CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	BLA
Application Number	761234
PDUFA Goal Date	March 19, 2022
OSE RCM #	2021-1434, 2021-1442
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D
Associate Director for REMS Design and Evaluation:	Laura Zendel, Pharm.D., BCPS
Review Completion Date	March 15, 2022
Subject	Evaluation of Need for a REMS
Established Name	nivolumab and relatlimab-rmbw
Trade Name	Opdualag
Name of Applicant	Bristol-Myers Squibb Company
Therapeutic Class	programmed death receptor-1 (PD-1) blocking antibody, lymphocyte activation gene-3 (LAG-3) blocking antibody
Formulation(s)	nivolumab 240 mg and relatlimab-rmbw 80 mg per 20 mL vial (nivolumab 12 mg and relatlimab-rmbw 4 mg per mL)
Dosing Regimen	Adult and pediatric patients 12 years of age or older who weigh at least 40 kg: nivolumab 480 mg and relatlimab-rmbw 160 mg intravenous infusion every 4 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Opdualag (nivolumab and relatlimab-rmbw) is necessary to ensure the benefits outweigh its risks. Bristol-Myers Squibb Company submitted a Biologic Licensing Application (BLA) 761234 for nivolumab and relatlimab-rmbw with the proposed indication for treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma. The serious risks associated with nivolumab and relatlimab-rmbw include severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), and embryo-fetal toxicity. The applicant did not submit a proposed REMS but submitted a risk management plan with pharmacovigilance activities, that includes voluntary patient directed materials.

DRM and Division of Oncology 3 (DO3) agree that a REMS is not necessary to ensure the benefits of nivolumab and relatlimab-rmbw outweigh its risks. The efficacy of nivolumab and relatlimab-rmbw was supported by the RELATIVITY-047 study, in which the nivolumab and relatlimab-rmbw group had a median progression-free survival (PFS) of 10.1 months and the nivolumab group had a median PFS of 4.6 months, hazard ratio 0.75. The serious risks associated with nivolumab and relatlimab-rmbw of severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. None of these risks rose to the level of a boxed warning. These adverse events are not new or unusual in pharmacotherapeutic regimens used for the treatment of unresectable or metastatic melanoma. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with nivolumab and relatlimab-rmbw.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Opdualag (nivolumab and relatlimab-rmbw) is necessary to ensure the benefits outweigh its risks. Bristol-Myers Squibb Company submitted a Biologic Licensing Application (BLA) 761234 for nivolumab and relatlimab-rmbw with the proposed indication for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.[1] This application is under review in the Division of Oncology 3 (DO3). The applicant did not submit a (b) (4)

2 Background

2.1 PRODUCT INFORMATION

Opdualag (nivolumab and relatlimab-rmbw) is a fixed-dose combination of a programmed death receptor-1 (PD-1) blocking antibody and a lymphocyte activation gene-3 (LAG-3) blocking antibody,

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

proposed for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma. Relatlimab-rmbw is a NME. Opdivo (nivolumab) was originally approved by the FDA in 2014 for the treatment of various cancers either alone or with combination chemotherapy. Nivolumab and relatlimab-rmbw is supplied as a nivolumab 240 mg and relatlimab-rmbw 80 mg per 20 mL vial (nivolumab 12 mg and relatlimab-rmbw 4 mg per mL). The proposed dosing regimen for adult and pediatric patients 12 years of age or older who weigh at least 40 kg is nivolumab 480 mg and relatlimab-rmbw 160 mg intravenous infusion every 4 weeks until disease progression or unacceptable toxicity occurs.[b] Nivolumab and relatlimab-rmbw is not currently approved in any jurisdiction. Nivolumab and relatlimab-rmbw was designated as an orphan product and received fast track designation.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for nivolumab and relatlimab-rmbw BLA 761234 relevant to this review:

- 08/18/2017: Orphan drug designation granted
- 11/20/2019: Fast track designation granted
- 07/19/2021: BLA 761234 submission for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma received
- 11/01/2021: 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 nivolumab and relatlimab-rmbw

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Melanoma of the skin is the 5th leading cancer type for new cancer cases in both males and females in the United States.[2] Risk factors include skin type, history of prior melanoma, multiple clinically atypical moles or dysplastic nevi, positive family history of melanoma, environmental factors, and inherited genetic mutations.[3] The estimated number of new cases of melanoma of the skin in the United States in men and in women is 57,180 and 42,600, respectively.[2,c] The percent of cases at diagnosis of localized, regional, and distant melanoma of the skin is 83%, 9%, and 4%, respectively.[4] In addition, the estimated number of deaths of melanoma of the skin in the United States in men and in women is 5080 and 2570,

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

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

respectively.[2] The five-year relative survival of localized, regional, and distant melanoma of the skin is 99.4%, 68%, and 29.8%, respectively.[4,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Current guidelines from the National Comprehensive Cancer Network (NCCN) for Melanoma: Cutaneous list anti PD-1 monotherapy (pembrolizumab, nivolumab), nivolumab/ipilimumab, and combination targeted therapy of *BRAF* V600-activating mutation in the "Preferred Regimens" section for systemic therapy for metastatic or unresectable disease.[3]

Yervoy (ipilimumab), a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody, was approved by the FDA for indications including treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older, treatment of adult patients with unresectable or metastatic melanoma in combination with nivolumab, and adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection including total lymphadenectomy.[5] Ipilimumab was approved in 2011 with a communication plan REMS to ensure the benefits of the drug outweigh the risks of severe and fatal immune-mediated adverse reactions and also a boxed warning for immune-mediated adverse reactions.[6,7] The communication plan REMS was released on March 16, 2015 as the key activities under the communication plan had been completed and the assessment demonstrated that the communication plan had met its goal.[8] The Division of Oncology Products 2 stated that the goals of the REMS had been met, the oncology community is now well versed in the diagnosis and treatment of immune mediated adverse reactions, and no new safety signals had been identified that require continuation of the Yervoy REMS communication plan.[9] The boxed warning for immune-mediated adverse reactions with ipilimumab was removed on June 29, 2020.[10] The FDA clinical reviewer stated that FDA considers that immune-mediated adverse reactions from the boxed warning are well understood and managed by the prescribing community and that including the information in Section 5 of the product labeling is adequate to communicate the risk. The other serious risks associated with ipilimumab include infusion-related reactions, complications of allogeneic hematopoietic stem cell transplant after Yervoy, embryo-fetal toxicity, and risk associated when administered in combination with nivolumab.

Keytruda (pembrolizumab), a PD-1 blocking antibody, was approved by the FDA for indications including the treatment of patients with unresectable or metastatic melanoma and for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection.[11] Opdivo (nivolumab), a PD-1 blocking antibody, was approved by the FDA for indications including the treatment of patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab, and the treatment of patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.[12] Both pembrolizumab and nivolumab were approved in 2014. The serious risks associated with

[d] 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.*

pembrolizumab and nivolumab include severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), increased mortality in patients with multiple myeloma when Keytruda/Opdivo is added to a thalidomide analogue and dexamethasone, and embryo-fetal toxicity. Pembrolizumab and nivolumab do not have a boxed warning in their respective labels and did not require a REMS to ensure the benefits outweighed their risks.

4 Benefit Assessment

The pivotal trial RELATIVITY-047 (NCT 03470922) supporting this application for efficacy and safety consisted of a Phase 2/3, double-blind, randomized study which evaluated nivolumab and relatlimab-rmbw in patients with previously untreated metastatic or unresectable Stage III or IV melanoma.[1,13] Patients (N=714) were randomized to nivolumab 480 mg and relatlimab-rmbw 160 mg intravenous infusion every 4 weeks (N=355) or nivolumab 480 mg intravenous infusion every 4 weeks (n=359). The primary endpoint was progression-free survival (PFS). The median PFS was 10.1 months in the nivolumab and relatlimab-rmbw group (95% CI 6.4 to 15.7) and 4.6 months in the nivolumab group (95% CI 3.4 to 5.6), hazard ratio 0.75 (95% CI 0.62 to 0.92), p = 0.0055. Secondary endpoints included overall survival (OS) and overall response rate (ORR). The median OS was not reached in the nivolumab and relatlimab-rmbw group (95% CI 34.2 to not reached) and 34.1 months in the nivolumab group (95% CI 25.2 to not reached), hazard ratio 0.8 (95% CI 0.64 to 1.01), p = not significant. The ORR was 43% in the nivolumab and relatlimab-rmbw group (95% CI 38 to 48) and 33% in the nivolumab group (95% CI 28 to 38). The FDA clinical reviewer concluded that nivolumab and relatlimab-rmbw was effective in adult and pediatric patients 12 years of age and older with previously untreated Stage III and Stage IV melanoma.[e]

5 Risk Assessment & Safe-Use Conditions

The safety of nivolumab and relatlimab-rmbw was evaluated in a Phase 2/3 clinical trial RELATIVITY-047 (NCT 03470922).[1,13,f] In the safety population, 355 patients received nivolumab and relatlimab-rmbw and 359 patients received nivolumab. Discontinuation due to a treatment emergent adverse event (TEAE) occurred in 69/355 (19%) in the nivolumab and relatlimab-rmbw group and 41/359 (11%) in the nivolumab group.[14] In addition, 345/355 (97%) of patients experienced a TEAE in the nivolumab and relatlimab-rmbw group and 339/359 (94%) of patients experienced a TEAE in the nivolumab group.[14] Common adverse reactions reported with nivolumab and relatlimab-rmbw included musculoskeletal pain, fatigue, rash, pruritus, and diarrhea. Common laboratory abnormalities reported with nivolumab

[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.*

[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.*

and relatlimab-rmbw included decreased hemoglobin, decreased lymphocytes, increased aspartate aminotransferase, increased alanine aminotransferase, and decreased sodium. The FDA clinical reviewer stated that there were no new safety concerns identified with nivolumab and relatlimab-rmbw.[13] However, some adverse events were increased in frequency or severity with nivolumab and relatlimab-rmbw, including myocarditis, CNS effects, and hypersensitivity/infusion-related reactions.

In study RELATIVITY-047, the applicant indicated that 3 deaths were attributed to study drug toxicity in the nivolumab and relatlimab-rmbw group and 2 deaths were attributed to study drug toxicity in the nivolumab group.[13] The causes of death attributed to study drug toxicity in the nivolumab and relatlimab-rmbw group included hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis.

The serious risks[g] associated with nivolumab and relatlimab-rmbw which include severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity are summarized in the sections below. These serious risks are also listed in the warnings and precautions section of the nivolumab label.[12] However, the risk of immune-mediated myocarditis is further described in Section 5.1 of the draft label, as there was an increase in an adverse event of immune-mediated myocarditis with nivolumab and relatlimab-rmbw.

5.1 SEVERE AND FATAL IMMUNE-MEDIATED ADVERSE REACTIONS

Section 5.1 of the draft labeling describes the risk of severe and fatal immune-mediated adverse reactions which include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, immune-mediated myocarditis, and other immune-mediated adverse reactions. These immune-mediated adverse reactions are summarized below.

The proposed label recommends monitoring for symptoms and signs of immune-mediated adverse reactions. It states to evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment, in cases of suspected immune-mediated adverse reactions to initiate appropriate workup to exclude alternative etiologies including infection, and to institute medical management promptly, including specialty consultation as appropriate. Dose modifications for nivolumab and relatlimab-rmbw will be addressed in section 2 of the proposed label. The proposed label recommends to withhold or permanently discontinue nivolumab and relatlimab-rmbw depending on the severity of immune-mediated adverse reactions. It also contains recommendations for supportive care of immune-mediated adverse reactions including administering systemic corticosteroids if interruption or discontinuation of nivolumab and relatlimab-rmbw is required. Section 5.1 of the draft

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

labeling also contains management guidelines for adverse reactions that do not necessarily require systemic steroids (endocrinopathies, dermatologic reactions) and these recommendations are summarized below. If approved, these risks will be communicated in the warnings and precautions section of the label.

Immune-mediated pneumonitis
An adverse event of immune-mediated pneumonitis occurred in 3.7% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 immune-mediated pneumonitis reported in 2.3% of patients and Grade 3 immune-mediated pneumonitis reported in 0.6% of patients.

Immune-mediated colitis
An adverse event of immune-mediated diarrhea or colitis occurred in 7% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 immune-mediated diarrhea or colitis reported in 4.5% of patients and Grade 3 immune-mediated diarrhea or colitis reported in 1.1% of patients.

Immune-mediated hepatitis
An adverse event of immune-mediated hepatitis occurred in 6% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 immune-mediated hepatitis reported in 1.4% of patients, Grade 3 immune-mediated hepatitis reported in 3.4% of patients, and Grade 4 immune-mediated hepatitis reported in 0.6% of patients

Immune-mediated endocrinopathies
An adverse event of adrenal insufficiency occurred in 4.2% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 adrenal insufficiency reported in 2.5% of patients and Grade 3 adrenal insufficiency reported in 1.4% of patients. The proposed label recommends for Grade 2 or higher adrenal insufficiency to initiate symptomatic treatment including hormone replacement as clinically indicated and to withhold nivolumab and relatlimab-rmbw depending on severity.

An adverse event of hypophysitis occurred in 2.5% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 hypophysitis reported in 1.4% of patients and Grade 3 hypophysitis reported in 0.3% of patients. The proposed label recommends to initiate hormone replacement as clinically indicated and to withhold or permanently discontinue nivolumab and relatlimab-rmbw depending on severity.

An adverse event of thyroiditis occurred in 2.8% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 thyroiditis reported in 1.1% of patients. An adverse event of hyperthyroidism occurred in 6% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 hyperthyroidism reported in 1.4% of patients. In addition, an adverse event of hypothyroidism occurred in 17% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 hypothyroidism reported in 11% of patients. The proposed label recommends to initiate hormone replacement or medical management as clinically indicated and to withhold or permanently discontinue nivolumab and relatlimab-rmbw depending on severity.

Section 5.1 of the draft labeling also states that Type 1 diabetes mellitus which can present as diabetic ketoacidosis may occur with nivolumab and relatlimab-rmbw. An adverse event of diabetes occurred in

0.3% of patients receiving nivolumab and relatlimab-rmbw, with Grade 3 diabetes reported in 0.3% of patients. The proposed label recommends to monitor patients for hyperglycemia or other signs and symptoms of diabetes, to initiate treatment with insulin as clinically indicated, and to withhold or permanently discontinue nivolumab and relatlimab-rmbw depending on severity.

Immune-mediated nephritis with renal dysfunction

An adverse event of immune-mediated nephritis and renal dysfunction occurred in 2% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 immune-mediated nephritis and renal dysfunction reported in 0.8% of patients, and Grade 3 immune-mediated nephritis and renal dysfunction reported in 1.1% of patients. The proposed label recommends to withhold or permanently discontinue nivolumab and relatlimab-rmbw depending on severity.

Immune-mediated dermatologic adverse reactions

Section 5.1 of the draft labeling states that immune-mediated rash or dermatitis may occur with nivolumab and relatlimab-rmbw. An adverse event of immune-mediated rash occurred in 9% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 immune-mediated rash reported in 3.4% of patients, and Grade 3 immune-mediated rash reported in 0.6% of patients. In addition, exfoliative dermatitis, including Stevens Johnson Syndrome, toxic epidermal necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms have been reported with PD-1/L-1 blocking antibodies. The proposed label states that topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes and to withhold or permanently discontinue nivolumab and relatlimab-rmbw depending on severity.

Immune-mediated myocarditis

An adverse event of immune-mediated myocarditis occurred in 1.7% of patients receiving nivolumab and relatlimab-rmbw, with Grade 2 immune-mediated myocarditis reported in 1.1% of patients, and Grade 3 immune-mediated myocarditis reported in 0.6% of patients. The proposed label recommends to assess patients with cardiac or cardio-pulmonary symptoms for potential myocarditis. It states if myocarditis is suspected to withhold the dose, promptly initiate high dose steroids (prednisone or methylprednisolone 1 to 2 mg/kg/day), and promptly arrange cardiology consultation with diagnostic workup. It also states to permanently discontinue nivolumab and relatlimab-rmbw for Grade 2-4 myocarditis.

Other immune-mediated adverse reactions

Section 5.1 of the draft labeling also describes other immune-mediated adverse reactions that were reported in < 1% of patients receiving nivolumab and relatlimab-rmbw or other PD-1/PD-L1 blocking antibodies.

5.2 INFUSION-RELATED REACTIONS

An adverse reaction of infusion-related reactions occurred in 7% of patients receiving nivolumab and relatlimab-rmbw as a 60-minute intravenous infusion. The proposed label recommends to discontinue nivolumab and relatlimab-rmbw in patients with severe or life-threatening infusion-related reactions and to interrupt or slow the rate of infusion in patients with mild or moderate infusion-related

reactions. If approved, these risks will be communicated in the warnings and precautions section of the label.

5.3 COMPLICATIONS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Allogeneic HSCT complications, including hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome, may occur in allogeneic HSCT patients treated with PD-1/PD-L1 receptor blocking antibody. The proposed label states to follow patients closely for evidence of transplant-related complications and intervene promptly. If approved, these risks will be communicated in the warnings and precautions section of the label.

5.4 EMBRYO-FETAL TOXICITY

Nivolumab and relatlimab-rmbw may cause fetal harm based on animal studies and the mechanism of action of the drug. Nivolumab has been reported to cause increased abortion and premature infant death when administered to cynomolgus monkeys from the onset of organogenesis through delivery in animal reproduction studies. No clinical data is available with nivolumab and relatlimab-rmbw in pregnancy in humans. The risk of embryo-fetal toxicity will be included in a Medication Guide and the warnings and precautions section of the label. The proposed label states to advise pregnant women of the potential risk to a fetus. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting nivolumab and relatlimab-rmbw and that effective contraception be used during treatment and for at least 5 months after the last dose.

6 Expected Postmarket Use

If approved, nivolumab and relatlimab-rmbw will primarily be used in both inpatient and outpatient (such as infusion centers) settings. The likely prescribers will be oncologists.

7 Risk Management Activities Proposed by the Applicant

The Applicant proposed risk management activities for nivolumab and relatlimab-rmbw including pharmacovigilance and labeling. (b) (4) .

Reviewer's Comments: We note that (b) (4)

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of nivolumab and relatlimab-rmbw on the basis of the efficacy and safety information currently available. Nivolumab and relatlimab-rmbw is a combination of a PD-1 blocking antibody and a LAG-3 blocking antibody and is a treatment option for adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma. The efficacy of nivolumab and relatlimab-rmbw was supported by the RELATIVITY-047 study, in which the nivolumab and relatlimab-rmbw group had a median PFS of 10.1 months and the nivolumab group had a median PFS of 4.6 months, hazard ratio 0.75. The serious risks associated with nivolumab and relatlimab-rmbw of severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The FDA clinical reviewer stated that there were no new safety concerns identified with nivolumab and relatlimab-rmbw. However, the risk of immune-mediated myocarditis is further described in Section 5.1 of the draft label, as there was an increase in an adverse event of immune-mediated myocarditis with nivolumab and relatlimab-rmbw. None of the risks associated with nivolumab and relatlimab-rmbw rise to the level of a boxed warning. (b) (4)

Melanoma of the skin is the 5th leading cancer type for new cancer cases in both males and females in the United States. The estimated number of new cases of melanoma of the skin in the United States in men and in women is 57,180 and 42,600, respectively. The percent of cases at diagnosis of localized, regional, and distant melanoma of the skin is 83%, 9%, and 4%, respectively. In addition, the five-year relative survival of localized, regional, and distant melanoma of the skin is 99.4%, 68%, and 29.8%, respectively. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with nivolumab and relatlimab-rmbw, as well as other therapies used in the treatment of unresectable or metastatic melanoma. If approved, based on the efficacy and risks associated with nivolumab and relatlimab-rmbw for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma, the DRM and DO3 agree that a REMS is not necessary to ensure that the benefits outweigh the risks as the risks can be adequately communicated in labeling.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for nivolumab and relatlimab-rmbw to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

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[5] Yervoy (ipilimumab) package insert. Princeton, NJ: Bristol-Myers Squibb Company, 2021 May.

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[8] Supplement approval release REMS requirement letter for Yervoy (ipilimumab) BLA 125377/71, March 16, 2015.

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[11] Keytruda (pembrolizumab) package insert. Whitehouse Station, NJ: Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc., 2022 February.

[12] Opdivo (nivolumab) package insert. Princeton, NJ: Bristol-Myers Squibb Company, 2021 August.

[13] Opdualag (nivolumab and relatlimab-rmbw) multi-disciplinary review and evaluation. Accessed February 21, 2022.

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