median time of survival once a patient is diagnosed with metastatic disease is less than one year. There are currently no FDA approved therapies specifically for the treatment of mMCC. First line recommendations from NCCN guidelines are to enroll the patient in a clinical trial if available, or administer chemotherapy as per clinical judgement. Clinical trials may be difficult to enroll in, especially depending on the patient's ability to access these opportunities. If chemotherapy is used, NCCN guidelines recommend cisplatin or carboplatin, with or without etopside, as well as other chemotherapy regimens that may be used for the treatment of small cell lung cancer. Adverse events of chemotherapy which range from severe myleosuppression, anemias, and various gastrointestinal toxicities may gravely affect the quality of life in this patient population. Toxicity-related deaths due to chemotherapy have been reported in 3-7% of patients with advanced MCC. Mortality rates have been reported as high as 16% in patients older than 65 years of age.[4] Duration of response in this patient population is often

brief, ranging from 3-9 months. This represents a disparity of effective treatment options for those afflicted with mMMC. The benefit of avelumab was seen in the Applicant's registrational trial, with approximately one-third of patients meeting the primary endpoint of overall response to treatment, and of these patients, the majority (86%) had DOR rates more than 6 months, and 45% with a DOR of more than 12 months. The risks of avelumab result from its mechanism of action of inhibitory effects of PD-L1. The PD-L1 molecule can cause immune-related adverse events (irAEs) once inhibited, due to restoration of the immune system. The irAEs reported in the pooled safety data and clinical trial for avelumab included: pneumonitis, hepatitis, colitis, endocrinopathies, and renal/nephritis. Many of these events were managed with corticosteroid administration, withholding the dose, or discontinuing treatment. Several of these events also resolved on their own.

There are other FDA approved drugs that also inhibit the PD/PD-L1 molecule which also exhibit irAEs. Ipilimumab (Yervoy®), approved in 2011 for the treatment of melanoma, was the first drug on the market to exhibit anti-cancer activity by inhibiting the PD molecule, and thus, many of the adverse events were new to the oncology prescribing population. In an attempt to communicate these risks to the prescribing population, labeling was maximized to include a Boxed Warning for the risks of severe and fatal immune-mediated adverse reactions.[8] In addition, Yervoy was approved with a REMS comprised of a communication plan. The goal of the REMS was to inform prescribers on these risks. In 2015, the REMS for Yervoy was eliminated because prescribers had shown adequate knowledge on the risk and management of immune-mediated reactions at the 18-month and 3-year REMS assessment, and the overall goals of the REMS were met. In addition, evaluation of drug use data and post-marketing reports of adverse events did not uncover any new safety events that would require continued or new communication within the next 6 months.[9,10]

Subsequently, in 2014, both nivolumab (Opdivo®)[11] and pembrolizumab (Keytruda®)[12] were anticancer agents approved for other tumor types, yet also inhibit the PD molecule like ipilimumab to exert anti-tumor activity. Atezolizumab (Tecentriq®)[13] was approved in October 2016, and is the only PD-L1 blocking antibody drug on the market. Like avelumab, all of these drugs have shown to exhibit immune-mediated reactions based on the blockade of the PD or PD-L1 molecule. Since these agents are all relatively new to market, there have been no major differences in safety events seen on whether the PD molecule versus PD-L1 molecule is inhibited. With the exception of ipilimumab, all drugs in the anti-PD or PD-L1 drug class remain under accelerated approval based on tumor response rates and duration of response.

Table 2 in the Appendix was presented at the Midcycle Clinical and Statistical Meeting that compared the pooled safety data of avelumab's irAEs with pooled safety data for nivolumab, and pembrolizumab. The irAE of these agents as compared to avelumab were all similar. Table 3 in the Appendix is a comparison of avelumab to the labeling of all drugs on the market currently approved with PD/PD-L1 blockade activity. Yervoy is the only drug that still has a Boxed Warning for irAEs, and none of these drugs are currently approved with a REMS. The prescribing community of oncologists has been exposed to several drugs with anti-cancer activity whose mechanism of action may result in irAEs. If approved, avelumab will be the second PD-L1 blocking antibody on the market, but the first FDA indicated treatment for mMCC.

The Clinical Reviewer recommends approval of avelumab on the basis of the efficacy and safety information currently available.

In summary, based on the review of the aforementioned information, this reviewer has concluded that a REMS is not necessary to ensure that the benefits outweigh the risk for for avelumab for the following reasons:

- The benefit of avelumab in the treatment of mMCC was demonstrated in the Applicant's registrational trial(approximately one-third of patients met the primary endpoint of overall response to treatment, and of these patients, the majority (86%) had DOR rates more than 6 months, and 45% with a DOR of more than 12 months).
- The risks associated with avelumab are in part due to its inhibitory effects of PD-L1. The PD-L1 molecule can cause immune-related adverse events (irAEs) once inhibited, due to restoration of the immune system. If approved, Avelumab will belong to a class with 3 other drugs(nivolumab, pembrolizumab and atezolizumab) in which irAEs are labeled in Warnings and Precautions. Patients must be given avelumab every 2 weeks, which gives the opportunity for AEs to be evaluated at minimum, at or during these treatment intervals.
- Prescribers are likely to be aware of the risks of irAEs, and the management thereof, with other drugs in this class.
- Due to prior approvals of drugs that have the same irAEs, the prescribers are likely to be aware of the risks of irAEs, and the management thereof, with other drugs in this class.

9 Conclusion & Recommendations

DRISK and DOP2 agree that the benefit-risk profile for avelumab is favorable, and therefore, a REMS is not necessary for avelumab to ensure the benefits outweigh the risks. At the time of this review, labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile so that this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:

1. EMD Serono Inc., Avelumab Clinical Modules: Clinical Summary, Safety, and Efficacy September 2016.
2. EMD Serono Inc., Avelumab Proposed Prescribing Information; September 2016.
3. EMD Serono Inc., Avelumab EU Risk Management Plan; September 2016.

11 Appendices

11.1 TABLE 2: IMMUNE-RELATED ADVERSE EVENTS COMPARED TO APPROVED PD-1 INHIBITORS[7]

irAE	Avelumab N = 1540 (%)*	Pembrolizumab N = 2799 (%)	Nivolumab N = 268 (%)
Pneumonitis	12 (0.8)	94 (3.4)	6 (2.2)
Hepatitis	14 (0.9)	19 (0.7)	3 (1.1)
Colitis/Diarrhea	15 (1)	48 (1.7)	6 (2.2)
Nephritis	1 (0.1)	2 (0.7)	9 (0.3)
Hypothryoidism; Hyperthyroidism; Thyroiditis	71 (4.6)	1349 (12.5)	29 (11)
Infusion reaction >Grade 3	14 (1)	6 (0.2)	

**These numbers are what was evaluated based on safety information available at the midcycle meeting on 12/8/2016 and differ from the most recent draft label of 2/3/2017 at the time of this writing. There are more numbers included in the pooled safety data set for avelumab (n=1738) in the draft label versus the number reflected in this table.*

11.2 TABLE 3: LABELING COMPARISON OF AVELUMAB TO APPROVED PD AND PD-L1 INHIBITORS[1,8,11,12,13]

	Avelumab	Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab
Approval	Pending 2017	2011	2014	2014	2016
Cancer Indication	Metastatic Merkel Cell Carcinoma	Unresectable, metatstatic, or cutaneous melanoma	Unresectable metastatic melanoma, metastatic NSCLC, renal cell carcinoma, Classical Hodgkin Lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, locally advanced or metastaic carcinoma	Unresectable or metastatic melanoma, metastatic NSCLC, metastatic HNSCC	Locally advanced or metastatic urothelial carcinoma, metatstatic NSCLC
Dose	10mg/kg IV over 60min every 2 weeks	3mg/kg IV over 90 minutes every 3 weeks for a total of 4 doses	Unresectable or metastatic melanoma: 240 mg every 2 weeks; with ipilimumab: nivolumab 1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then nivolumab 240 mg every 2 weeks. Metastatic non-small cell lung cancer: 240 mg every 2 weeks. Advanced renal cell carcinoma : 240 mg every 2 weeks. Classical Hodgkin lymphoma: 3 mg/kg every 2 weeks.	Melanoma: 2 mg/kg every 3 weeks. NSCLC: 200 mg every 3 weeks. HNSCC: 200 mg every 3 weeks. Administer as an IV infusion over 30 minutes	1200 mg as an intravenous infusion over 60 minutes every 3 weeks
Accelerated approval?	Yes	Original approval – yes; no longer under accelerated approval	Yes	Yes	Yes
REMS?	No	Yes – 2011; released in 2015	No	No	No
Boxed Warning?	No	Yes	No	No	No
Warnings and Precautions (Of note: all of these are immune-mediated AE's)	Pneumonitis(5.1); Hepatitis (5.2); Colitis (5.3); Endocrinopathies (5.4) Other Immune-mediated AEs (5.6); Infusion-related AEs (5.7) Embryo-fetal toxicity (5.8)	Enterocolitis (5.1); Hepatitis (5.2) Dermatitis (5.3) Neuropathies (5.4); Endocrinopathies (5.5) Other (5.6); Embryo-fetal toxicity (5.7)	Pneumonitis (5.1); Colitis (5.2); Hepatitis (5.3); Endocrinopathies (5.4); Nephritis and Renal Dysfunction (5.5); Skin reactions (5.6); Encephalitis (5.7); Infusion reactions (5.9); Complications of allogenic HSCT (5.10); Embryo-fetal toxicity (5.11)	Pneumonitis (5.1); Colitis (5.2); Hepatitis (5.3); Endocrinopathies (5.4) Nephritis (5.5); Infusion related reactions (5.7); Embryo-fetal toxicity (5.8)	Pneumonitis (5.1); Hepatitis (5.2); Colitis (5.3); Endocrinopathies (5.4); Myasthenia Gravis, Guillian Barre or Meningoencephalitis (5.5); Infection (5.6); Infusion-related reaction (5.7); Embryo-fetal toxicity (5.8)

12 REFERENCES

[1] Avelumab draft label February 3, 2017

[2] Avelumab Clinical Overview, EMD Serono Inc, pg 11

[3] Hughes M, et al. Merkel Cell Carcinoma: Epidemiology, Target and Therapy. Curr Dermatol Rep. 2014; 3(1): 46-53

[4] Iyer J et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel Cell Carcinoma. Cancer Med 2016 July 19

[5] Kaae J, et al. Merkel cell carcinoma: incidence, mortality, and risk of other cancers. J Natl Cancer Inst 2010;102(11):793-801

[6] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Merkel Cell Carcinoma. Version 1.2017 – October 3, 2016. NCCN.org

[7] Midcycle Clinical and Statistical Slides BLA 761049 – Avelumab for the treatment of patients with metastatic Merkel Cell Carcinoma (mMCC). December 8, 2016

[8] Yervoy U.S. Prescribing Information, revised 10/2015

[9] Ju J. DRISK Review of the 3-Year Assessment for the Ipilimumab REMS. July 3, 2014.

[10] Weaver J. DRISK Review to eliminate the Yervoy REMS. March 6, 2015

[11] Opdivo US Prescribing information, revised 2/2017

[12] Keytruda US Prescribing Information, revised 10/2016

[13] Tecentriq US Prescribing Information, October 2016

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/s/

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02/21/2017

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