OPDIVO®

(nivolumab)

Injection for intravenous infusion

Immune-Related Adverse Reaction Management Guide

Indications

Melanoma[1]

OPDIVO as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Non-Small Cell Lung Cancer (NSCLC)[1]

OPDIVO is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

Important safety information

This guide is intended to provide information about the management of the important identified adverse reactions when prescribing nivolumab for melanoma and NSCLC including immune-related pneumonitis, colitis, hepatitis, nephritis or renal dysfunction, endocrinopathies, rash and other adverse reactions.

All patients receiving treatment with nivolumab must be given a Patient Alert Card to educate them about the symptoms of these important adverse reactions and the need to report them to their treating doctor immediately. Treating doctors should also advise their patients to keep the Patient Alert Card with them at all times and show it to any healthcare professional who may treat them. You can obtain Patient Alert Card by calling AM Mangion Ltd on 00 356 2397 6333 or email on pv@ammangion.com.mt

For more information, please refer to OPDIVO® Summary of Product Characteristics or www.opdivo.co.uk

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 reactions via Medicines Authority Post-Licensing Directorate, 203, level 3, Rue D'Argens, Gzira GZR 1368, Malta or at http:/www.medicinesauthority.gov.mt/adrportal
Adverse reactions should also be reported to Bristol-Myers Squibb Medical Information on 00356 23976333 or pv@ammangion.com.mt

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What is Nivolumab?[1]

Nivolumab is a medicine designed to help the immune system to fight tumours by increasing the activity of T-cells. 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.[1]

Common adverse reactions[1]

Melanoma

In the pooled dataset of two phase III studies in melanoma (CA209066 and CA209037), the most frequent adverse reactions (≥ 10%) were fatigue (33%), rash (20%), pruritus (18%), diarrhoea (16%), and nausea (14%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

NSCLC

In the pooled dataset of two studies in squamous NSCLC (CA209017 and CA209063), the most frequent adverse reactions (≥ 10% of patients) were fatigue (33%), decreased appetite (15%), and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

CA209037 – A phase III, randomised, open-label study including patients who had progressed on or after ipilimumab and if *BRAF* V600 mutation positive had also progressed on or after *BRAF* kinase inhibitor therapy. A total of 405 patients were randomised to receive either nivolumab (n = 272) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or chemotherapy (n = 133) which consisted of the investigator's choice of either dacarbazine (1000 mg/m^2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks).

CA209066 – A phase III, randomised, double-blind study including patients (18 years or older) with confirmed, treatment-naive, Stage III or IV *BRAF* wild-type melanoma and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1. A total of 418 patients were randomised to receive either nivolumab (n = 210) administered intravenously over 60 minutes at 3 mg/kg every 2 weeks or dacarbazine (n = 208) at 1000 mg/m^2 every 3 weeks.

CA209017 **–** A phase III, randomised, open-label study (CA209017) including patients with metastatic squamous NSCLC (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (n = 135) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 137) 75 mg/m^2 every 3 weeks.

CA209063 – a single-arm, open-label study conducted in 117 patients with locally advanced or metastatic squamous NSCLC after two or more lines of therapy**.**

Recognise and Manage Adverse Reactions Associated With Therapy

Nivolumab is associated with immune-related adverse reactions[1]

- Early identification of adverse reactions and timely intervention are an important part of the appropriate use of nivolumab
- Patients should be monitored continuously (including at least up to 5 months after the last dose) as an adverse reaction with nivolumab may occur at any time during or after discontinuation of nivolumab therapy[1]

If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement[1]

- Rapid tapering may lead to worsening of the adverse reaction[1]
- Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use[1]
- Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy[1]

Nivolumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy[1]

Treatment with nivolumab should be permanently discontinued for:[1]

- Any severe immune-related adverse reaction that recurs
- Any life threatening immune-related adverse
- Grade 2 or 3 immune-related adverse reactions that persist despite treatment modifications
- Inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day

Immune-Related Pneumonitis[1]

- Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab treatment
- Monitor patients for signs and symptoms of pneumonitis (see below)

Pneumonitis[1]

Signs and symptoms

- Breathing difficulties or cough
- Radiographic changes (e.g., focal ground glass opacities, patchy filtrates)
- Dyspnoea
- Hypoxia

Infectious and disease-related aetiologies should be ruled out

Melanoma (CA209037 and CA209066)[1]

In the Phase III studies of nivolumab for melanoma (CA209066 and CA209037), the incidence of pneumonitis, including interstitial lung disease, was 2.3% (11/474). All of these cases were Grade 1 or 2 in severity.

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
2.1 months (range: 0.8-5.1)	1.4 months (range: 0.2-2.8)	8 patients (73%)

NSCLC (CA209017 and CA209063)[1]

In the two studies of nivolumab for NSCLC (CA209017 and CA209063), the incidence of pneumonitis, including interstitial lung disease, was 5.2% (13/248). Grade 2 and Grade 3 cases were reported in 2.8% (7/248) and 1.6% (4/248) of patients, respectively. No Grade 4 or 5 cases were reported in these studies.

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
11.6 weeks (range: 2.6-85.1)	3.9 weeks (range: 0.6-13.4)	13 patients (100%)

Managing Immune-Related Pulmonary Adverse Reactions[1]

Monitor patients for signs and symptoms of pneumonitis and rule out infectious and disease-related aetiologies.

Grade of pneumonitis (NCI CTCAE v4)	**Grade 2 (symptomatic) pneumonitis**	**Grade 3 or 4 pneumonitis**
Nivolumab treatment and monitoring	Withhold nivolumab until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete	Permanently discontinue nivolumab
Steroids	Initiate corticosteroids at a dose of 1 mg/kg/day methylprednisolone IV or oral equivalents	Initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone IV or oral equivalents

NCI-CTCAE v4 – National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

Follow-up[1]

Grade 2	Upon improvement, nivolumab 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 IV or oral equivalents and nivolumab must be permanently discontinued

Immune-Related Colitis[1]

- Severe diarrhoea or colitis has been observed with nivolumab treatment
- Patients should be monitored for diarrhoea and additional symptoms of colitis (see below)

Diarrhoea and colitis[1]

Signs and symptoms

- Watery, loose or soft stools
- Abdominal pain
- Mucus or blood in stool

Infectious and disease-related aetiologies should be ruled out

Melanoma (CA209037 and CA209066)[1]

In the Phase III studies of nivolumab for melanoma (CA209066 and CA209037), the incidence of diarrhoea or colitis was 16.5% (78/474). Grade 2 and Grade 3 cases were reported in 3.2% (15/474) and 1.3% (6/474) of patients, respectively. No Grade 4 or 5 cases were reported in these studies.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
1.9 months (range: 0.0-13.3)	0.3 month (range: 0.0-12.5[+])	68 patients (88%)

[+] denotes a censored observation

NSCLC (CA209017 and CA209063)[1]

In the two studies of nivolumab for NSCLC (CA209017 and CA209063), the incidence of diarrhoea or colitis was 9.3% (23/248). Grade 2 and Grade 3 cases were reported in 2% (5/248) and 1.6% (4/248) of patients, respectively. No Grade 4 or 5 cases were reported in these studies.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
5.6 weeks (range: 0.1-91.0)	2.0 weeks (range: 0.1-31.0)	19 patients (83%)

Managing Immune-Related Gastrointestinal Adverse Reactions[1]

Monitor patients for diarrhoea and additional symptoms of colitis. Infectious and disease-related aetiologies should be ruled out.

Grade of diarrhoea or colitis (NCI CTCAE v4)	**Grade 2 diarrhoea or colitis**	**Grade 3 diarrhoea or colitis**	**Grade 4 diarrhoea or colitis**
Nivolumab treatment and monitoring	Withhold nivolumab until symptoms resolve and management with corticosteroids, if needed, is complete		Permanently discontinue nivolumab
Steroids	If persistent, manage with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalents	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents

NCI-CTCAE v4 – National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

Follow-up[1]

Grade 2	**Grade 3**
Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed	Upon improvement, nivolumab 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 IV or oral equivalents and nivolumab must be permanently discontinued.	If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab must be permanently discontinued

Immune-Related Hepatitis[1]

- Severe hepatitis has been observed with nivolumab treatment
- Monitor patients for signs and symptoms of hepatitis (see below)

Hepatotoxicity[1]
Signs and symptoms

- Elevations in transaminases
- Total bilirubin elevations
- Eye or skin yellowing (jaundice)
- Pain on the right side of the stomach area
- Tiredness

Infectious and disease-related aetiologies should be ruled out

Melanoma (CA209037 and CA209066)[1]

In the Phase III studies of nivolumab for melanoma (CA209066 and CA209037), the incidence of liver function test abnormalities was 6.8% (32/474). Grade 2, Grade 3, and Grade 4 cases were reported in 0.8% (4/474), 1.5% (7/474), and 0.4% (2/474) of patients, respectively. No Grade 5 cases were reported in these studies

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
2.8 months (range: 0.5-14.0)	0.7 month (range: 0.2-9.6^{+})	26 patients (81%)

NSCLC (CA209017 and CA209063)[1]

In the two studies of nivolumab for NSCLC (CA209017 and CA209063), the incidence of liver function test abnormalities was 1.2% (3/248). Grade 2 cases were reported in 0.4% (1/248) of patients. No Grade 3-5 cases were reported in these studies.

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
25.1 weeks (range: 4.1-31.1)	4.1 weeks (range: 2.9-22.3^{+})	2 patients (67%)

$^{+}$ denotes a censored observation

Managing Immune-Related Hepatic Adverse Reactions[1]

Grade of Liver test evaluation (NCI CTCAE v4)	Grade 2 elevation in transaminase or total bilirubin	Grade 3 or 4 elevation in transaminase or total bilirubin
Nivolumab treatment and monitoring	Withhold nivolumab until laboratory values return to baseline and management with corticosteroids, if needed, is complete	Permanently discontinue nivolumab
Steroids	Persistent elevations in laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalents	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents

NCI-CTCAE v4 – National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

Follow-up[1]

Grade 2	Upon improvement, nivolumab 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 IV or oral equivalents and nivolumab must be permanently discontinued

Immune-Related Nephritis or Renal Dysfunction[1]

- Severe nephritis or renal dysfunction has been observed with nivolumab treatment
- Monitor patients for signs and symptoms of nephritis and renal dysfunction (see below)

Nephrotoxicity[1]
Signs and symptoms

- Asymptomatic increase in serum creatinine
- Other abnormal kidney function tests
- Decreased volume of urine

Disease-related aetiologies should be ruled out

Melanoma (CA209037 and CA209066)[1]

In the Phase III studies of nivolumab for melanoma (CA209066 and CA209037), the incidence of nephritis or renal dysfunction was 1.9% (9/474). Grade 2 and Grade 3 cases were reported in 0.2% (1/474) and 0.6% (3/474) of patients, respectively. No Grade 4 or 5 nephritis or renal dysfunction was reported in these studies.

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
3.5 months (range: 0.9-6.4)	1.25 months (range: 0.5- 4.7[+])	7 patients (78%)

NSCLC (CA209017 and CA209063)[1]

In the two studies of nivolumab for NSCLC (CA209017 and CA209063), the incidence of nephritis or renal dysfunction was 3.2% (8/248). Grade 2 and Grade 3 cases were reported in 1.2% (3/248) and 0.4% (1/248) of patients, respectively. No Grade 4 or 5 nephritis or renal dysfunction was reported in these studies.

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
10.5 weeks (range: 2.1-27.0)	5.9 weeks (range: 0.7- 37.6[+])	5 patients (71%)

[+] denotes a censored observation

Managing Immune-Related Renal Adverse Reactions[1]

Monitor patients for signs and symptoms of nephritis and rule out disease-related aetiologies[1]

Grade of serum Creatinine Elevation (NCI CTCAE v4)	**Grade 2 or 3 serum creatinine elevation**	**Grade 4 serum creatinine elevation**
Nivolumab treatment and monitoring	Withhold nivolumab until creatinine returns to baseline and management with corticosteroids is complete	Permanently discontinue nivolumab
Steroids	Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalents	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents

NCI-CTCAE v4 – National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

Follow-up[1]

Grade 2 or 3 serum creatinine elevation	Upon improvement, nivolumab 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 IV or oral equivalents, and nivolumab must be permanently discontinued

Immune-Related Endocrinopathies[1]

- Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab treatment
- Monitor patients for clinical signs and symptoms of endocrinopathies and for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) (see below)

Endocrinopathies[1]

Signs and symptoms

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Visual disturbances
- Weight change
- Excessive thirst
- Passing of a greatly increased amount of urine
- Increase in appetite with a loss of weight
- Feeling tired, drowsy, weak, depressed, irritable and generally unwell
- Other non-specific symptoms

Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related

Melanoma (CA209037 and CA209066)[1]

In the Phase III studies of nivolumab for melanoma (CA209066 and CA209037), the incidence of:

- Thyroid disorders, including hypothyroidism or hyperthyroidism, was 7.6% (36/474). Grade 2 and Grade 3 thyroid disorders were reported in 4.2% (20/474) and 0.2% (1/474) of patients, respectively
- Hypophysitis (Grade 3), adrenal insufficiency (Grade 2), diabetes mellitus (Grade 2), and diabetic ketoacidosis (Grade 3) were each reported in 1 patient (0.2% each)

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
2.4 months (range: 0.8-10.8)	6.4 months (0.2-15.4[+])	18 patients (45%)

NSCLC (CA209017 and CA209063)[1]

In the two studies of nivolumab for NSCLC (CA209017 and CA209063), the incidence of thyroid disorders, including hypothyroidism or thyroiditis, was 4.4% (11/248). Grade 2 cases were reported in 3.6% (9/248) of patients.

- No Grade 3-5 thyroid disorders were reported
- The incidence of adrenal insufficiency was 0.4% (1/248; Grade 3)
- There were no reports of hypophysitis, diabetes mellitus, or diabetic ketoacidosis in these studies

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
17.8 weeks (range: 6.1-33.1)	20.6 weeks (0.4-47.6[+])	6 patients (50%)

[+] denotes a censored observation

Managing Immune-Related Endocrinopathies[1]

	For symptomatic hypothyroidism	For symptomatic hyperthyroidism	For symptomatic adrenal insufficiency	For symptomatic hypophysitis	For symptomatic diabetes
Treatment modification	Treatment with nivolumab should be withheld	Treatment with nivolumab should be withheld and methimazole should be initiated as needed	Treatment with nivolumab should be witheld		
Hormone replacement	Initiate thyroid hormone replacement as needed			Initiate hormone replacement as needed	Initiate insulin replacement as needed
Steroids		Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents if acute inflammation of the thyroid is suspected	Physiologic corticosteroid replacement should be initiated as needed	Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents if acute inflammation of the pituitary gland is suspected	
Monitoring	Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised		Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised	Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised	Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised

Follow-up[1]

	Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed	Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed		Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed	

Immune-Related Rash[1]

- Severe rash has been observed with nivolumab treatment that may be immune-related
- Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents

Rash[1]
Signs and symptoms
- Inflammation of the skin that can lead to rash and itching

Melanoma (CA209037 and CA209066)[1]
In the Phase III studies of nivolumab for melanoma (CA209066 and CA209037, the incidence of rash was 36.1% (171/474). Grade 2 and Grade 3 cases were reported in 6.1% (29/474) and 0.8% (4/474) of patients respectively. No Grade 4 or 5 cases were reported in these studies.

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
1.4 months (range: 0.0-13.1)	4.6 months (0.0-19.1[+])	87 patients (51%)

NSCLC (CA209017 and CA209063)[1]

In the two studies of nivolumab for NSCLC (CA209017 and CA209063), the incidence of rash was 12.1% (30/248). Grade 2 and Grade 3 cases were reported in 1.6% (4/248) and 0.8% (2/248) of patients, respectively. No Grade 4 or 5 rash was reported in these studies.

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
8.1 weeks (range: 0.3-51.9)	5.7 weeks (range: 0.1- 46.9[+])	24 patients (83%)

[+] denotes a censored observation

Managing Immune-Related Rash[1]

Grade of rash (NCI CTCAE v4)	Grade 3 rash	Grade 4 rash
Nivolumab treatment and monitoring	Withhold dose until symptoms resolve and management with corticosteroids is complete	Permanently discontinue nivolumab
Steroids	Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day prednisone equivalents	

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Other Immune-Related Adverse Reactions[1]

The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab in clinical trials across doses and tumour types:[1]

- Pancreatitis
- Uveitis
- Demyelination
- Autoimmune neuropathy (including facial and abducens nerve paresis)
- Guillain-Barré syndrome
- Hypopituitarism
- Myasthenic syndrome

- For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes[1]
- Based on the severity of the adverse reaction, nivolumab should be withheld and corticosteroids administered[1]
- Upon improvement, nivolumab may be resumed after corticosteroid taper[1]
- Nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction[1]

Treatment Modifications in Response to Immune-Related Adverse Reactions[1]

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability[1]

Recommended Treatment Modifications for Nivolumab when treating melanoma or NSCLC[1]

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold nivolumab until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue nivolumab
Immune- related colitis	Grade 2 or 3 diarrhoea or colitis	Withhold nivolumab until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue nivolumab
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold nivolumab until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue nivolumab
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold nivolumab until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue nivolumab
Immune-related endocrinopathies	Symptomatic endocrinopathies (including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency and diabetes)	Withhold nivolumab until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Nivolumab should be continued in the presence of hormone replacement therapy as long as no symptoms are present
Immune-related rash	Grade 3 rash	Withhold dose until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue nivolumab

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

Treatment with nivolumab should be permanently discontinued for any severe immune-related adverse reaction that recurs, any life threatening immune-related adverse, Grade 2 or 3 immune-

related adverse reactions that persist despite treatment modifications or for inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day[1]

Healthcare professionals are asked to report any suspected adverse reactions via the national reporting – www.medicinesauthority.gov.mt/adrportal found in Appendix V of OPDIVO's summary of product of characteristics]

If you require any further information regarding the use of OPDIVO™, please contact Bristol-Myers Squibb Medical Information department on telephone 00 356 23976333 or email: pv@ammangion.com.mt

References:

1. Opdivo. Summary of product characteristics.