OPDIVO®▼

(nivolumab)

Risk Minimisation Information for Healthcare Professionals

For the complete list of authorised indications and full prescribing information, please refer to the nivolumab Summary of Product Characteristics (SmPC).

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.
Healthcare professionals are asked to report any Suspected Adverse Drug Reactions (side effects) or medication errors using the Medicines Authority ADR reporting form, which is available online at ***http://www.medicinesauthority.gov.mt/adrportal***, and sent by post or email to:
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: ***postlicensing.medicinesauthority.com***
Adverse reactions should also be reported to Bristol-Myers Squibb Medical Information at ***00 356 23976333*** or ***pv@amamngion.com***.

Bristol-Myers Squibb

This Guide

- Is provided for healthcare professionals (HCPs) who are involved in the treatment of patients with nivolumab or nivolumab in combination with ipilimumab.
    - When nivolumab is administered in combination with ipilimumab, please also refer to the SmPC for ipilimumab prior to initiation of treatment.
- Is essential to ensure the safe and effective use of nivolumab or nivolumab in combination with ipilimumab and appropriate management of possible immune-related adverse reactions (irARs).
- Is to be read before prescribing and administering nivolumab or nivolumab in combination with ipilimumab.
    - For the complete list of authorised indications (including in combination with ipilimumab) and full prescribing information, please refer to the nivolumab SmPC.
- Introduces a Patient Alert Card that must be discussed with patients before each treatment cycle and at each visit, in order to reinforce their understanding of side effects and the need to contact an HCP if they develop side effects.

A digital version of the Risk Minimisation Information is available at the following website address: ***http://opdivo-hcp-mt.com***.

Summary of Important Safety Information

- Nivolumab, as monotherapy or in combination with ipilimumab, increases the risk of severe irARs, which can include pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin reactions and other irARs (see details later), as well as potential complications of allogeneic haematopoietic stem cell transplant (HSCT).
- IrARs can occur several months after the last dose of nivolumab.
- Early diagnosis and appropriate management of irARs are essential to minimise life-threatening complications.
- Suspected adverse reactions must be promptly evaluated to exclude infectious or other alternate aetiologies.
- Based on the severity of the irAR, the treatment should be withheld or discontinued and systemic corticosteroid therapy with or without additional immunosuppressive therapy may be required.
- In addition to corticosteroids, hormone replacement therapy may be required for the management of endocrinopathies. Upon improvement, treatment may be resumed after corticosteroid taper; treatment must be permanently discontinued for any severe irAR that recurs and for any life-threatening irAR.
- Patients and caregivers should be informed about the symptoms of irARs and the importance of reporting them immediately to the treating physician.

What is Nivolumab?

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Nivolumab in combination with ipilimumab

Nivolumab (anti-PD-1) in combination with ipilimumab (anti-CTLA-4) is approved in selected indications as specified in the nivolumab SmPC.

Ipilimumab is a fully human, monoclonal IgG1 antibody that increases T-cell activity to attack tumour cells by inhibiting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4).

Checklist for Patient Visits

FIRST VISIT

- Make the appropriate checks:
  - Signs and symptoms of electrolyte disturbances, dehydration, endocrinopathies, hyperglycaemia, and changes in thyroid function
  - Liver function tests – nivolumab must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe (total bilirubin > 3 × ULN with any AST) hepatic impairment
  - Any previous clinical conditions
  - If the patient has had an allogeneic stem cell transplant
  - If the patient is allergic to the active substance or to any of the excipients
  - If the patient is taking systemic corticosteroids and other immunosuppressants before starting nivolumab
  - If the patient is pregnant or planning to become pregnant, or if the patient is breastfeeding
  - If the patient belongs to any special population group in which caution is required, including where there is limited or absent data
  - Signs and symptoms of conditions that are in the *Warnings and Precautions* or *Contraindications* sections of the nivolumab SmPC
- Discuss the treatment with the patient, fill in the Patient Alert Card, and advise the patient to carry this card at all times
- Tell the patient not to treat their own symptoms and to seek immediate medical attention should any adverse reaction occur or worsen
- Inform the patient that they may experience growth of existing tumours or develop new tumours, and that this does not necessarily mean that the treatment is ineffective

ANY FOLLOWING VISIT

- Make the appropriate checks (as per the list for the first visit)
- Check for signs and symptoms of irARs
- Remind the patient not to treat their own symptoms
- Remind the patient to contact you immediately should they experience an adverse reaction, even if mild
- Remind the patient that early diagnosis and appropriate management are essential to minimise the severity of adverse reactions and their associated complications
- Remind the patient to carry the Patient Alert Card at all times

Early Diagnosis and Appropriate Management of Immune-Related Adverse Reactions

- Prompt recognition of adverse reactions and appropriate treatment are essential to minimise life-threatening complications.
- Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.
- For irARs Grade 2 or higher, seek early input from the relevant specialist (e.g. a gastroenterologist for colitis) on adverse reaction management.
- Corticosteroids with or without additional immunosuppressive therapy may be required for the management of severe irARs.
    - If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least one-month duration should be initiated upon improvement, as rapid tapering may lead to worsening or recurrence of the adverse reaction.
    - Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.
    - Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy.
    - Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.
- In addition to corticosteroids, hormone replacement therapy may be required for the management of endocrinopathies.
- Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months, followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab or nivolumab in combination with ipilimumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.
- When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either nivolumab monotherapy or the combination treatment may be resumed based on the evaluation of the individual patient.
- Treatment with nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for
    - Any Grade 4 irAR.
    - Any Grade 3 irAR that recurs.
    - First onset of these Grade 3 irARs: pneumonitis, elevation in AST/ alanine aminotransferase (ALT)/bilirubin, confirmed Stevens-Johnson syndrome (SJS), adrenal insufficiency, or myocarditis.
    - First onset of Grade 3 diarrhoea/colitis with combination nivolumab and ipilimumab treatment or during the monotherapy phase of nivolumab following combination treatment.
    - Any Grade 2 or 3 irAR that persists despite treatment modification.
    - Inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day.
- Please refer to the nivolumab SmPC (and ipilimumab SmPC if you are using combination therapy) for further information about appropriate management.

Management of Specific Immune-Related Adverse Reactions

This section provides further, detailed guidance on the management of irARs.
Grade definitions for irARs are shown according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

Pneumonitis Monitor for e.g. radiographic changes like focal ground glass opacities or patchy infiltrates, dyspnoea and hypoxia	
Severity of irAR	**Recommended treatment modification (nivolumab or nivolumab + ipilimumab)**
Pneumonitis ***Grade 2:*** Symptomatic; medical intervention indicated; limiting instrumental Activities of Daily Living (ADL)	**Withhold treatment.** • Initiate corticosteroids at a dose of 1 mg/kg/day methylprednisolone equivalents. • Upon improvement, treatment may be resumed after corticosteroid taper. • If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents and treatment must be permanently discontinued.
Pneumonitis ***Grade 3:*** Severe symptoms; limiting self-care ADL; oxygen indicated ***Grade 4:*** Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	**Permanently discontinue treatment.** • Initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

<table>
<tr><th colspan="2">Colitis
Monitor for e.g. diarrhoea, abdominal pain, mucus or blood in stool</th></tr>
<tr><th>Severity of irAR</th><th>Recommended treatment modification (nivolumab or nivolumab + ipilimumab)</th></tr>
<tr><td>Diarrhoea
Grade 2: Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td><td rowspan="2">Withhold treatment.
• If persistent, manage with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents.
• Upon improvement, treatment may be resumed after corticosteroid taper, if needed.
• If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and treatment must be permanently discontinued.</td></tr>
<tr><td>Colitis
Grade 2: Abdominal pain; mucus or blood in stool</td></tr>
<tr><td>Diarrhoea (nivolumab monotherapy, not including second phase of treatment following combination therapy)
Grade 3: Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL</td><td rowspan="2">Withhold treatment.
• Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
• Upon improvement, nivolumab monotherapy may be resumed after corticosteroid taper.
• If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab monotherapy must be permanently discontinued.</td></tr>
<tr><td>Colitis (nivolumab monotherapy, not including second phase of treatment following combination therapy)
Grade 3: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs</td></tr>
<tr><td>Diarrhoea (combination therapy or second phase of nivolumab monotherapy following combination therapy)
Grade 3: Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL</td><td rowspan="4">Permanently discontinue treatment.
• Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.</td></tr>
<tr><td>Colitis (combination therapy or second phase of nivolumab monotherapy following combination therapy)
Grade 3: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs</td></tr>
<tr><td>Diarrhoea
Grade 4: Life-threatening consequences; urgent intervention indicated</td></tr>
<tr><td>Colitis
Grade 4: Life-threatening consequences; urgent intervention indicated</td></tr>
</table>

Note: Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-related colitis if infections or other aetiologies of diarrhoea are excluded.

<table>
<tr><th colspan="2">Hepatitis
Monitor for e.g. transaminase or total bilirubin elevations</th></tr>
<tr><th>Severity of irAR</th><th>Recommended treatment modification (nivolumab or nivolumab + ipilimumab)</th></tr>
<tr><td>Transaminase elevation
Grade 2: ALT/AST increase > 3.0 - 5.0 × ULN</td><td rowspan="2">Withhold treatment.
• Persistent elevations in laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents.
• Upon improvement, treatment may be resumed after corticosteroid taper, if needed.
• If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and treatment must be permanently discontinued.</td></tr>
<tr><td>Total bilirubin elevation
Grade 2: > 1.5 - 3.0 × ULN</td></tr>
<tr><td>Transaminase elevation
Grade 3: ALT/AST increase > 5.0 - 20.0 × ULN
Grade 4: ALT/AST increase > 20.0 × ULN</td><td rowspan="2">Permanently discontinue treatment.
• Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.</td></tr>
<tr><td>Total bilirubin elevation
Grade 3: > 3.0 - 10.0 × ULN
Grade 4: > 10.0 × ULN</td></tr>
</table>

Skin Adverse Reactions Monitor for e.g. rash, pruritus, SJS, toxic epidermal necrolysis [TEN]	
Severity of irAR	**Recommended treatment modification (nivolumab or nivolumab + ipilimumab)**
Rash ***Grade 3*** (rash acneiform): Papules and/or pustules covering >30% Body Surface Area (BSA), which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	**Withhold treatment until symptoms resolve.** • Severe rash should be managed with high-dose corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
Rash ***Grade 4*** (rash acneiform): Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	**Permanently discontinue treatment.** • Severe rash should be managed with high-dose corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
SJS or TEN	**If suspected SJS or TEN, withhold treatment.** • Refer the patient to a specialised unit for assessment and treatment. **If confirmed SJS or TEN, permanently discontinue treatment.**

Nephritis and Renal Dysfunction Monitor for e.g. asymptomatic increase of serum creatinine	
Severity of irAR	**Recommended treatment modification (nivolumab or nivolumab + ipilimumab)**
Serum creatinine elevation ***Grade 2:*** > 1.5 - 3.0 × baseline; > 1.5 - 3.0 × ULN ***Grade 3:*** > 3.0 baseline; > 3.0 - 6.0 × ULN	**Withhold treatment.** • Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. • Upon improvement, treatment may be resumed after corticosteroid taper. • If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and treatment must be permanently discontinued.
Serum creatinine elevation ***Grade 4:*** > 6.0 × ULN	**Permanently discontinue treatment.** • Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Endocrinopathies Monitor for e.g. hypothyroidism, hyperthyroidism, adrenal insufficiency including secondary adrenocortical insufficiency, hypophysitis including hypopituitarism, diabetes, diabetic ketoacidosis		
Severity of irAR	**Recommended treatment modification (nivolumab or nivolumab + ipilimumab)**	
Hypothyroidism ***Grade 2:*** Symptomatic; thyroid replacement indicated; limiting instrumental ADL ***Grade 3:*** Severe symptoms; limiting self-care ADL; hospitalisation indicated	**Withhold treatment**	• Initiate thyroid hormone replacement as needed. • Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised.
Hypothyroidism ***Grade 4:*** Life-threatening consequences; urgent intervention indicated	**Permanently discontinue treatment**	
Hyperthyroidism ***Grade 2:*** Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL ***Grade 3:*** Severe symptoms; limiting self-care ADL; hospitalisation indicated	**Withhold treatment**	• Initiate antithyroid medication as needed. • Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents if acute inflammation of the thyroid is suspected. • Upon improvement (of Grade 2 or 3 events), treatment may be resumed after corticosteroid taper, if needed. • Monitoring of thyroid function should continue.
Hyperthyroidism ***Grade 4:*** Life-threatening consequences; urgent intervention indicated	**Permanently discontinue treatment**	
Adrenal insufficiency ***Grade 2:*** Moderate symptoms; medical intervention indicated	**Withhold treatment**	• Physiologic corticosteroid replacement should be initiated as needed. • Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised.
Adrenal insufficiency ***Grade 3:*** Severe symptoms; hospitalisation indicated ***Grade 4:*** Life-threatening consequences; urgent intervention indicated	**Permanently discontinue treatment**	
Hypophysitis ***Grade 2*** (Endocrine disorders – Other): Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL ***Grade 3*** (Endocrine disorders – Other): Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self-care ADL	**Withhold treatment**	• Initiate hormone replacement as needed. • Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents if acute inflammation of the pituitary gland is suspected. • Upon improvement (of Grade 2 or 3 events), treatment may be resumed after corticosteroid taper, if needed. • Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.
Hypophysitis ***Grade 4*** (Endocrine disorders – Other): Life-threatening consequences; urgent intervention indicated	**Permanently discontinue treatment**	
Diabetes ***Grade 3*** (Hyperglycaemia): >250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalisation indicated ***Grade 3*** (Acidosis): pH <7.3	**Withhold treatment**	• Initiate insulin replacement as needed. • Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised.
Diabetes ***Grade 4*** (Hyperglycaemia): >500 mg/dL; >27.8 mmol/L; life-threatening consequences ***Grade 4*** (Acidosis): Life-threatening consequences	**Permanently discontinue treatment**	

Other Immune-Related Adverse Reactions

The following irARs were reported in less than 1% of patients treated with nivolumab monotherapy or nivolumab in combination with ipilimumab in clinical trials across doses and tumour types:

- Pancreatitis
- Uveitis
- Demyelination
- Autoimmune neuropathy (including facial and abducens nerve paresis)
- Guillain-Barré syndrome
- Myasthenic syndrome
- Encephalitis
- Gastritis
- Sarcoidosis
- Duodenitis

❖ Rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued and appropriate treatment instituted.

❖ Cases of Vogt-Koyanagi-Harada syndrome have been reported post-marketing.

❖ Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

Other irARs	
Severity of irAR	**Recommended treatment modification (nivolumab or nivolumab + ipilimumab)**
Myocarditis ***Grade 3:*** Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	**Permanently discontinue treatment.** • Refer to a specialist for assessment and treatment without delay.
Other irARs ***Grade 3 – first occurrence*** (general): Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL	**Withhold treatment until symptoms resolve.** • Initiate treatment with corticosteroids. • Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper.
Other irARs ***Grade 2 – persistent despite treatment modification*** (general): Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL ***Grade 3 – recurrent or persistent despite treatment modification*** (general): Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL ***Grade 4*** (general): Life-threatening consequences; urgent intervention indicated	**Permanently discontinue treatment.** • If Grade 4, initiate treatment with corticosteroids.
Other irARs ***Inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day***	

Potential Risk of Complications of Allogeneic Haematopoietic Stem Cell Transplant When Nivolumab is Given Prior to or Following Transplant

Preliminary results from the follow-up of patients with classical Hodgkin Lymphoma (cHL) 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. Until further data become available, careful consideration to the potential benefits of allogeneic HSCT and the possible increased risk of transplant related complications should be made case-by-case.

In patients treated with nivolumab after allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting. Treatment with nivolumab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of GVHD. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients.

Infusion Reactions

Infusion Reactions

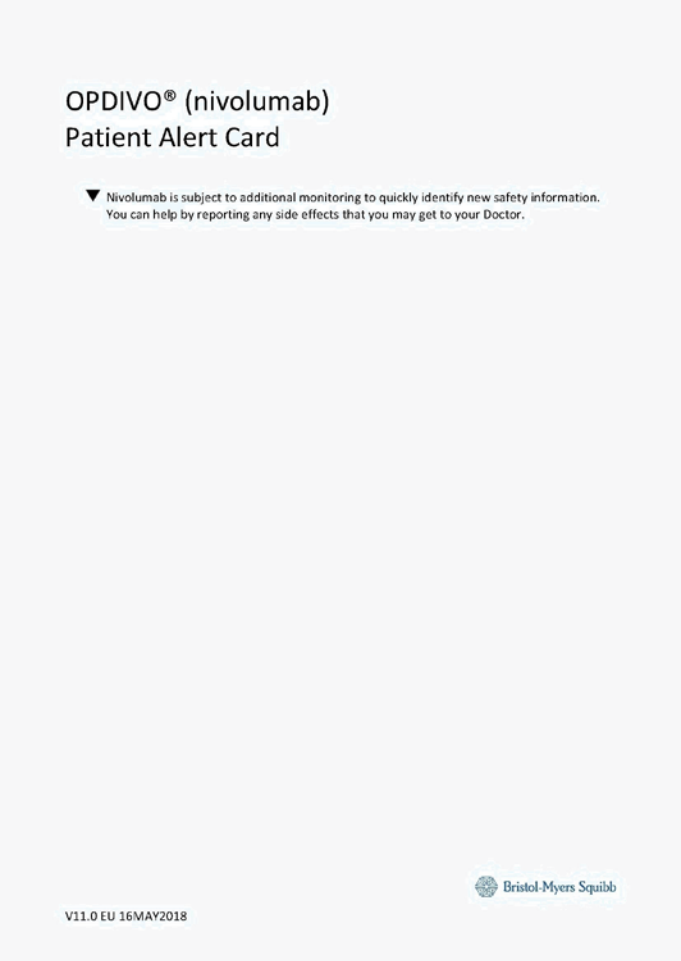
Severity	Recommended treatment modification (nivolumab or nivolumab + ipilimumab)
Mild or moderate	Closely monitor administration of treatment and use premedication according to local guidelines for prophylaxis of infusion reactions.
Severe or life-threatening	Treatment must be discontinued, and appropriate medical therapy administered.

Patient Alert Card

This educational material is designed to help patients (or their caregivers) understand their treatment and how to act should they experience adverse reactions. It is important that you distribute the Patient Alert Card to any patient receiving nivolumab or nivolumab in combination with ipilimumab for the first time and remind the patient at each visit. You can use the Patient Alert Card to discuss treatment and the related risks.

You should complete your contact details in the Patient Alert Card and advise the patient to carry it at all times and to show it to all HCPs involved in the patient's medical care.

You can obtain a Patient Alert Card at ***AM Mangion Ltd via 00 356 23976333 or pv@ammangion.com***



All Healthcare professionals are asked to report any Suspected Adverse Drug Reactions (side effects) or medication errors using the Medicines Authority ADR reporting form, which is available online at ***http://www.medicinesauthority.gov.mt/adrportal***, and sent by post or email to:
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: ***postlicensing.medicinesauthority.com***

To learn more about nivolumab or nivolumab in combination with ipilimumab, please contact Bristol-Myers Squibb Medical Information at *00 356 23976333 or via email -pv@ammangion.com*.

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