

Summary of risk management plan for OPDIVO (nivolumab)

This is a summary of the risk management plan (RMP) for OPDIVO. The RMP details important risks of OPDIVO, how these risks can be minimized, and how more information will be obtained about OPDIVO's risks and uncertainties (missing information).

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

This summary of the RMP for OPDIVO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 OPDIVO's RMP.

I. The medicine and what it is used for

OPDIVO is authorized for the treatment of advanced melanoma, melanoma after complete resection in adults, advanced or metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin Lymphoma (cHL), squamous cell cancer of the head and neck (SCCHN), and urothelial carcinoma (UC) (see SmPC for the full indication). It contains nivolumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of OPDIVO's benefits can be found in OPDIVO's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's [webpage](#).

II. Risks associated with the medicine and activities to minimise or further characterize the risks

Important risks of OPDIVO, together with measures to minimise such risks and the proposed studies for learning more about OPDIVO'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 authorized 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 minimization* measures.

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

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 OPDIVO is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of OPDIVO 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 OPDIVO. 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

<i>Important identified risks</i>	Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune-related skin ARs Other immune-related ARs Severe infusion reactions
<i>Important potential risks</i>	Embryofetal toxicity Immunogenicity Cardiac arrhythmias (previously treated melanoma indication, only) Complications of allogeneic HSCT following nivolumab therapy in cHL Risk of GVHD with nivolumab after allogeneic HSCT
<i>Missing information</i>	Pediatric patients <18 years of age Elderly patients with: <ul style="list-style-type: none"> – cHL ≥ 65 years of age – SCCHN ≥ 75 years of age Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab Use in patients who have undergone influenza vaccination Patients with brain metastases: <ul style="list-style-type: none"> – Advanced melanoma, SCCHN, and UC – active brain or

List of important risks and missing information

-
-
- leptomeningeal metastases
 - NSCLC – active brain metastases
 - RCC – any history of or concurrent brain metastases
-
-

II.B Summary of important risks

Important identified risks

Immune-related pneumonitis

Evidence for linking the risk to the medicine	Immune-related pneumonitis has been reported in subjects with a variety of tumor types and in subjects with and without lung metastases. The majority of cases reported were Grade 1-2 and subjects presented with either asymptomatic radiographic changes (eg, focal ground glass opacities, patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3-4 pulmonary toxicities were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. Severe pneumonitis can be life-threatening if not diagnosed early and managed appropriately.
Risk factors and risk groups	Death due to pulmonary toxicity, including pulmonary embolism, has been reported with nivolumab in combination with ipilimumab. Interstitial lung disease (ILD) can develop or exacerbate as a consequence of radiotherapy, chemotherapy, or pulmonary resection. Other risk factors of ILD include older age, reduced normal lung on computed tomography scan, smoking history, and concomitant or previous lung infection
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Adverse Reaction Management Guide; Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none">• CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice 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 has been reported in subjects with a variety of tumor types. The majority of subjects had mild to moderate (Grade 1-2) diarrhea or colitis. Grade 3-4 cases were more common with nivolumab in combination with ipilimumab. Diarrhea/colitis was manageable using the established management guidelines. The majority of cases resolved with drug interruption and, in severe cases, with steroids treatment. 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: Adverse Reaction Management Guide; Patient Alert Card

Important identified risks

Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none">CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice <p>See section II.C of this summary for an overview of the post-authorization development plan.</p>
Immune-related hepatitis	
Evidence for linking the risk to the medicine	<p>Immune-related hepatitis has been reported in subjects with a variety of tumor types. Subjects may be asymptomatic. In clinical studies, hepatotoxicities manifesting as transaminase elevations were detectable with liver function testing and signs and symptoms monitoring. Most were Grade 1-2 transaminase elevation or hepatitis. 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 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.</p>
Risk factors and risk groups	<p>Active autoimmune hepatitis, which may also be associated with previous chemotherapy or immunotherapy, such as IL-2 or interferon (IFN).</p>
Risk minimization measures	<p>Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8</p> <p>Additional risk minimization measures: Adverse Reaction Management Guide; Patient Alert Card</p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none">CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice <p>See section II.C of this summary for an overview of the post-authorization development plan.</p>
Immune-related nephritis and renal dysfunction	
Evidence for linking the risk to the medicine	<p>Immune-related nephritis and renal dysfunction have been reported in subjects with a variety of tumor types. Most patients present with asymptomatic increase in serum creatinine. Most were Grade 1-2 severity. 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.</p>
Risk factors and risk groups	<p>Active autoimmune diseases with potential for renal involvement.</p>
Risk minimization measures	<p>Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8</p> <p>Additional risk minimization measures: Adverse Reaction Management Guide; Patient Alert Card</p>
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none">CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice <p>See section II.C of this summary for an overview of the post-authorization development plan.</p>
Immune-related endocrinopathies	
Evidence for linking the risk to the	<p>Immune-related endocrinopathies have been reported in subjects with a</p>

Important identified risks

medicine	variety of tumor types. Immune-related endocrinopathies have been observed with nivolumab monotherapy and the most common disorder was hypothyroidism with Grade 1-2 severity in majority of the cases. Endocrinopathies were more frequent with nivolumab in combination with ipilimumab. Less frequently observed endocrinopathies included adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis. Patients are typically 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 may also be associated with previous chemotherapy or immunotherapy, such as IL-2, interferon, or anti-CTLA4.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Adverse Reaction Management Guide; Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none">• CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice 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 reported in subjects with a variety of tumor types. Mild to moderate (Grade 1-2) immune-related skin ARs are common with nivolumab monotherapy, while severe (Grade 3-4) immune-related skin ARs are of low frequency with nivolumab monotherapy and more frequent with nivolumab in combination with ipilimumab. Rare cases of SJS and TEN, some with fatal outcome, have been observed. 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: Adverse Reaction Management Guide; Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none">• CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice 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 uncommon but considered important identified risks, include uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, myositis, myocarditis, rhabdomyolysis, encephalitis, solid organ transplant rejection, and Vogt-Koyanagi-Harada. Other immune-related ARs can be serious and life-threatening. Patients are usually clinically managed with steroids and the events generally resolved. Severe (Grade 3-4) immune-related ARs are
---	--

Important identified risks

Risk factors and risk groups	reported in minority of patients. Active autoimmune diseases may also be associated with previous chemotherapy or immunotherapy, such as IL-2, interferon, or anti-CTLA4.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimization measures: Adverse Reaction Management Guide; Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none">CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice See section II.C of this summary for an overview of the post-authorization development plan.

Severe infusion reactions

Evidence for linking the risk to the medicine	As with any other intravenous administered drugs, infusion-related reactions can occur with nivolumab. Premedications were generally not required prior to nivolumab administration during clinical trials with nivolumab. Severe infusion reactions were uncommon but can lead to discontinuation.
Risk factors and risk groups	None.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.4 and 4.8

Important potential risks

Embryofetal toxicity

Evidence for linking the risk to the medicine	Contraception is required for women of child bearing potential (WOCBP) and for men with WOCBP partner during nivolumab clinical trials. Preclinical study suggested potential risk of third trimester fetal loss and premature birth with increased neonatal mortality if exposed to nivolumab during pregnancy.
Risk factors and risk groups	Exposure during pregnancy.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.6 and 5.3

Immunogenicity

Evidence for linking the risk to the medicine	No increased risk of hypersensitivity or infusion reaction in patients with positive ADA vs negative ADA subjects. No life threatening or fatal outcomes have been reported. Low rates of immunogenicity have been observed and no impact of has been observed on safety or efficacy even following prolonged dose interruptions and rechallenge.
Risk factors and risk groups	Occurrence of immunogenicity is dependent on several factors related to drugs of interest and patient characteristics, such as drug characteristics, processing, doses, and route of administration, and patients' age, genetic factors, immune status, disease status, concomitant medications.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.8

Cardiac arrhythmias (previously treated melanoma indication, only)

Evidence for linking the risk to the	The frequency of all causality cardiac arrhythmia were balanced between nivolumab and comparator arms in completed Phase 3 randomized,
--------------------------------------	--

Important potential risks

medicine	comparator controlled studies across multiple tumor types. One exception was in the study of previously treated advanced melanoma where cardiac arrhythmia was higher in nivolumab arm than in the comparator arm. The most common arrhythmias were tachycardia and atrial fibrillation, most were of Grade 1-2, and most were not considered drug-related by the investigators. The explanation for this higher rate of cardiac arrhythmia in this previously treated advanced melanoma is unclear; however, there were high background rates of baseline medical history of cardiovascular and respiratory system diseases and of atrial arrhythmia.
Risk factors and risk groups	Risk factors include increasing age, high blood pressure, hypercholesterolemia, heart disorders (myocardial infarction, congestive heart failure, valvular diseases), hyperthyroidism, and other risk factors such as obesity, diabetes, lung disease, sleep apnea, metabolic syndrome.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.8
Complications of allogeneic HSCT following nivolumab therapy in cHL	
Evidence for linking the risk to the medicine	Preliminary results from the follow-up of patients undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft versus host disease (GVHD) and transplant-related mortality (TRM). Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case (see SmPC Section 4.8).
Risk factors and risk groups	Potential risk factors include the degree of HLA match and related versus unrelated donor, number of previous therapies, patient age, transplant conditioning regimen, and time from nivolumab therapy to transplant.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 recommends case by case considerations, and close monitoring of patients undergoing allogeneic HSCT for hyperacute GVHD, Grade 3-4 acute GVHD, steroid requiring febrile syndrome, hepatic veno-occlusive disease, and other transplant related complications. Related information is found in SmPC Section 4.8. Additional risk minimization measures: Adverse Reaction Management Guide; Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none">• CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCT See section II.C of this summary for an overview of the post-authorization development plan.
Risk of GVHD with nivolumab after allogeneic HSCT	
Evidence for linking the risk to the medicine	In patients treated with nivolumab post allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting.
Risk factors and risk groups	Patients who have previously undergone allogeneic HSCT prior to nivolumab therapy.
Risk minimization measures	SmPC Section 4.4 provides warnings of the increased risk of severe GVHD and death in patients who have had prior allogeneic HSCT. Related information is found in SmPC Section 4.8 Undesirable effects

Important potential risks

Additional pharmacovigilance activities	Additional risk minimization measures: Adverse Reaction Management Guide; Patient Alert Card
---	--

Missing information

Pediatric patients <18 years of age

Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2, subsection on Pediatric population
----------------------------	--

Elderly patients with cHL ≥ 65 years of age and SCCHN ≥ 75 years of age

Risk minimization measures	Routine risk minimization measures: Sections 4.2, 4.8, and 5.1 of the SmPC
----------------------------	--

Patients with severe hepatic and/or renal impairment

Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.2 and 5.2
----------------------------	---

Patients with autoimmune disease

Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4
----------------------------	--

Patients already receiving systemic immunosuppressants before starting nivolumab

Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.4 and 4.5
----------------------------	---

Use in patients who have undergone influenza vaccination

Risk minimization measures	Routine risk minimization measures: Safety monitoring and signal detection
----------------------------	--

Patients with brain metastases: Advanced melanoma, SCCHN, and UC – active brain or leptomeningeal metastases; NSCLC – active brain metastases; RCC – any history of or concurrent brain metastases

Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4
----------------------------	--

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

Planned and ongoing post-authorization efficacy studies

Study short name and title	Summary of objectives
Efficacy studies which are conditions of the marketing authorization	
Final clinical study report for CA209205: Non-comparative, multi-cohort, single-arm, open-label, Phase 2 study of nivolumab (BMS-936558) in cHL subjects after failure of ASCT	Final CSR addendum to report mature OS and data from the discontinuation schedule in Cohort C
Final clinical study report for CA209238: A Phase 3, randomized double-blind study of OPDIVO versus Yervoy in patients who have undergone complete resection of Stage IIIb/c or Stage IV	Final CSR to report OS data.

Planned and ongoing post-authorization efficacy studies

Study short name and title	Summary of objectives
Efficacy studies which are conditions of the marketing authorization	
melanoma	
Biomarker commitments:	
Combination with ipilimumab: CA209038, CA209067 and CA209069	To further investigate the value of biomarkers in melanoma by IHC or genomics-based methods as predictive of nivolumab + ipilimumab combination therapy efficacy. Levels of myeloid-derived suppressor cells in circulation will be explored in study CA209038.
CA209238	To further investigate the value of biomarkers other than PD-L1 and PD-L2 expression status at tumor cell membrane level by IHC or genomics-based methods as predictive of nivolumab efficacy in the adjuvant treatment of melanoma.
CA209017, CA209057, and CA209026	To further investigate the value biomarkers other than PD-L1 expression status at tumor cell membrane level by IHC or genomics-based methods as predictive of nivolumab efficacy.
CA209025 and CA209009	To further investigate the value biomarkers other than PD-L1 expression status at tumor cell membrane level by IHC or genomics-based methods as predictive of nivolumab efficacy.
CA209275 and CA209032	To further investigate the value biomarkers other than PD-L1 expression status at tumor cell membrane level by IHC or genomics-based methods as predictive of nivolumab efficacy.
CA209009, CA209038 and CA209064 analyses	To further investigate the relation between PD-L1 and PD-L2 expression in Phase 1 studies.
CA209066, CA209057, and CA209025 analyses	To further investigate the associative analyses between PD-L1 and PD-L2 expression.
CA209141	To further investigate the association between improved clinical outcomes to nivolumab and the presence of 1) PD-L2 expression, and 2) high inflamed phenotype.
CA209275	To explore in UC patients the early identification of those who do/do not respond to treatment with nivolumab as well as to evaluate the association between improved clinical outcomes to nivolumab and the presence of mutational and neoantigen load, PD-L1 expression on tumor- and tumor-associated immune cells using validated approaches as feasible.
Final clinical study report for a randomized, clinical study comparing the efficacy and safety of the combination of nivolumab and ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor-risk advanced renal cell carcinoma and with an	To further evaluate the efficacy and safety of the combination of nivolumab and ipilimumab compared to nivolumab monotherapy.

Planned and ongoing post-authorization efficacy studies

Study short name and title	Summary of objectives
Efficacy studies which are conditions of the marketing authorization	
appropriate spectrum of PD-L1 expression levels.	
Efficacy studies which are Specific Obligations	
None	NA

II.C.2 Other studies in post-authorization development plan

Category 3 ongoing and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic hematopoietic stem cell transplant Ongoing	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic hematopoietic stem cell transplant