OPDIVO®

(nivolumab)

Injection for intravenous infusion

Immune-Related Adverse Reaction Management Guide

Indication

OPDIVO® (nivolumab) as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.[1]

Important safety information

This guide is intended to provide information about the management of the important identified risks of prescribing nivolumab 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 immune-related 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 AM Mangion Ltd Tel 00 356 23976333 pv@ammangion.com.mt

For more information, please refer to OPDIVO™ Summary of Product Characteristics

www.ema.europa.eu

▼ 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 pv@ammangion.com.mt. Adverse reactions should also be reported to AM Mangion Ltd on 00 356 23976333 or pv@ammangion.com.mt or www.medicinesauthority.gov.mt/adrportal

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Explore the Following Sections to Learn More About Managing Immune-Related Adverse Reactions:

Nivolumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.[1]

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]

- In the pooled dataset of two phase 3 studies in melanoma (CA209066 and CA209037), the most frequent adverse reactions (≥ 10%) were fatigue, rash, pruritus, diarrhoea, and nausea*†

*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.

Recognise and Manage Adverse Reactions Associated With Therapy

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

- Early identification of adverse reactions and intervention are an important part of the appropriate use of nivolumab
- Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab may occur at any time during or even months 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 considered to prevent opportunistic infections in patients receiving immunosuppressive therapy[1]

Do not resume nivolumab while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy[1]

Treatment with nivolumab should be permanently discontinued for 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]

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)
- In two Phase III studies of nivolumab (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

Pneumonitis[1]

Signs and symptoms

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

Rule out infectious and disease-related aetiologies

CA209066 and CA209037

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%)

Managing Immune-Related Pulmonary Adverse Reactions[1]

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

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

Grade 2	**Upon improvement** resume nivolumab after corticosteroid taper.	
	If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 2 to 4 mg/kg/day methylprednisolone IV or oral equivalents and permanently discontinue nivolumab	

Immune-Related Colitis[1]

- Severe diarrhoea or colitis has been observed with nivolumab treatment
- Monitor patients for diarrhoea and additional symptoms of colitis (see below)
- In two Phase III studies of nivolumab (CA209066 and CA209037), the incidence of diarrhoea or colitis was 16.5% (78/474). Grade 2 and 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

Diarrhoea and colitis[1]

Signs and symptoms

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

Rule out infectious and disease-related aetiologies

CA209066 and CA209037

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

+Censored observation

Managing Immune-Related Gastrointestinal Adverse Reactions[1]

Monitor patients for diarrhoea and additional symptoms of colitis and rule out infectious and disease-related aetiologies.[1]

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	

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

Follow-up[1]

Grade 2	**Grade 3**
Upon improvement, resume nivolumab after corticosteroid taper, if needed	Upon improvement resume nivolumab after corticosteroid taper
If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents and permanently discontinue nivolumab	If worsening or no improvement occurs despite initiation of corticosteroids, permanently discontinue nivolumab

Immune-Related Hepatitis[1]

- Severe hepatitis has been observed with nivolumab treatment
- Monitor patients for signs and symptoms of hepatitis (see below)
- In two Phase III studies of nivolumab (CA209066 and CA209037), the incidence of liver function test abnormalities was 6.8% (32/474). Grade 2, 3 and 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

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

Rule out infectious and disease-related aetiologies

CA209066 and CA209037

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

+Censored observation

Managing Immune-Related Hepatic Adverse Reactions[1]

Monitor patients for signs and symptoms of hepatitis and rule out infectious and disease-related aetiologies[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	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

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

Follow-up

Grade 2	**Upon improvement** resume nivolumab after corticosteroid taper, if needed.	
	If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents and permanently discontinue nivolumab	

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)
- In two Phase III studies of nivolumab (CA209066 and CA209037), the incidence of nephritis or renal dysfunction was 1.9% (9/474). Grade 2 and 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

Nephrotoxicity[1]

Signs and symptoms

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

Rule out disease-related aetiologies

CA209066 and CA209037

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%)

+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

Follow-up[1]

Grade 2 or 3 serum creatinine elevation	**Upon improvement** resume nivolumab after corticosteroid taper.	
	If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents and permanently discontinue nivolumab	

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

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 signs and symptoms of endocrinopathies (see below)
- In two Phase III studies for nivolumab (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)

Endocrinopathies[1]

Signs and symptoms

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

If signs or symptoms are present, complete endocrine function evaluation

CA209066 and CA209037

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

+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 withheld		Treatment with nivolumab should be withheld
Hormone replacement	Thyroid hormone replacement should be initiated as needed		Initiate physiologic corticosteroid replacement as required	Initiate hormone replacement as required	Insulin replacement should be initiated as needed
Steroids		Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents should also be considered if acute inflammation of the thyroid is suspected		Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents should also be considered if acute inflammation of the pituitary gland is suspected	
Monitoring	Continue to monitor thyroid function to ensure appropriate hormone replacement is utilised		Continue to monitor adrenal function and hormone levels to ensure appropriate corticosteroid replacement is utilised	Continue to monitor pituitary function and hormone levels to ensure appropriate hormone replacement is utilised	Continue to monitor blood sugar levels 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	

Immune-Related Rash[1]

- Severe rash has been observed with nivolumab treatment
- In two Phase III studies of nivolumab (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

Rash[1]

Rash is a composite term which includes:

- Maculopapular rash
- Rash erythematous
- Rash pruritic
- Rash follicula
- Rash macular
- Rash papular
- Rash pustular
- Rash vesicular
- Dermatitis
- Dermatitis acneiform
- Dermatitis allergic
- Dermatitis exfoliative
- Inflammation of the skin that can lead to rash and itching

CA209066 and CA209037

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

Managing Immune-Related Rash[1]

Grade of rash (NCI CTCAE v4)	**Grade 3 rash**	**Grade 4 rash**
Nivolumab treatment and monitoring	Nivolumab treatment should be withheld 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	

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

+Censored observation

Other Immune-Related Adverse Reactions

- 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:
  - 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.
- Based on the severity of the adverse reaction, nivolumab should be withheld and corticosteroids administered.
- Upon improvement, nivolumab may be resumed after corticosteroid taper.
- Nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Treatment Modifications in Response to Immune-Related Adverse Reactions

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[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 mellitus)	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).[1]

Treatment with nivolumab should also be permanently discontinued for 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 by pv@ammangion.com.mt

If you require any further information regarding the use of OPDIVO™, please contact AM Mangion Ltd on 00 356 23976333; pv@ammangion.com.mt

References:

1. Opdivo. Summary of product characteristics.

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