BRISTOL-MYERS SQUIBB RESEARCH AND DEVELOPMENT

SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR RELATLIMAB + NIVOLUMAB FDC (OPDUALAG®)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of OPDUALAG® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, eg by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of OPDUALAG® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bristol-Myers Squibb SA is fully responsible for the accuracy and correctness of the content of the published summary RMP for OPDUALAG®.

1 SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the risk management plan (RMP) for Opdualag (relatlimab + nivolumab fixed dose combination FDC). The RMP details important risks of Opdualag, how these risks can be minimised, and how more information will be obtained about Opdualag's risks and uncertainties (missing information).

Opdualag's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Opdualag should be used.

This summary of the RMP for Opdualag should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Opdualag's RMP.

1.1 The Medicine and What it is Used For

Opdualag is authorised for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents (12 years and older and weighing at least 40 kg) (see SmPC for the full indication). It contains relatlimab and nivolumab as the active substances as part of a FDC and it is given by intravenous infusion.

Further information about the evaluation of Opdualag's benefits can be found in Opdualag's EPAR, including its plain-language summary, available on the EMA website under the medicine's webpage: https://www.ema.europa.eu/en/medicines/what-we-publishwhen/european-public-assessment-reports-background-context.

1.2 Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Opdualag, together with measures to minimise such risks and the proposed studies for learning more about Opdualag's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of Opdualag, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Opdualag is not yet available, it is listed under 'missing information' below.

1.2.1 List of Important Risks and Missing Information

Important risks of Opdualag are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Opdualag. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related endocrinopathies Immune-related nephritis and renal dysfunction Immune-related skin ARs Immune-related myocarditis Other immune-related ARs
Important potential risks	Embryofetal toxicity
Missing information	Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age

1.2.2 Summary of Important Risks

Important Identified Risks

Immune-related pneumonitis	
Evidence for linking the risk to the medicine	Immune-related pneumonitis or interstitial lung disease cases were observed with relatlimab + nivolumab FDC. The majority of cases reported were Grade 1-2. Severe (Grade 3-4) cases were more common with relatlimab + nivolumab FDC than with nivolumab monotherapy. One fatal case of pneumonitis was reported with relatlimab + nivolumab FDC. Severe pneumonitis can be life-threatening if not diagnosed early and managed appropriately.
Risk factors and risk groups	Risk factors include older age, reduced lung function, smoking history, concomitant or previous lung infection, previous radiotherapy or chemotherapy, and pulmonary resection.

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Important Identified Risks

Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorization development plan.
Immune-related colitis	
Evidence for linking the risk to the medicine	Immune-related colitis cases were observed with relatlimab + nivolumab FDC. The majority of subjects had mild to moderate (Grade 1-2) diarrhea or colitis. Severe diarrhoea or colitis (Grade 3-4) cases were more common with relatlimab + nivolumab FDC than with nivolumab monotherapy. Diarrhea/colitis was manageable using the established management guidelines. The majority of cases resolved with drug interruption and/or, immunosuppressive therapy. Severe or persistent diarrhea and colitis can be life-threatening if not recognized early and managed appropriately.
Risk factors and risk groups	Patients with active inflammatory bowel disease.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorization development plan.
Immune-related hepatitis	
Evidence for linking the risk to the medicine	Immune-related hepatitis cases were observed with relatlimab + nivolumab FDC. The majority of cases reported were Grade 1-2. Severe (Grade 3-4) cases were more common with relatlimab + nivolumab FDC than with nivolumab monotherapy. Subjects may be also asymptomatic. In clinical studies, hepatotoxicities manifesting as transaminase elevations was the most frequently observed AE and was detectable with liver function testing and signs and symptoms monitoring. Immune-related hepatitis can be serious or life-threatening and even fatal if not treated promptly. Subjects with immune-related hepatitis are generally managed clinically with steroid therapy or other immunosuppressants with resolution of the event. Prompt review of blood tests, recognition of signs and symptoms, and implementation of the recommended management guidelines may prevent serious complications.
Risk factors and risk groups	Active autoimmune hepatitis.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorization development plan.

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Important Identified Risks

Immune-related endocrinopathies	
Evidence for linking the risk to the medicine	Immune-related endocrinopathies have been observed with relatlimab + nivolumab FDC and thyroid disorders, adrenal disorders, pituitary disorders were more common with relatlimab and nivolumab FDC than with nivolumab monotherapy. The most common thyroid disorders were hypothyroidism and hyperthyroidism, however, no severe (Grade 3-4) thyroid disorders were reported. Severe (Grade 3-4) adrenal, pituitary and diabetes cases have been observed but all at low frequency. Patients are typically well-managed with hormone replacement and/or steroid treatment. Lifelong hormone replacement may be required. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications.
Risk factors and risk groups	Active autoimmune diseases of the endocrine glands.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorization development plan.
Immune-related nephritis and renal dysfunction	
Evidence for linking the risk to the medicine	Immune-related nephritis and renal dysfunction have been observed with relatlimab + nivolumab FDC. Most cases were Grade 1-2. Severe nephritis and renal dysfunction cases were more common with relatlimab + nivolumab FDC than with nivolumab monotherapy. Immune-related nephritis and renal dysfunction can be serious or life-threatening. Subjects with immune-related nephritis and renal dysfunction are generally managed clinically with steroid therapy with resolution of the event. Prompt recognition of signs and symptoms, prompt review of blood tests and implementation of the recommended management guidelines may prevent serious complications.
Risk factors and risk groups	Active autoimmune diseases with potential for renal involvement.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorization development plan.
Immune-related skin ARs	
Evidence for linking the risk to the medicine	Immune-related skin ARs have been observed with relatlimab + nivolumab FDC. Skin immune-related reactions were higher for relatlimab + nivolumab FDC than with nivolumab monotherapy with the majority being mild to moderate (Grade 1-2). The severe (Grade 3-4) immune related skin ARs (rash) were of low frequency with relatlimab + nivolumab FDC and

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Important Identified Risks

	nivolumab monotherapy. Early detection and timely treatment are key to recovery and to prevent severe complications.
Risk factors and risk groups	Active autoimmune skin disorders.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorization development plan.
Immune-related myocarditis	
Evidence for linking the risk to the medicine	Myocarditis was observed with a low frequency in patients treated with relatlimab +nivolumab FDC, and the majority of cases were mild to moderate (Grade 1-2). Severe myocarditis was also observed, however, all cases in patients receiving relatlimab+nivolumab FDC were manageable within established irAR management practices and resolved. Myocarditis can be life-threatening if not managed appropriately. Some asymptomatic cases of myocarditis were detected through troponin lab monitoring in patients receiving relatlimab+nivolumab. However, troponin is a sensitive, but non-specific, marker of cardiac pathology and myocarditis accounted for a minority of the troponin elevation events observed within the study, most of which required no immunosuppression. The risk of immune-mediated myocarditis with IO agents is now well-recognised among clinical practitioners, and guidelines for IO toxicity management including myocarditis are available globally. Careful patient follow-up, a high index of suspicion, and management according to well-established IO treatment algorithms are appropriate to detect myocarditis and prevent poor outcomes.
Risk factors and risk groups	The risks are unknown.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorization development plan.
Other immune-related ARs	
Evidence for linking the risk to the medicine	Selected other immune-related ARs, which are considered important identified risks, include uveitis, pancreatitis, Guillain-Barre syndrome, myositis/ rhabdomyolysis, encephalitis, hemolytic anemia, Vogt Koyanagi-Harada syndrome (VKH), hemophagocytic lymphohistiocytosis (HLH) were observed with relatlimab + nivolumab FDC. The above mentioned other immune-related ARs have also been reported with nivolumab monotherapy or nivolumab in combination with other approved agents. Additionally, the following other immune-related ARs have been reported with nivolumab monotherapy or nivolumab in combination with other approved agents: demyelination, autoimmune neuropathy

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Important Identified Risks

	(including facial and abducens nerve paresis), myasthenia gravis, myasthenic syndrome, aseptic meningitis, gastritis, sarcoidosis, duodenitis, hypoparathyroidism, and cystitis noninfective. Solid organ transplant rejection has been reported in the post marketing setting in patients treated with PD-1 inhibitors. In patients treated with nivolumab before or after allogeneic HSCT, rapid onset and severe graft versus host disease (GVHD), some with fatal outcome, have been reported. Severe (Grade 3-4) other immune-related ARs were reported in minority of patients. Other immune-related ARs can be serious and life threatening. Patients are usually clinically managed with steroids/other immunosuppressants and the events generally resolved. The majority of cases for uveitis or pancreatitis were not severe, therefore, not considered to be standalone risks. The frequency for uveitis and pancreatitis was similar between the relatlimab + nivolumab FDC and nivolumab monotherapy arms.
Risk factors and risk groups	Active autoimmune diseases.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risks

Embryofetal toxicity	
Evidence for linking the risk to the medicine	Effective contraception should be used for women of childbearing potential (WOCBP) during relatlimab + nivolumab FDC clinical trials. Relatlimab + nivolumab FDC has not been evaluated in pregnant monkeys; however, preclinical data suggests potential risk of third trimester fetal loss and premature birth with increased neonatal mortality if exposed to nivolumab during pregnancy. Based on the mechanism of action, potential risks of relatlimab and nivolumab during pregnancy include increased rates of abortion and stillbirth.
Risk factors and risk groups	Exposure during pregnancy.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.6 and 5.3 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None See section II.C of this summary for an overview of the post-authorisation development plan.

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Missing Information

Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age	
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2 and 4.8 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS CA224122 See section II.C of this summary for an overview of the post-authorisation development plan.

1.3 Post-authorisation Development Plan

1.3.1 Studies which are Conditions of the Marketing Authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of Opdualag.

1.3.2 Other Studies in Post-authorisation Development Plan

Category 3 Planned Additional Pharmacovigilance Activities

Study short name and title	Rationale and study objectives
CA224122: Long-term follow-up of paediatric patients exposed to relatlimab + nivolumab FDC in the DMTR. Planned	The primary objective is to evaluate Grades 3-4 AEs (which includes irARs) experienced by paediatric patients ≥ 12 to < 18 years of age, along with their management, and outcome. Secondary objectives include evaluating long-term outcomes (with emphasis on growth and development). Long term safety (including growth and development disorders) in paediatric patients ≥ 12 to < 18 years of age. Use in these patients is part of the proposed on-label indication for Opdualag but there is no data from clinical development in this patient population.

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