OPDIVO®

(nivolumab)

Injection for intravenous infusion

Immune-Related Adverse Reaction Management Guide

Indications

Melanoma[1]
OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression.

Non-Small Cell Lung Cancer (NSCLC)[1]
OPDIVO is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.

Renal Cell Carcinoma (RCC)[1]
OPDIVO as monotherapy is indicated for the treatment of patients with advanced renal cell carcinoma after prior therapy in adults.

Important safety information

This guide is intended to provide information about the management of the important identified adverse reactions when prescribing nivolumab or nivolumab in combination with ipilimumab for melanoma, or nivolumab as monotherapy for NSCLC and Renal Cell Carcinoma including immune-related pneumonitis, colitis, hepatitis, nephritis or renal dysfunction, endocrinopathies, rash, infusion reactions, and other adverse reactions.

All patients receiving treatment with nivolumab monotherapy or in combination with ipilimumab 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 telephone 00 356 23976333 or email: pv@ammangion.com.mt

For more information, refer to OPDIVO® Summary of Product Characteristics
When nivolumab is used in combination with ipilimumab, refer to the Summary of Product Characteristic of ipilimumab prior to initiation of treatment

▼ 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

Bristol-Myers Squibb Company

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

What is Nivolumab?[1]

Nivolumab is a human immunoglobuline 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.[1]
Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in metastatic melanoma.

Common adverse reactions[1]

In the pooled dataset of **nivolumab 3 mg/kg as monotherapy** across tumour type (CA209066, CA209037, CA209067 (monotherapy group only), CA209017, CA209057, CA209063 and CA209025), the most frequent adverse reactions (≥ 10%) were fatigue (34%), rash (19%), pruritus (14%), diarrhoea (13%), nausea (13%) and decrease appetite (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).
In the pooled dataset of **nivolumab in combination with ipilimumab in melanoma** (CA209067 [combination group], CA209069, and CA209004-cohort 8), the most frequent adverse reactions (≥ 10%) were rash (51%), fatigue (43%), diarrhoea (42%), pruritus (35%), nausea (25%), pyrexia (19%), decreased appetite (15%), hypothyroidism (15%), vomiting (14%), colitis (14%), abdominal pain (13%), arthralgia (11%), and headache (11%). 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**.**

CA209057 - A phase III, randomised, open-label study (CA209057) including patients (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 582 patients were randomised to receive either nivolumab 3 mg/kg (n = 292) administered intravenously over 60 minutes every 2 weeks or docetaxel (n = 290) 75 mg/m2 every 3 weeks

CA209067 – A phase 3, randomised, double blind study that included adult patients (18 years or older) with confirmed unresectable Stage III or Stage IV melanoma, regardless of PD-L1 expression. Patients were to have ECOG performance status score of 0 or 1. Patients who had not received prior systemic anticancer therapy for unresectable or metastatic melanoma were enrolled. A total of 945 patients were randomised to receive nivolumab in combination with ipilimumab (n = 314), nivolumab as monotherapy (n = 316), or ipilimumab alone (n = 315)

CA209025 – A phase III, randomised, open-label study including patients (18 years or older) with advanced Renal Cell Carcinoma who have experienced disease progression during or after 1 or 2 prior anti-angiogenic therapy regimens and no more than 3 total prior systemic treatment regimens.
A total of 821 patients were randomised to receive either nivolumab 3 mg/kg (n=410) administered intravenously over 60 minutes every 2 weeks or everolimus (n=411) 10 mg daily, administered orally.

CA209069 - A randomised, Phase 2, double-blind study evaluating the safety and efficacy of nivolumab in combination with ipilimumab compared with ipilimumab alone in 142 patients with advanced (unresectable or metastatic) melanoma.

Recognise and Manage Adverse Reactions Associated With Therapy

Nivolumab or nivolumab in combination with ipilimumab 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 or nivolumab in combination with ipilimumab
- Patients should be monitored continuously (including 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[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 or recurrence 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 or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy[1]

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 the combination treatment or nivolumab monotherapy could be resumed based on the evaluation of the individual patient.

Treatment with nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for[1]:

- Any severe (grade 3) immune-related adverse reaction that recurs
- Any life threatening (grade 4) immune-related adverse reactions
- Grade 2 or 3 immune-related adverse reactions that persist despite treatment modifications
- Inability to reduce corticosteroid dose to 10 mg prednisone (8 mg methylprednisolone) or equivalent per day

Immune-Related Pneumonitis[1]

- Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with the use of nivolumab or nivolumab in combination with ipilimumab
- 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

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease, was 3.2% (56/1728). Grade 1 and Grade 2 cases were reported in 0.7% (12/1728) and 1.7% (29/1728) of patients, respectively. Grade 3 and Grade 4 cases were reported in 0.8% (14/1728) and <0.1% (1/1728) of patients, respectively No Grade 5 cases were reported.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
3.6 months (range: 0.4-19.6)	5.3 weeks (range: 0.6-53.1[+])	47 patients (84%)

In patients treated with nivolumab in combination with ipilimumab, the incidence of pneumonitis including interstitial lung disease, was 7.4% (33/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.5% (20/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis worsened over 11 days with a fatal outcome.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
2.3 months (range: 0.7-6.7)	6.1 weeks (range: 0.3-46.9[+])	29 patients (87.9%)

[+] denotes a censored observation

Managing Immune-Related Pneumonitis[1]

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

Grade of pneumonitis	Grade 2 (symptomatic) pneumonitis	Grade 3 or 4 pneumonitis
Nivolumab or nivolumab in combination with ipilimumab (treatment) adjustment and monitoring	Withhold treatment until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete	Permanently discontinue treatment
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] 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 IV or oral equivalents and treatment must be permanently discontinued

Pneumonitis (according to NCI CTCAE v4)
Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2: Symptomatic; medical intervention indicated; limiting instrumental ADL
Grade 3: Severe symptoms; limiting self care ADL; oxygen indicated
Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Grade 5: Death

Immune-Related Colitis[1]

- Severe diarrhoea or colitis has been observed with nivolumab or nivolumab in combination with ipilimumab
- 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

In patients treated with nivolumab monotherapy, the incidence of diarrhoea or colitis was 13.6% (235/1728). Grade 1 and Grade 2 cases were reported in 9.0% (156/1728) and 3.0% (52/1728) of patients, respectively. Grade 3 cases were reported in 1.6% (27/1728) of patients, respectively No Grade 4 or 5 cases were reported.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
1.8 months (range: 0.0-20.9)	2.1 weeks (range: 0.1-88.3+)	207 patients (89%)

In patients treated with nivolumab in combination with ipilimumab, the incidence of diarrhoea or colitis was 45.5% (204/448). Grade 2, Grade 3, and Grade 4 cases were reported in 13.2% (59/448), 15.4% (69/448), and 0.4% (2/448) of patients, respectively. No Grade 5 cases were reported.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
1.1 months (range: 0.0-10.4)	3.0 weeks (range: 0.1-78.7+)	184 patients (90.6%)

+ denotes a censored observation

Managing Immune-Related Colitis[1]

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

Grade of diarrhoea or colitis	Grade 2 diarrhoea or colitis	Grade 3 diarrhoea or colitis	Grade 4 diarrhoea or colitis
Nivolumab monotherapy adjustments and monitoring	Withhold nivolumab until symptoms resolve and management with corticosteroids, if needed, is complete		Permanently discontinue treatment
Nivolumab in combination with ipilimumab (treatment) adjustment and monitoring	Withhold treatment until symptoms resolve and management with corticosteroids, if needed, is complete	Permanently discontinue treatment	
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

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	Grade 2	Grade 3
Follow-up[1]	Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed	Upon improvement, nivolumab monotherapy 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 or nivolumab in combination with ipilimumab must be permanently discontinued.	If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab monotherapy must be permanently discontinued

Colitis (according to NCI CTCAE v4)
Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2: Abdominal pain; mucus or blood in stool
Grade 3: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death

Immune-Related Hepatitis[1]

- Severe hepatitis has been observed with nivolumab or nivolumab in combination with ipilimumab
- Monitor patients for signs and symptoms of hepatitis (see below)

Hepatotoxicity[1]
Signs and symptoms

- Elevations in transaminases
- Total bilirubin elevations
- Jaundice
- Pain on the right side of the stomach area
- Tiredness

Infectious and disease-related aetiologies should be ruled out

In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 7.0% (121/1728). Grade 1 and Grade 2 cases were reported in 3.9% (68/1728) and 1.3% (22/1728) of patients, respectively. Grade 3 and Grade 4 cases were reported in 1.4% (25/1728) and 0.3% (6/1728) of patients, respectively No Grade 5 cases were reported.

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
1.9 months (range: 0.0-18.7)	5.1 weeks (range: 0.1-82.6[+])	95 patients (79%)

In patients treated with nivolumab in combination with ipilimumab, the incidence of liver function test abnormalities was 27.9% (125/448). Grade 2, Grade 3, and Grade 4 cases were reported in 6.3% (28/448), 15.0% (67/448), and 1.8% (8/448) of patients, respectively. No Grade 5 cases were reported.

Median time to onset:[1]	**Median time to resolution:**[1]	**Cases resolved:**[1]
1.4 months (range: 0.0-11.0)	5.0 weeks (range: 0.1-53.1)	116 patients (92.8%)

[+] denotes a censored observation

Managing Immune-Related Hepatitis[1]

Grade of Liver test evaluation	Grade 2 elevation in transaminase or total bilirubin	Grade 3 or 4 elevation in transaminase or total bilirubin
Nivolumab or nivolumab in combination with ipilimumab (treatment) adjustment and monitoring	Withhold treatment until laboratory values return to baseline and management with corticosteroids, if needed, is complete	Permanently discontinue treatment
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]	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 IV or oral equivalents and treatment must be permanently discontinued

Hepatobiliary disorders (according to NCI CTCAE v4)
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death

Alanine (ALT) / Aspartate (AST) aminotransferase increase (according to NCI CTCAE v4)
Grade 1: >ULN - 3.0 x ULN
Grade 2: >3.0 - 5.0 x ULN
Grade 3: >5.0 - 20.0 x ULN
Grade 4: >20.0 x ULN
Grade 5: -

Bilirubine increase (according to NCI CTCAE v4)
Grade 1: >ULN - 1.5 x ULN
Grade 2: >1.5 - 3.0 x ULN
Grade 3: >3.0 - 10.0 x ULN
Grade 4: >10.0 x ULN
Grade 5: -

Immune-Related Nephritis and Renal Dysfunction[1]

- Severe nephritis and renal dysfunction has been observed with nivolumab or nivolumab in combination with ipilimumab
- 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

In patients treated with nivolumab monotherapy, the incidence of nephritis and renal dysfunction was 3.2% (55/1728). Grade 1 and Grade 2 cases were reported in 1.9% (32/1728) and 0.8% (14/1728) of patients, respectively. Grade 3 and Grade 4 cases were reported in 0.5% (8/1728) and <0.1% (1/1728) of patients, respectively No Grade 5 nephritis or renal dysfunction was reported.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
2.3 months (range: 0.0-18.2)	11.1 weeks (range: 0.1- 77.1[+])	33 patients (62%)

In patients treated with nivolumab in combination with ipilimumab, the incidence of nephritis and renal dysfunction was 4.2% (19/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.1% (5/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
2.6 months (range: 0.5-14.7)	1.9 weeks (range: 0.4- 42.6[+])	17 patients (89.5%)

[+] denotes a censored observation

Managing Immune-Related Nephritis and Renal Dysfunctions[1]

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

Grade of serum Creatinine Elevation	Grade 2 or 3 serum creatinine elevation	Grade 4 serum creatinine elevation
Nivolumab or nivolumab in combination with ipilimumab (treatment) adjustment and monitoring	Withhold treatment until creatinine returns to baseline and management with corticosteroids is complete	Permanently discontinue treatment
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]

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 IV or oral equivalents, and treatment must be permanently discontinued

Renal and urinary disorders (according to NCI CTCAE v4)
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2: Moderate, local or noninvasive intervention indicated; limiting instrumental ADL
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death

Immune-Related Endocrinopathies[1]

- Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab treatment as monotherapy or in combination with ipilimumab
- Monitor patients for clinical signs and symptoms of endocrinopathies and for hyperglycemia and 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

In patients treated with nivolumab monotherapy, the incidence of thyroid disorders was 8.6% (149/1728). Grade 1 and Grade 2 thyroid disorders cases were reported in 3.6% (62/1728) and 4.9% (85/1728) of patients, respectively. Grade 3 thyroid disorders were reported in 0.1% (2/1728) of patients.
Hypophysitis (1 Grade1, 1 Grade 2 and 3 Grade 3), adrenal insufficiency (1 Grade 1, 5 Grade 2 and 4 Grade 3), diabetes mellitus (1 Grade 2), and diabetic ketoacidosis (2 Grade 3) were reported. No Grade 4 or 5 endocrinopathies were reported.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
2.8 months (range: 0.4-14.0)	66.6 weeks (0.4-96.1[+])	74 patients (45%)

In patients treated with nivolumab in combination with ipilimumab, the incidence of thyroid disorders was 23.7% (106/448). Grade 2 and Grade 3 thyroid disorders were reported in 13.4% (60/448) and 1.6% (7/448) of patients, respectively. Grade 2 and Grade 3 hypophysitis occurred in 6.0% (27/448) and 1.8% (8/448) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency each occurred in 1.1% (5/448), and Grade 4 adrenal insufficiency occurred in 0.2% (1/448) of patients. Grade 1 and Grade 2 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No Grade 5 endocrinopathy was reported.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
1.5 months (range: 0.0-10.1)	---------- (0.4-74.4[+])	59 patients (45%)

[+] denotes a censored observation

Managing Immune-Related Endocrinopathies[1]

	Symptomatic hypothyroidism	Symptomatic hyperthyroidism	Symptomatic adrenal insufficiency	Symptomatic hypophysitis	Symptomatic diabetes
Nivolumab or nivolumab in combination with ipilimumab (treatment) modification	Treatment should be withheld. Treatment must be permanently discontinued for life threatening situations	Treatment should be withheld. Initiate antithyroid medication as needed	Treatment should be withheld for grade 2 adrenal insufficiency. Treatment must be permanently discontinued for grade 3 and 4 adrenal insufficiency	Treatment should be withheld for grade 2 or 3 hypophisitis. Treatment must be permanently discontinued for grade 4 hypophysitis	Treatment should be withheld for symptomatic diabetes. Treatment must be permanently discontinued for life threatening diabetes
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, treatment may be resumed after corticosteroid taper, if needed		Upon improvement, treatment may be resumed after corticosteroid taper, if needed	

according to NCI CTCAE v4	Grade1	Grade2	Grade3	Grade4	Grade5
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypophysitis (endocrine disorders general)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Diabetes mellitus (hyperglycaemia)	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death
Acidosis	pH <normal, but >=7.3		pH <7.3	Life-threatening consequences	Death

Immune-Related Rash[1]

- Severe rash has been observed with nivolumab in combination with ipilimumab and, less commonly, with nivolumab as monotherapy
- 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
- blisters, ulcers, peeling

In patients treated with nivolumab monotherapy, the incidence of rash was 28.0% (484/1728). Grade 1 cases have been reported in 21.9% (378/1728) of patients. Grade 2 and Grade 3 cases were reported in 5.2% (89/1728) and 1.0% (17/1728) of patients, respectively. No Grade 4 or 5 cases were reported.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
1.4 months (range: 0.0-17.2)	18.1 weeks (0.1-113.7[+])	295 patients (62%)

In patients treated with nivolumab in combination with ipilimumab, the incidence of rash was 63.4% (284/448). Grade 2 and Grade 3 cases were reported in 19.2% (86/448) and 7.4% (33/448) of patients, respectively. No Grade 4 or 5 cases were reported.

Median time to onset:[1]	**Median time to resolution:[1]**	**Cases resolved:[1]**
0.5 months (range: 0.0-9.7)	10.4 weeks (0.1-74.0[+])	192 patients (68%)

[+] denotes a censored observation

Managing Immune-Related Rash[1]

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

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

Toxic Epidermal Necrolysis - Steven-Johnson Syndrome

Rare cases of toxic epidermal necrolysis (TEN), some of them with fatal outcome, have been observed

Symptoms or signs of Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) with nivolumab or nivolumab in combination with ipilimumab	Discontinue treatment and refer the patient to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab or nivolumab in combination with ipilimumab, permanent discontinuation of treatment is recommended

Allergic reaction (according to NCI CTCAE v4)
Grade 1: Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs
Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death

Rash acneiform
Grade 1: Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness
Grade 2: Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL
Grade 3: Papules and/or pustules covering >30% 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
Grade 4: 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
Grade 5: Death

Toxic epidermal necrolysis
Grade 4: Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)
Grade 5: Death

0ther Immune□Related Adverse Reactions[1]

The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab monotherapy 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

Across clinical trials of nivolumab in combination with ipilimumab, the following additional clinically significant, immune-related adverse reactions were reported in less than 1% of patients:

- Gastritis
- Sarcoidosis
- Duodenitis.

- 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 or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered[1]
- Upon improvement, treatment may be resumed after corticosteroid taper[1]
- Treatment must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction[1]

Infusion Reactions

In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.1% (71/1728), including 3 Grade 3 and 2 Grade 4 cases.

In patients treated with nivolumab in combination with ipilimumab, the incidence of hypersensitivity/infusion reactions was 3.8% (17/448); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.2% (10/448) of patients. No Grade 3-5 cases were reported.

In case of a severe or life-threatening infusion reaction, the nivolumab or nivolumab in combination with ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab or nivolumab in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions

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 or nivolumab in combination with ipilimumab[1] Immune-related adverse reaction	**Severity**	**Treatment modification**
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune- related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis - nivolumab monotherapy	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete Permanently discontinue treatment
	- nivolumab + ipilimumab Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) 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 treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency, Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present
	Grade 4 hypothyroidism, Grade 4 hyperthyroidism, Grade 4 hypophysitis, Grade 3 or 4 adrenal insufficiency, Grade 4 diabetes	Permanently discontinue treatment
Immune-related rash	Grade 3 rash	Withhold dose until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash (including TEN and SJS)	Permanently discontinue treatment
Other adverse reaction	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent grade 3; persistent grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone (8 mg methylprednisolone) or equivalent per day	Permanently discontinue treatment

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

Healthcare professionals are asked to report any suspected adverse reactions via the national reporting via Medicines Authority Post-Licensing Directorate, 203, level 3, Rue D'Argens, Gzira GZR 1368, Malta or at http:/www.medicinesauthority.gov.mt/adrportal 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 00356 23976333 or pv@ammangion.com.mt

References:

1. Opdivo. Summary of product characteristics.

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