

Healthcare professionals are asked to report any suspected adverse reactions to:

- Bristol Myers Squibb, Saudi Arabia:
At: safety_saudi Arabia@bms.com or call: +966 11 219 9780
- The national Pharmacovigilance and Drug safety Center :
At: <https://ade.sfda.gov.sa/index.aspx> or call +966 11203 8222
Ext: 2356, 5729 or 5721
Toll free number: 8002490000

References:

1. Opdivo. Summary of product characteristics.



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1506SA15NP02618-01

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 e-mailing Safety_SaudiArabia@bms.com

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

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 the National Reporting Channels.



1506SA15NP02618-01

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

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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 reactions¹

- In the pooled dataset of two phase 3 studies in melanoma (CA209066 and CA209037), the most frequent adverse reactions ($\geq 10\%$) 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/m² every 3 weeks) or carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m² 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/m² every 3 weeks.

Recognise and Manage Adverse Reactions Associated With Therapy

Nivolumab is associated with immune-related adverse reactions¹

- 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 therapy¹

If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement¹

- Rapid tapering may lead to worsening of the adverse reaction¹
- Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use¹
- Prophylactic antibiotics should be considered to prevent opportunistic infections in patients receiving immunosuppressive therapy¹

Do not resume nivolumab while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy¹

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 day¹

Immune-Related Pneumonitis¹

- 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

Pneumonitis¹

Signs and symptoms

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

Rule out infectious and disease-related aetiologies

CA209066 and CA209037

Median time to onset:¹
2.1 months
(range: 0.8 -5.1)

Median time to resolution:¹
1.4 months
(range: 0.2 - 2.8)

Cases resolved:¹
8 patients
(73%)

Managing Immune-Related Pulmonary Adverse Reactions¹

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

| Grade of pneumonitis (NCI CTCAE v4) | Grade 1 | Grade 2 (symptomatic) pneumonitis | Grade 3 or 4 pneumonitis |
|---|--|--|--|
| Nivolumab treatment and monitoring | Consider withholding Nivolumab | Withhold nivolumab until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete | Permanently discontinue nivolumab |
| Monitoring | Follow Standard of Care in Saudi Arabia Medical Practice | Follow Standard of Care in Saudi Arabia Medical Practice | Follow Standard of Care in Saudi Arabia Medical Practice |
| 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 |
| Pulmonary test | | Consider bronchoscopy, lung biopsy | Consider bronchoscopy, lung biopsy |

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

Follow-up¹

| | Grade 1 | Grade 2 |
|-------------------------|---|---|
| Upon improvement | Resume Nivolumab, if withheld when stable | Taper steroids over at least 1 month before resuming Nivolumab |
| If worsening | Follow Standard of Care in Saudi Arabia Medical Practice. | 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 Colitis¹

- 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 colitis¹

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
1.9 months
(range: 0.0 - 13.3)

Median time to resolution:¹
0.3 months
(range: 0.0 - 12.5⁺)

Cases resolved:¹
68 patients
(88%)

Managing Immune-Related Gastrointestinal Adverse Reactions¹

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 1 diarrhoea or colitis | Grade 2 diarrhoea or colitis | Grade 3 diarrhoea or colitis | Grade 4 diarrhoea or colitis |
|--|------------------------------|--|--|-----------------------------------|
| Nivolumab treatment and monitoring | Continue Nivolumab | 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-up¹

| Grade 1 | Grade 2 | Grade 3 |
|---|---|---|
| Close monitoring for worsening symptoms as per the standard of care in Saudi Arabia Medical Practice. | Upon improvement -Resume Nivolumab -If steroids have been administered, taper steroids over at least 1 month before resuming Nivolumab | Upon improvement If steroids have been administered, taper steroids over at least 1 month before resuming Nivolumab |
| | 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 |

¹+Censored observation

Immune-related Hepatitis¹

- 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% (29/474). 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

Hepatitis¹

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
2.8 months
(range: 0.5 - 14.0)

Median time to resolution:¹
0.7 months
(range: 0.2 - 9.6⁺)

Cases resolved:¹
26 patients
(81%)

Managing Immune-Related Hepatic Adverse Reactions¹

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 1 elevation in transaminase or total bilirubin | Grade 2 elevation in transaminase or total bilirubin | Grade 3 or 4 elevation in transaminase or total bilirubin |
|---|--|---|--|
| Nivolumab treatment and monitoring | Continue Nivolumab | Withhold nivolumab until laboratory values return to baseline and management with corticosteroids, if needed, is complete | Permanently discontinue nivolumab |
| Monitoring | Follow Standard of Care in Saudi Arabia Medical Practice | Follow Standard of Care in Saudi Arabia Medical Practice | Follow Standard of Care in Saudi Arabia Medical Practice |
| 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-up¹

| Grade 1 | Grade 2 |
|---|---|
| Follow Standard of Care in Saudi Arabia Medical Practice. | Upon improvement Resume Nivolumab -If steroids have been administered, taper steroids over at least 1 month before resuming Nivolumab |
| | 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 |

⁺Censored observation

Immune-Related Nephritis Renal Dysfunction¹

- 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.

Nephrotoxicity¹

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
3.5 months
(range: 0.9 - 6.4)

Median time to resolution:¹
1.25 months
(range: 0.5 - 4.7⁺)

Cases resolved:¹
7 patients
(78%)

Managing Immune-Related Renal Adverse Reactions¹

Monitor patients for signs and symptoms of nephritis and rule out disease related aetiologies.¹

| Grade of serum Creatinine Elevation (NCI CTCAE v4) | Grade 1 serum creatinine elevation | Grade 2 or 3 serum creatinine elevation | Grade 4 serum creatinine elevation |
|--|--|---|--|
| Nivolumab treatment and monitoring | Continue Nivolumab | Withhold nivolumab until creatinine returns to baseline and management with corticosteroids is complete | Permanently discontinue nivolumab |
| Monitoring | Follow Standard of Care in Saudi Arabia Medical Practice | Follow Standard of Care in Saudi Arabia Medical Practice | Follow Standard of Care in Saudi Arabia Medical Practice |
| 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 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-up¹

| Grade 1 creatinine elevation | Grade 2 or 3 serum creatinine elevation | Grade 4 creatinine elevation |
|--|---|--|
| If improved, Monitor and Follow the standard of Care in Saudi Arabia Medical Practice. | Upon improvement Resume Nivolumab -Taper steroids over at least 1 month before resuming Nivolumab | Upon improvement Resume Nivolumab -Taper steroids over at least 1 month |
| | 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 | |

⁺Censored observation

Immune-Related Endocrinopathies¹

- 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)

Endocrinopathies¹

Signs and symptoms

- Fatigue
- Weight change
- Headache
- Mental status change
- Abdominal pain
- Unusual bowel habit
- Hypotension
- Visual disturbance
- Excessive thirst
- Passing a greatly increased amount of urine

CA209066 and CA209037

Median time to onset:¹
2.4 months
(range: 0.8 - 10.8)

Median time to resolution:¹
6.4 months
(range: 0.2 - 15.4⁺)

Cases resolved:¹
18 patients
(45%)

Managing Immune-Related Endocrinopathies¹

| | 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-up¹

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

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

¹+Censored observation

Immune-Related Rash¹

- 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% (4/747) of patients, respectively. No grade 4 or 5 cases were reported in these studies

Rash¹

Rash is composite term which includes:

- Maculopopular 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

Managing Immune-Related Rash¹

| Grade of rash (NCI-CTCAE v4) | Grade 1 and 2 rash | Grade 3 rash | Grade 4 rash |
|---|---|--|-----------------------------------|
| Nivolumab treatment and monitoring | Continue Nivolumab | Nivolumab treatment should be withheld until symptoms resolve and management with corticosteroids is complete | Permanently discontinue nivolumab |
| Steroids | Follow Standard of Care in Saudi Arabia Medical Practice. | 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

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, and 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.

CA209066 and CA209037

Median time to onset:¹
1.4 months
(range: 0.0 - 13.1)

Median time to resolution:¹
4.6 months
(range: 0.0 - 19.1⁺)

Cases resolved:¹
87 patients
(51%)

¹+Censored observation

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 1 pneumonitis | Consider withholding Nivolumab |
| | 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 1 diarrhoea or colitis | Continue Nivolumab |
| | 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 1 elevation in AST, ALT, or total bilirubin | Continue Nivolumab |
| | 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 1 creatinine elevation | Continue Nivolumab |
| | 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 1 and 2 rash | Continue Nivolumab |
| | 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