OPDIVO (nivolumab) + YERVOY (ipilimumab)

REGIMEN

OPDIVO (nivolumab)

Immune-Related Adverse Reaction (irAR) Management Guide

- OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy[1]
- OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-squamous NSCLC with progression on or after prior chemotherapy. In patients with tumour *EGFR* or *ALK* genomic aberrations, OPDIVO should be used after progression on or after targeted therapy[1]
- OPDIVO as monotherapy is indicated for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma[1]
- OPDIVO in combination with YERVOY (ipilimumab) is indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH)[1]
- OPDIVO as monotherapy is indicated for the treatment of patients with advanced clear cell renal cell carcinoma (RCC) after prior anti-angiogenic therapy in adults[1]

Please refer to OPDIVO Data Sheet for more information on treatment.

Bristol-Myers Squibb | Immuno-Oncology

Important safety information

This guide is intended to provide information to healthcare professionals about the management of the important identified irARs associated with the use of OPDIVO as monotherapy or in combination with YERVOY. Associated irARs can be severe or life-threatening and may involve the pulmonary, gastrointestinal, hepatic, renal, endocrine, skin, neurological and other organ systems.

More frequent and more serious irARs are seen with OPDIVO + YERVOY Regimen than with the use of OPDIVO or YERVOY as single agents.

Before commencing treatment with OPDIVO monotherapy or OPDIVO + YERVOY Regimen, please review the treatment algorithms in this booklet, as well as the Data Sheets for both OPDIVO and YERVOY, as guides for the management of irARs.

Appropriate patient selection, early diagnosis and appropriate monitoring and management are essential to minimise risk in patients.

It is recommended that OPDIVO + YERVOY Regimen should be administered and monitored under the supervision of physicians experienced with the use of immunotherapy in the treatment of unresectable or metastatic melanoma.

All patients receiving OPDIVO monotherapy or OPDIVO + YERVOY Regimen must be given a Patient Alert Card to educate them about the symptoms of irARs and the need to report them to their treating doctor immediately. Treating doctors should also advise their patients to keep their Patient Alert Card with them at all times and show it to any healthcare professional who may treat them.

To request digital copies of this guide or the Patient Alert Cards with a patient information booklet, please contact BMS Medical Information on **0800 167 567** or medinfo.australia@bms.com.

MedSafe encourages the reporting of suspected adverse reactions to medicines.

Please refer to Page 22 for details on reporting a suspected adverse reaction.

Contents

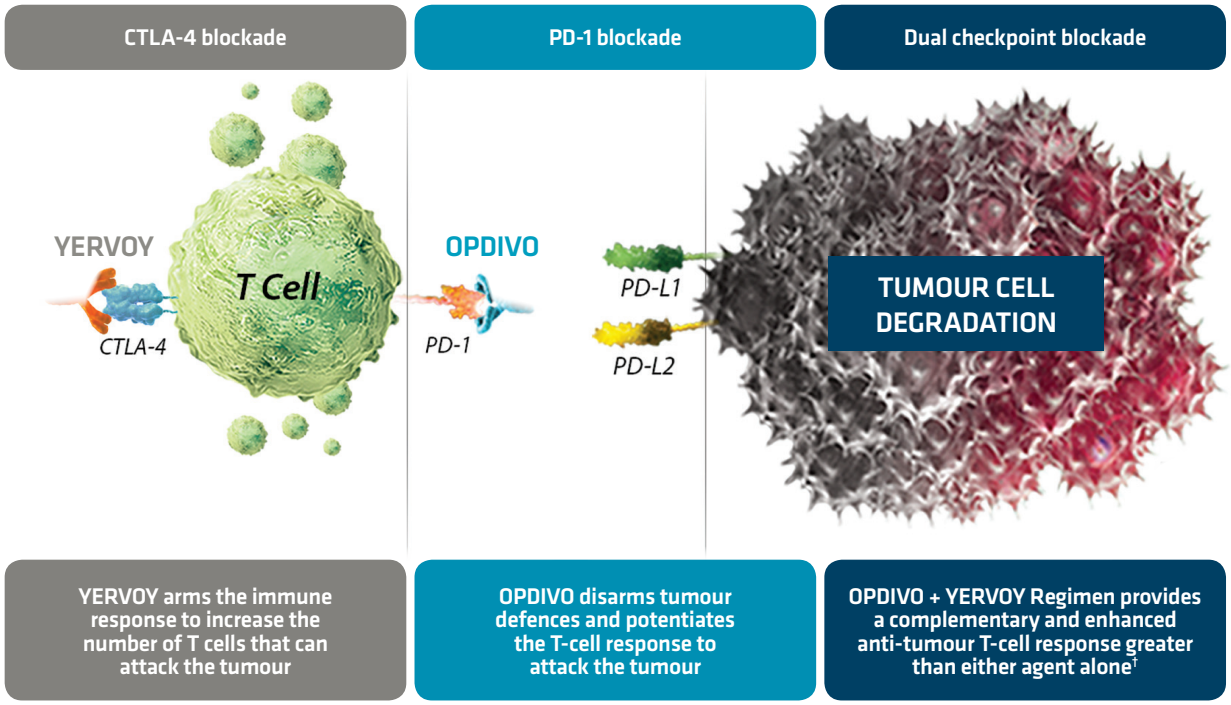
What is the mode of action for OPDIVO?[1–3]

OPDIVO is a fully human monoclonal antibody that binds to programmed death-1 (PD-1) receptor, a negative regulator of activated T cells. Engagement of PD-1 by its ligands PD-L1 and PD-L2, which are expressed on antigen-presenting cells, on tumours and other cells in the tumour micro-environment, inhibits the ability of activated T cells to proliferate and secrete cytokines. OPDIVO potentiates T-cell responses, including anti-tumour responses, by blocking the PD-1 pathway.[1]

What is the mode of action for YERVOY?[3,5]

YERVOY is a fully human monoclonal antibody that inhibits cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a key immune checkpoint receptor in the activation of T cells. Tumours exploit the CTLA-4 pathway to promote the function of immunosuppressive regulatory T cells, but limit the activation of tumour-reactive T cells. By binding to CTLA-4, YERVOY overcomes this method of tumour-induced suppression to increase the number of activated, tumour-reactive T cells that can be mobilised in a directed immune response.

OPDIVO and YERVOY have distinct and complementary modes of action[1,5]



CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2.

†OPDIVO + YERVOY Combination Regimen is indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH).

How do OPDIVO and YERVOY work together to treat metastatic melanoma?[1,5]

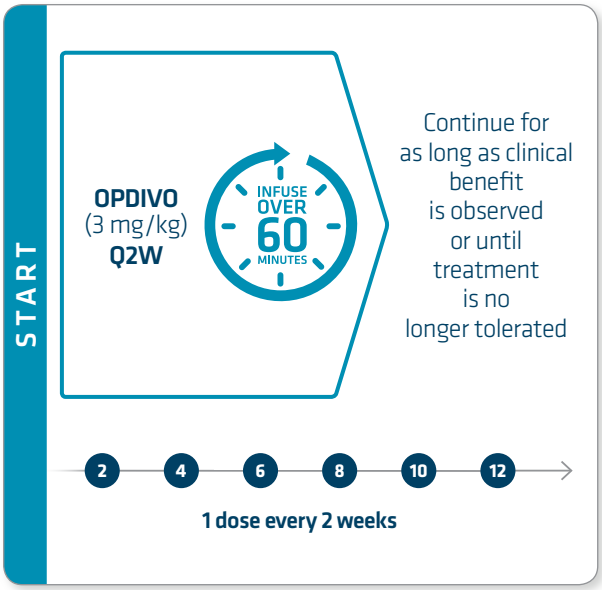
Combined, OPDIVO and YERVOY complement each other by way of their distinct modes of action to elevate the activity of tumour-reactive T cells to a level not achievable by the blockade of either CTLA-4 or PD-1 alone, resulting in a vastly improved anti-tumour response in patients with metastatic melanoma.

Management recommendations for irARs[1]

- OPDIVO monotherapy and OPDIVO + YERVOY Regimen are associated with severe or life-threatening irARs that require immediate treatment
- Most irARs (except for endocrinopathies) improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications
- Management of these adverse reactions varies depending upon the affected organ system, symptom severity, symptom duration and individual patient circumstances
- Use the information in this booklet and the Data Sheets for OPDIVO and YERVOY to assist in your management decisions for associated irARs

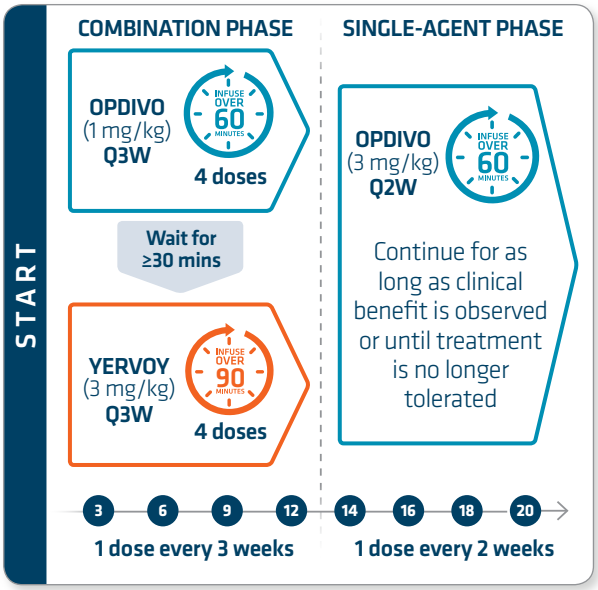
Dosing and administration[1,5]

OPDIVO monotherapy



- Administer OPDIVO as a single agent at a dose of 3 mg/kg IV every 2 weeks

OPDIVO + YERVOY Regimen



- Administer OPDIVO 1 mg/kg intravenously over 60 minutes
- Administer YERVOY 3 mg/kg intravenously over 90 minutes on the same day
- Use separate infusion bags and filters for each infusion
- Repeat every 3 weeks for 4 doses

This marks the completion of YERVOY treatment. Continue treatment using OPDIVO as a single agent at a dose of 3 mg/kg intravenously every 2 weeks.

Continue treatment with OPDIVO as long as clinical benefit is observed or until either treatment is no longer tolerated by the patient.

The infusions must not be administered as intravenous push or bolus injections.

Dose escalation or reduction for OPDIVO used alone or in combination with YERVOY is not recommended.

Monitoring[1,5]

- Patients should be carefully monitored for symptoms that could indicate emerging irARs, as they can occur at any time during or even months after discontinuation of immunotherapy treatment
- Ensure that blood parameters (liver function tests, serum creatinine and thyroid function tests) are evaluated at baseline and on a regular basis as indicated, based on clinical evaluation
- Early identification of adverse reactions and intervention are an important part of the appropriate use of OPDIVO monotherapy or OPDIVO + YERVOY Regimen. Early diagnosis of irARs is essential to minimise risk of potentially life-threatening complications
- Please advise patients to report any irARs immediately to allow appropriate management of irARs. Also, remind patients that they should not attempt to treat or manage side effects with over-the-counter medications, herbal remedies or supplements unless approved by their treating medical oncologist

Treatment of irARs[1,5]

- Corticosteroids are a primary therapy for irAR management
- If immunosuppression with corticosteroids is used to treat an irAR, a taper of at least 1 month duration should be initiated upon improvement
  - Rapid tapering may lead to worsening of the adverse reaction
  - Non-corticosteroid immunosuppressive therapy, such as infliximab or mycophenolate mofetil,[5] should be added if there is worsening or no improvement despite corticosteroid use
- Prophylactic antibiotics should be considered to prevent opportunistic infections in patients receiving immunosuppressive therapy

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

Treatment with OPDIVO monotherapy or OPDIVO + YERVOY Regimen should be permanently discontinued for any severe irAR that recurs, any life-threatening irAR, Grade 2 or 3 irARs that persist despite treatment modifications or in cases where it is not possble to reduce the corticosteroid dose to 10 mg prednisone or equivalent per day.[1]

Immune-related pulmonary adverse reactions[1]

- Severe pneumonitis or interstitial lung disease, including fatal cases, have been observed
- Monitor patients for signs and symptoms of pneumonitis (see below)
- Infectious and other disease-related aetiologies should be ruled out before treating as an irAR

Pneumonitis[1]

Signs and symptoms

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

OPDIVO monotherapy[1]* (range)	Median time to onset	Median time to resolution†	Cases resolved	Median corticosteroid treatment duration
	3.6 months (0.4–19.6)	5.3 weeks (0.6–53.1)	84.0%	3.6 weeks (0.1–13.1)

*Data based on patients who received OPDIVO 3 mg/kg monotherapy in 7 clinical studies in melanoma, NSCLC and RCC (CA209066, CA209037, CA209067, CA209017, CA209057, CA209063 and CA209025).

†Time to resolution may include censored observations.

OPDIVO + YERVOY Regimen[2#] (range)	Median time to onset	Median time to resolution‡	Cases resolved	Median corticosteroid treatment duration	Permanent discontinuation of treatment
	7.9 weeks (3.0–29.1)	6.1 weeks (0.3–46.9)	87.9%	4.3 weeks (0.7–51.1)	2%

#Data based on patients who received OPDIVO + YERVOY Regimen in 3 clinical studies in melanoma (CA209067, CA209069 and CA209004 – cohort 8).

‡Time to resolution may include censored observations.

Managing immune-related pulmonary adverse reactions[1,4]

Grade of pneumonitis (NCI-CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	**Consider delay of O or O + Y** • Monitor symptoms every 2–3 days	• Re-image at least every 3 weeks • If worsens, treat as Grade 2 or 3/4
Grade 2 Symptomatic pneumonitis	**Withhold O or O + Y** **AND** • Administer corticosteroids (initial dose of 1 mg/kg/day methylprednisolone equivalents)	• Re-image every 1–3 days • Upon improvement of symptoms and radiographic abnormalities, initiate a corticosteroid taper of at least 1 month • Resume O or O + Y treatment after corticosteroid taper is completed • If worsens or no symptom improvement after 2 weeks, treat as Grade 3/4
Grade 3/4 New or worsening hypoxia, life-threatening	**Permanently discontinue O or O + Y** **AND** • Initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents • Add prophylactic antibiotics for opportunistic infections	• If patient improves to baseline, taper steroids over at least 6 weeks • If worsens or no symptom improvement after 48 hours, add additional immunosuppressive therapy

NCI-CTCAE v4, National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0; O, OPDIVO monotherapy; O + Y, OPDIVO + YERVOY Regimen.

Immune-related gastrointestinal adverse reactions[1]

- Severe diarrhoea, colitis and fatal intestinal perforation have been observed. Other disease-related aetiologies and infections should be ruled out prior to treating as an irAR
- Monitor patients for diarrhoea and additional symptoms of colitis (see below)

Diarrhoea and colitis[1]

Signs and symptoms

- Watery, loose or soft stools
- Increased frequency of stools
- Abdominal pain
- Mucus or blood in stool
- Constitutional symptoms (fever, fatigue, weight loss)

OPDIVO monotherapy[1]* (range)	Median time to onset	Median time to resolution†	Cases resolved	Median corticosteroid treatment duration
	1.8 months (0.0–20.9)	2.1 weeks (0.1–88.3)	89.0%	3.0 weeks (0.4–40.3)

*Data based on patients who received OPDIVO 3 mg/kg monotherapy in 7 clinical studies in melanoma, NSCLC and RCC (CA209066, CA209037, CA209067, CA209017, CA209057, CA209063 and CA209025).

†Time to resolution may include censored observations.

OPDIVO + YERVOY Regimen[2]# (range)	Median time to onset	Median time to resolution‡	Cases resolved	Median corticosteroid treatment duration	Permanent discontinuation of treatment
	4.9 weeks (1 day–45.2 weeks)	3.0 weeks (0.1–78.7)	90.6%	4.6 weeks (0.1–50.7)	15.8%

#Data based on patients who received OPDIVO + YERVOY Regimen in 3 clinical studies in melanoma (CA209067, CA209069 and CA209004 – cohort 8).

†Time to resolution may include censored observations.

Managing immune-related gastrointestinal adverse reactions[1,4]

Grade of diarrhoea and colitis (NCI-CTCAE v4)	Management	Follow-up
Grade 1 Diarrhoea: <4 stools per day over baseline Colitis asymptomatic	**Continue O or O + Y** • Treat symptomatically	• Closely monitor patient • If symptoms worsen, treat as Grade 2 or 3/4
Grade 2 Diarrhoea: 4–6 stools per day over baseline Colitis: abdominal pain; mucus or blood in stool	**Withhold O or O + Y** **AND** • If persistent, administer corticosteroids (initial dose of 0.5–1 mg/kg/day methylprednisolone equivalents)	• Upon improvement to Grade 1, initiate a corticosteroid taper of at least 1 month • Resume O or O + Y treatment after corticosteroid taper is completed • If worsens or persists >3–5 days after corticosteroid initiation, treat as Grade 3/4
Grade 3 Diarrhoea: >7 stools per day over baseline, incontinence Colitis: severe abdominal pain, medical intervention required	**Withhold O** **OR** **Permanently discontinue O + Y** **AND** • Administer corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents • Add prophylactic antibiotics for opportunistic infections • For corticosteroid-refractory diarrhoea/colitis, initiate other systemic immunosuppressants such as anti-TNFα agents	• If patient improves to Grade 1, taper steroids over 1 month • If worsens or persists >3–5 days, treat as Grade 4
Grade 4 Life-threatening, perforation	**Permanently discontinue O or O + Y** **AND** • Administer corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents • Add prophylactic antibiotics for opportunistic infections • For corticosteroid-refractory diarrhoea/colitis, initiate other systemic immunosuppressants such as anti-TNFα agents	• If patient improves to Grade 1, taper steroids over 1 month • If does not improve after 3–5 days or recurs after improvement, add systemic immunosuppressants such as anti-TNFα agents (e.g. infliximab) Note: Infliximab must not be used if gastrointestinal perforation or sepsis is suspected[5]

NCI-CTCAE v4, National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0; O, OPDIVO monotherapy; O + Y, OPDIVO + YERVOY Regimen.

Immune-related hepatic adverse reactions[1]

- Severe hepatitis has been observed and other disease-related aetiologies and infections should be ruled out before treating as an irAR
- Fatal hepatic failure has been observed with YERVOY monotherapy[5]
- Monitor patients for signs and symptoms of hepatotoxicity (see below)
- Elevation in liver function tests may develop in the absence of clinical symptoms

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

OPDIVO monotherapy[1]* (range)	Median time to onset	Median time to resolution†	Cases resolved	Median corticosteroid treatment duration
	1.9 months (0.0–18.7)	5.1 weeks (0.1–82.6)	79.0%	4.0 weeks (0.4–8.9)

*Data based on patients who received OPDIVO 3 mg/kg monotherapy in 7 clinical studies in melanoma, NSCLC and RCC (CA209066, CA209037, CA209067, CA209017, CA209057, CA209063 and CA209025).

†Time to resolution may include censored observations.

OPDIVO + YERVOY Regimen[2]# (range)	Median time to onset	Median time to resolution‡	Cases resolved	Median corticosteroid treatment duration	Permanent discontinuation of treatment
	6.1 weeks (1 day–47.8 weeks)	5.0 weeks (0.1–53.1)	92.8%	3.8 weeks (0.1–57.6)	9.2%

#Data based on patients who received OPDIVO + YERVOY Regimen in 3 clinical studies in melanoma (CA209067, CA209069 and CA209004 – cohort 8).

‡Time to resolution may include censored observations.

Managing immune-related hepatic adverse reactions[1,4]

Grade of hepatotoxicity (NCI-CTCAE v4)	Management	Follow-up
Grade 1 AST/ALT >ULN to 3 × ULN and/or T. bili >ULN to 1.5 × ULN	**Continue O or O + Y**	• Closely monitor patient • If worsens, treat as Grade 2 or 3/4
Grade 2 AST/ALT >3 to 5 × ULN and/or T. bili >1.5 to 3 × ULN	**Withhold O or O + Y until LFTs return to baseline** • Upon improvement to baseline, initiate O or O + Y treatment	• If persists for >3–5 days or worsens, administer corticosteroids (initial dose of 0.5–1 mg/kg/day methylprednisolone equivalents) • Upon improvement to baseline, resume O or O + Y after corticosteroid taper is completed • If worsens or persists >3–5 days after corticosteroid initiation, treat as Grade 3/4
Grade 3/4 AST/ALT >5 × ULN and/or T. bili >3 × ULN	**Permanently discontinue O or O + Y** **AND** • Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents • Add prophylactic antibiotics for opportunistic infections	• If patient improves to Grade 2, taper steroids over 1 month • If worsens or persists for >3–5 days or rebounds, add non-corticosteroid immunosuppressive therapy (e.g. mycophenolate mofetil)[5]

NCI-CTCAE v4, National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0; O, OPDIVO monotherapy; O + Y, OPDIVO + YERVOY Regimen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LFTs, liver function tests; T.bili, total bilirubin; ULN, upper limit of the normal range.

Immune-related renal adverse reactions[1]

- Severe nephritis or renal dysfunction has been observed and other disease-related aetiologies should be ruled out before treating as an irAR
- Monitor patients for signs and symptoms of nephrotoxicity (see below)
- Creatinine elevations may develop in the absence of clinical symptom

Nephrotoxicity[1]

Signs and symptoms

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

	Median time to onset	Median time to resolution†	Cases resolved	Median corticosteroid treatment duration
OPDIVO monotherapy[1]* (range)	2.3 months (0.0–18.2)	11.1 weeks (0.1–77.1+)	62.0%	3.0 weeks (0.1–67.0)

*Data based on patients who received OPDIVO 3 mg/kg monotherapy in 7 clinical studies in melanoma, NSCLC and RCC (CA209066, CA209037, CA209067, CA209017, CA209057, CA209063 and CA209025).

†Time to resolution may include censored observations.

	Median time to onset	Median time to resolution‡	Cases resolved	Median corticosteroid treatment duration	Permanent discontinuation of treatment
OPDIVO + YERVOY Regimen[2]# (range)	11.1 weeks (2.2–63.9)	1.9 weeks (0.4–42.6)	89.5%	2.5 weeks (0.1–4.1)	0.9%

#Data based on patients who received OPDIVO + YERVOY Regimen in 3 clinical studies in melanoma (CA209067, CA209069 and CA209004 – cohort 8).

‡Time to resolution may include censored observations.

Managing immune-related renal adverse reactions[1,4]

Grade of creatinine elevation (NCI-CTCAE v4)	Management	Follow-up
Grade 1 Creatinine >ULN to 1.5 × ULN or > than baseline but ≤1.5 × baseline	**Continue O or O + Y**	• Closely monitor patient • If worsens, treat as Grade 2 or 3/4
Grade 2/3 Creatinine >1.5 × baseline to ≤6 × ULN	**Withhold O or O + Y** **AND** • Administer corticosteroids (dose of 0.5–1 mg/kg/day methylprednisolone equivalents)	• Once creatinine returns to baseline, initiate a corticosteroid taper of at least 1 month • Resume O or O + Y treatment after corticosteroid taper is completed • If elevations persist >7 days or worsen, treat as Grade 4
Grade 4 Creatinine >6 × ULN	**Permanently discontinue O or O + Y** **AND** • Administer corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents	• Upon improvement to Grade 1, taper steroids over 1 month

NCI-CTCAE v4, National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0; O, OPDIVO monotherapy; O + Y, OPDIVO + YERVOY Regimen; ULN, upper limit of normal range.

Immune-related endocrinopathies[1]

- Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and hypopituitarism, diabetes mellitus and diabetic ketoacidosis have been observed. Other disease-related aetiologies should be ruled out prior to treating as an irAR
- Patients should be monitored for clinical signs and symptoms of endocrinopathies (see below), hyperglycaemia and for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation)

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
- Electrolyte disturbances

If signs or symptoms are present, complete endocrine function evaluation

OPDIVO monotherapy[1]* (range)	Median time to onset	Median time to resolution†	Cases resolved	Median corticosteroid treatment duration
	2.8 months (0.4–14.0)	66.6 weeks (0.4–96.1)	45.0%	1.6 weeks (0.1–4.9)

*Data based on patients who received OPDIVO 3 mg/kg monotherapy in 7 clinical studies in melanoma, NSCLC and RCC (CA209066, CA209037, CA209067, CA209017, CA209057, CA209063 and CA209025).

†Time to resolution may include censored observations.

OPDIVO + YERVOY Regimen[2#] (range)	Median time to onset	Median time to resolution‡	Cases resolved	Median corticosteroid treatment duration	Permanent discontinuation of treatment
	6.7 weeks (1 day–43.9 weeks)	(0.4–74.4 weeks)	45.0%	2.9 weeks (0.1–12.7)	2.5%

#Data based on patients who received OPDIVO + YERVOY Regimen in 3 clinical studies in melanoma (CA209067, CA209069 and CA209004 – cohort 8).

‡Time to resolution may include censored observations.

Managing immune-related endocrinopathies[1,4]

Endocrine adverse reaction	Management	Follow-up
Symptomatic hypothyroidism and hyperthyroidism	**Withhold O or O + Y** **AND** • If acute inflammation of the thyroid is suspected, initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents • For symptomatic hypothyroidism: initiate thyroid hormone as needed • For symptomatic hyperthyroidism: initiate anti-thyroid medicine as needed • Monitor thyroid function to ensure appropriate hormone replacement is utilised	• Upon improvement, initiate a corticosteroid taper of at least 1 month • Resume O or O + Y after corticosteroid taper is completed • O or O + Y should be continued in the presence of hormone replacement therapy as long as no symptoms are present
Life-threatening hypo/hyperthyroidism	**Permanently discontinue O or O + Y**	
Symptomatic adrenal insufficiency	**Withhold O or O + Y** **AND** • Initiate physiological corticosteroid replacement as needed • Monitor adrenal function and hormone levels to ensure appropriate corticosteroid replacement is utilised	
Severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency	**Permanently discontinue O or O + Y**	
Symptomatic diabetes	**Withhold O or O + Y** **AND** • Initiate insulin replacement as needed • Monitor blood sugar levels to ensure appropriate insulin replacement is utilised	
Life-threatening diabetes	**Permanently discontinue O or O + Y**	
Symptomatic hypophysitis	**Withhold O or O + Y** **AND** • Initiate hormone replacement as needed • If acute inflammation of the pituitary gland is suspected, initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents • Monitor pituitary function and hormone levels to ensure appropriate hormone replacement is utilised	• Upon improvement, initiate a corticosteroid taper of at least 1 month • Resume O or O + Y after corticosteroid taper is completed
Life-threatening hypophysitis	**Permanently discontinue O or O + Y**	

O, OPDIVO monotherapy; O + Y, OPDIVO + YERVOY Regimen.

Immune-related skin adverse reactions[1]

- Severe rash has been observed with OPDIVO + YERVOY Regimen and less commonly with OPDIVO monotherapy. Other disease-related aetiologies should be ruled out prior to treating as an irAR
- Rare cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcomes, have been observed[5]
- Caution should be used when considering the use of OPDIVO monotherapy or OPDIVO + YERVOY Regimen in a patient who has experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents
- Monitor patients for signs and symptoms of rash (see below)

Skin adverse reactions[1]

Signs and symptoms

- Inflammation of the skin
- Pruritus
- Erythema
- Vitiligo
- Blister, ulcers, peeling

OPDIVO monotherapy[1]* (range)	Median time to onset	Median time to resolution†	Cases resolved	Median corticosteroid treatment duration
	1.4 months (0.0–17.2)	18.1 weeks (0.1–113.7)	62.0%	2.1 weeks (0.1–38.7)

*Data based on patients who received OPDIVO 3 mg/kg monotherapy in 7 clinical studies in melanoma, NSCLC and RCC (CA209066, CA209037, CA209067, CA209017, CA209057, CA209063 and CA209025).

†Time to resolution may include censored observations.

OPDIVO + YERVOY Regimen[2]# (range)	Median time to onset	Median time to resolution‡	Cases resolved	Median corticosteroid treatment duration	Permanent discontinuation of treatment
	0.5 months (0.0–9.7)	10.4 weeks (0.1–74.0)	67.6%	1.6 weeks (0.3–15.6)	0.7%

#Data based on patients who received OPDIVO + YERVOY Regimen in 3 clinical studies in melanoma (CA209067, CA209069 and CA209004 – cohort 8).

‡Time to resolution may include censored observations.

Managing immune-related skin adverse reactions[1,4]

Grade of rash (NCI-CTCAE v4)	Management	Follow-up
Grade 1/2 Rash covering ≤30% body surface area	**Continue O or O + Y treatment** **AND** • Initiate symptomatic treatment (oral antihistamines, topical corticosteroids)	• If persists >1–2 weeks or recurs, withhold O or O + Y treatment and initiate 0.5–1.0 mg/kg/day methylprednisolone equivalents • If worsens, treat as Grade 3/4
Grade 3 Rash covering >30% body surface area, or suspected SJS or TEN	**Withhold O or O + Y** **AND** • Administer high-dose corticosteroids at a dose of 1–2 mg/kg/day methylprednisolone equivalents • For suspected SJS or TEN, refer the patient to a specialised unit for assessment and treatment	• If improves to Grade 1, taper steroids over 1 month and restart O or O + Y treatment • Add prophylactic antibiotics for opportunistic infections
Grade 4 Life-threatening consequence, or confirmed SJS or TEN	**Permanently discontinue O or O + Y** • For severe rash, manage with high-dose corticosteroids at a dose of 1–2 mg/kg/day methylprednisolone equivalents • For confirmed SJS or TEN, refer the patient to a specialised unit for assessment and treatment	• If improves to Grade 1, taper steroids over at least 1 month • Add prophylactic antibiotics for opportunistic infections

NCI-CTCAE v4, National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0; O, OPDIVO monotherapy; O + Y, OPDIVO + YERVOY Regimen; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.

Immune-related neurological adverse reactions[1,5]

The following neurological irARs were reported in patients treated with **immunotherapy** in clinical trials across doses and tumour types:

- Encephalitis
- Myasthenic syndrome/ myasthenia gravis
- Demyelination
- Autoimmune neuropathy (including facial and abducens nerve paresis)
- Guillain–Barré syndrome (fatal cases reported in association with YERVOY monotherapy)
- Other neurological adverse reactions associated with YERVOY monotherapy including motor neuropathy, muscle weakness and sensory neuropathy

- Withhold OPDIVO monotherapy and OPDIVO + YERVOY Regimen in patients with new-onset, moderate to severe neurological signs or symptoms
- For suspected irARs, adequate evaluation should be performed to confirm aetiology or rule out infections or other causes
- While other aetiologies are being ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents, followed by a corticosteroid taper
- Permanently discontinue OPDIVO monotherapy or OPDIVO + YERVOY Regimen for immune-related encephalitis and myasthenic syndrome/myasthenia gravis

Other irARs[1,5]

The following irARs were reported in patients treated with **immunotherapy** in clinical trials across doses and tumour types:

- Pancreatitis
- Uveitis
- Hypopituitarism
- Eosinophilia
- Myositis
- Myocarditis
- Lipase elevation
- Gastritis
- Sarcoidosis
- Duodenitis
- Rhabdomyolysis

- For suspected irARs, adequate evaluation should be performed to confirm aetiology or rule out other causes
- Based on the severity of the irAR, OPDIVO monotherapy and OPDIVO + YERVOY Regimen should be withheld and corticosteroids administered
- Upon improvement, OPDIVO monotherapy or OPDIVO + YERVOY Regimen may be resumed after corticosteroid taper
- OPDIVO monotherapy or OPDIVO + YERVOY Regimen must be permanently discontinued for any severe irARs that recur and for any life-threatening irARs

Treatment modifications in response to irARs[1]

Immune-related adverse reaction	Management	Follow-up
Any Grade 1 event (mild) **Grade 2 Skin reactions**	**Continue O or O + Y** • Supportive care • Symptomatic treatment	• Monitor for worsening symptoms • **If worsens,** treat as Grade 2 or 3/4, as applicable
Grade 2 Diarrhoea/colitis **Grade 2 Hepatitis** **Grade 2 Adrenal insufficiencies** **Grade 2/3 Symptomatic endocrinopathies***	**Withhold O or O + Y until symptoms resolve** **AND** • Initiate corticosteroids ***(if needed)*** **Initiate hormone replacement therapy as needed*	**If symptoms improve:** • Taper corticosteroid over at least 1 month • Resume O or O + Y after completing corticosteroid taper • Monitor for worsening symptoms **Continue O or O + Y in the presence of hormone replacement therapy as long as no symptoms are present* **If symptoms worsen/persist without improvement:** • Permanently discontinue O or O + Y • Increase dose of corticosteroid
Grade 2 Pneumonitis **Grade 2/3 Nephritis and renal dysfunction** **Grade 3 Skin reactions, SJS and TEN** **Grade 3 Diarrhoea/colitis *(O monotherapy)***	**Withhold O or O + Y until symptoms resolve** **AND** • Initiate corticosteroids • For suspected SJS or TEN, refer the patient to a specialised unit for assessment and treatment	
Grade 3 Diabetes	**Withhold O or O + Y** **AND** • Initiate insulin replacement as needed	
Grade 3/4 Pneumonitis **Grade 4 Skin reactions, SJS and TEN** **Immune-related encephalitis and myasthenic syndrome/ myasthenia gravis** **Grade 3 Myotoxicity** **Grade 3/4 Adrenal insufficiency** **Grade 3/4 Hepatitis** **Grade 4 Nephritis** **Grade 4 Diabetes** **Grade 4 Hypo/hyperthyroidism** **Grade 4 Hypophysitis** **Grade 3/4 Diarrhoea/colitis *(O + Y Regimen only)*** **Grade 4 Diarrhoea/colitis *(O monotherapy only)***	**Permanently discontinue O or O + Y** **AND** • Initiate high-dose corticosteroids • Add prophylactic antibiotics for opportunistic infections as needed • For confirmed SJS or TEN, refer the patient to a specialised unit for assessment and treatment	**Other conditions requiring permanent discontinuation of O or O + Y:** • Recurrent Grade 3 events • Inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day

O, OPDIVO monotherapy; O + Y, OPDIVO + YERVOY Regimen; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.
For more detailed symptom-based treatment recommendations, please refer to the OPDIVO Data Sheet.

Infusion reactions[1,5]

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

Suspected adverse reaction reporting

MedSafe encourages healthcare professionals to report any suspected adverse reaction to a medicine (including prescription, over-the-counter and complementary medicines) or vaccine. MedSafe particularly requests reports of suspected reactions that are serious or unexpected or may have been caused by a new medicine or a drug interaction. Reports are included in the national adverse reaction database, which is regularly analysed to detect safety signals.

For further details on reporting a suspected adverse reaction, please refer to the MedSafe website: www.medsafe.govt.nz/safety/report-a-problem.asp

If you report a suspected adverse drug reaction to MedSafe, BMS would appreciate receiving a copy:

Bristol-Myers Squibb Australia Pty Ltd
Email: medinfo.australia@bms.com

If you require any further information regarding the use of OPDIVO monotherapy or OPDIVO + YERVOY Regimen, please contact Bristol-Myers Squibb Medical Information on 0800 167 567 or email medinfo.australia@bms.com

Pharmaceutical Schedule information: OPDIVO is listed on the Pharmaceutical Schedule fully funded with Special Authority criteria for the treatment of patients with metastatic or unresectable melanoma stage III or IV. Refer to the Pharmaceutical Schedule for full Special Authority information. Patients meeting the OPDIVO Special Authority criteria wishing to use OPDIVO in combination with YERVOY will have to pay for YERVOY. OPDIVO is not funded for locally advanced or metastatic squamous or non-squamous non-small cell lung cancer or renal cell carcinoma. Patients will have to pay for OPDIVO in these indications.

Please refer to the Data Sheet before prescribing. The Data Sheet is available upon request from the BMS Medical Information Department: 0800 167 567 or can be accessed at: www.medsafe.govt.nz

NAME OF THE MEDICINE: OPDIVO® (nivolumab): 10 mg/mL concentrate solution for infusion. **CLASSIFICATION:** Prescription Medicine. **INDICATIONS:** OPDIVO, as monotherapy is indicated for the treatment of patients with unresectable (Stage III) or metastatic (Stage IV) melanoma. OPDIVO, in combination with YERVOY (ipilimumab) is indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH). OPDIVO, as monotherapy is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. OPDIVO, as monotherapy is indicated for the treatment of locally advanced or metastatic non-squamous NSCLC with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, OPDIVO should be used after progression on or after targeted therapy. OPDIVO as monotherapy is indicated for the treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy in adults. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **PRECAUTIONS:** OPDIVO as monotherapy and administered in combination with YERVOY is associated with immune-related adverse reactions (irARs) including pneumonitis, colitis, hepatitis, nephritis, renal dysfunction, skin adverse reactions (including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, some with fatal outcome), endocrinopathies and neurological adverse reactions (including encephalitis and myasthenic gravis). Caution in patients with autoimmune disease, immunosuppressive therapy, symptomatic interstitial lung disease, active brain metastases, moderate or severe hepatic impairment, or in patients who experienced a severe or life-threatening skin adverse reaction to prior immunostimulatory anti-cancer therapy. OPDIVO is not approved for combination with EGFR TKI use in NSCLC. Use in children below 18 years of age is not recommended. **Pregnancy Category D.** Refer to the Data Sheet (DS) for a complete list of precautions. **INTERACTIONS WITH OTHER MEDICINES:** OPDIVO is not metabolised by drug-metabolising enzymes, therefore it is not anticipated to have pharmacokinetic-based interactions. **ADVERSE EFFECTS:** Most frequently reported adverse events (≥10%) for OPDIVO as monotherapy are fatigue, musculoskeletal pain, rash, diarrhoea, constipation, nausea, pruritus, vomiting, abdominal pain, oedema, dyspnoea, erythema, vitiligo, arthralgia, headache, peripheral neuropathy, upper respiratory tract infection, pyrexia, chest pain, cough, sleep disorder, dizziness and decreased appetite. Most frequently reported adverse events (≥10%) for OPDIVO administered in combination with YERVOY are fatigue, musculoskeletal pain, rash, diarrhoea, constipation, nausea, pruritus, vomiting, abdominal pain, chills, oedema, vitiligo, arthralgia, headache, hypophysitis, blurred vision, colitis, dehydration, dizziness, hypothyroidism, hyperthyroidism, sleep disorder, pneumonitis, pyrexia, dyspnoea, cough, decreased weight, upper respiratory tract infection and decreased appetite. Other irARs (some with fatal outcome) such as pancreatitis, uveitis, demyelination, autoimmune neuropathy, Guillain–Barré syndrome, hypopituitarism, myasthenic syndrome, encephalitis, myositis, myocarditis and rhabdomyolysis have also been reported in clinical trials with OPDIVO monotherapy. Other irARs (some with fatal outcome) such as pancreatitis, uveitis, Guillain–Barré syndrome, hypopituitarism, gastritis, sarcoidosis, duodenitis, encephalitis, myositis, myocarditis and rhabdomyolysis have also been reported in clinical trials with OPDIVO in combination with YERVOY. Please refer to the DS for a full list of adverse events. **DOSAGE AND ADMINISTRATION:** Recommended dose of OPDIVO as monotherapy is 3 mg/kg administered intravenously (IV) over 60 minutes every 2 weeks. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. OPDIVO in combination with YERVOY (metastatic [Stage IV] melanoma with M1c disease or elevated LDH): Please review the YERVOY Data Sheet prior to initiation of OPDIVO in combination with YERVOY. The recommended dose of OPDIVO in the combination phase is 1mg/kg administered IV over 60 minutes every 3 weeks for the first 4 doses followed by YERVOY 3mg/kg administered IV over 90 minutes. The recommended dose of OPDIVO in the single-agent phase is 3mg/kg as monotherapy administered IV over 60 minutes every 2 weeks. Continue treatment with OPDIVO as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Management of irARs may require withholding of a dose and initiation of corticosteroid or other immunosuppressive therapy or permanent discontinuation of OPDIVO therapy. When OPDIVO is administered in combination with YERVOY if either agent is withheld, the other agent should also be withheld. Please refer to the DS for further details. Prepared from the OPDIVO NZ Data Sheet (April 2017). 1506NZ1701870-01-01.

ALK=anaplastic lymphoma receptor tyrosine kinase; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer.

References: 1. OPDIVO (nivolumab) Data Sheet, April 2017. **2.** Hamid O and Caravajal RD. *Expert Opin Biol Ther* 2013;13(6):847–861. **3.** Ascierto PA and Marincola FM. *J Transl Med* 2014;12:141. **4.** Robert C, Long GV, Brady B, *et al. N Engl J Med* 2015;372:320–330. **5.** YERVOY (ipilimumab) Data Sheet, August 2016.

 BMS Medical Information: 0800 167 567. Bristol-Myers Squibb New Zealand Ltd, Private Bag 92518, Auckland 1141. TAPS Approval No. MR5264. Mercury approval: 1506NZ1702856-01. Date of preparation: June 2017. BMSA0464.

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OPDIVO (nivolumab) + YERVOY (ipilimumab) REGIMEN

OPDIVO (nivolumab)