Nivolumab 3mg/kg with Ipilimumab 1mg/kg Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Nivolumab in combination with ipilimumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (RCC).	C64	00551a	ODMS 01/02/2021
Nivolumab in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults[i]	C43	00551b	ODMS 1/10/2020

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Nivolumab and ipilimumab are administered once every 21 days for the first 4 cycles. From cycle 5, nivolumab is administered as monotherapy at either 240mg every 14 days (Refer to NCCP Regimen 00483) or at 480mg every 28 days (Refer to NCCP Regimen 00484) until disease progression or unacceptable toxicity develops.
For the monotherapy phase, the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240mg every 14 days; or
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480mg every 28 days.

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

Facilities to treat anaphylaxis MUST be present when nivolumab and ipilimumab are administered.

Cycles 1-4

Drug	Dose	Route	Diluent & Rate	Cycle
Nivolumab	3mg/kg	IV infusion	Infuse over 30 minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm	Every 21 days for 4 cycles
Ipilimumab	1mg/kg	IV infusion Observe post infusion*	0.9% sodium chloride to a concentration between 1 and 4mg/ml over 30min using a 0.2-1.2 µm low-protein binding in-line filter.	Every 21 days for 4 cycles
Nivolumab or Ipilimumab **must not** be administered as an intravenous push or bolus injection.				
Nivolumab can be infused directly as a 10 mg/ml solution or can be diluted to as low as 1 mg/ml with sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection.				
*Vital signs including temperature, pulse and BP should be taken every 30 mins for the duration of the infusion and 1 hour following completion of the infusion.				
The line should be flushed with 0.9% sodium chloride after the ipilimumab infusion has finished.				

Cycle 5 onwards

Drug	Dose	Route	Diluent & Rate	Cycle
Nivolumab	240mg	IV infusion	Infuse over 30 minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm	Every 14 days ongoing to progression or toxicity
			OR	
Nivolumab	480mg	IV infusion	Infuse over 60 minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm	Every 28 days ongoing to progression or toxicity

ELIGIBILITY:

- Indication as above
- Aged 18 years or above
- Adequate haematological, hepatic and renal function
- RCC
  - ECOG 0-2
  - Histological confirmation of RCC with a clear-cell component
  - Intermediate and poor risk categories as determined by International Metastatic RCC database Consortium (IMDC) study
- Melanoma
  - ECOG 0-1
- Nivolumab and ipilimumab are not recommended during pregnancy and in women of childbearing potential not using effective contraception, unless prescribing consultant deems clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab.

CAUTION:

Use with caution in:

- Patients with clinically significant autoimmune disease
- RCC
  - Ongoing symptomatic cardiac dysrhythmias, uncontrolled atrial fibrillation, or prolongation of the Fridericia corrected QT (QTcF)
  - Poorly controlled hypertension (defined as systolic blood pressure (SBP) of ≥150 mmHg or diastolic blood pressure (DBP) of ≥90 mmHg), despite antihypertensive therapy

EXCLUSIONS:

- Hypersensitivity to nivolumab, ipilimumab or to any of the excipients
- Patients who have previously received treatment for melanoma with PD-1/ PD-L1 inhibitors
- Prior systemic treatment for advanced renal cell carcinoma
- Untreated symptomatic CNS metastases.
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids).
- Any active clinically significant infection requiring therapy
- Symptomatic interstitial lung disease
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- Thyroid Function Tests (TFTs)
- Melanoma: BRAF status
- Virology: All patients should be tested for both HBsAg and HBcoreAb as per local policy and Hepatitis C (HCV RNA)

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Glucose prior to each cycle
- TFTs prior to each cycle

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of nivolumab in combination with ipilimumab therapy and institution of systemic high-dose corticosteroid.

- If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use. Nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.
- Nivolumab in combination with ipilimumab must be permanently discontinued for;
    - Any severe immune-related adverse reaction that recurs.
    - Any life-threatening immune-related adverse reaction.
    - Any grade 4 or recurrent grade 3 adverse reactions, persistent grade 2 or 3 adverse reactions despite management.
- 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.
- Guidelines for withholding of doses or permanent discontinuation are described in Table 1 below.
- For dose modifications during nivolumab monotherapy treatment, please refer to:
    - Nivolumab monotherapy 240mg (NCCP Regimen 00483) or
    - Nivolumab monotherapy 480mg (NCCP Regimen 00484)

Table 1: Dose Modification of nivolumab and ipilimumab in combination therapy for adverse events

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[a]	Permanently discontinue treatment
	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 Grade 4 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 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 Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash Grade 4 rash Steven-Johnsons syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete Permanently discontinue treatment Permanently discontinue treatment
Immune-related myocarditis	Grade 2 myocarditis Grade 3 or 4 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[b] Permanently discontinue treatment

Other immune-related adverse reactions	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 10mg prednisone 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). [a]During administration of the second phase of treatment (nivolumab monotherapy) following combination treatment, permanently discontinue treatment if Grade 3 diarrhoea or colitis occurs. [b]The safety of re-initiating nivolumab or nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.		

Renal and Hepatic Impairment:

Table 2: Dose modification of nivolumab and ipilimumab in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Nivolumab	**Mild-Moderate**	No dose adjustment necessary	**Mild**	No dose adjustment necessary
	Severe	Has not been studied	**Moderate -Severe**	Has not been studied. Nivolumab must be administered with caution in patients with: • moderate (total bilirubin >1.5x to 3x ULN and any AST) or • severe (total bilirubin >3x ULN and any AST)
Ipilimumab	No specific dose adjustment is necessary in patients with mild to moderate renal dysfunction.		No specific dose adjustment is necessary in patients with mild hepatic impairment. Administer with caution in patients with transaminase levels ≥5x ULN or bilirubin levels >3x ULN at baseline.	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Nivolumab: Minimal **(Refer to local Policy)**

Ipilimumab: Low **(Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Cardiac adverse events and pulmonary embolism**: Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during combination treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions.
- **Immune related adverse reactions:** Please see Table 3 for dose modifications of nivolumab with ipilimumab combination.
  For dose modifications during nivolumab monotherapy treatment, please refer to:
  - Nivolumab monotherapy 240mg (NCCP Regimen 00483) or
  - Nivolumab monotherapy 480mg (NCCP Regimen 00484)

Table 3: Management of immune-related adverse reactions to nivolumab and ipilimumab in combination therapy

Adverse reaction	Withhold / discontinue	Recommended action -1st occurrence
Immune-related pneumonitis Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g. focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.		
Grade 2 (symptomatic)	Withhold nivolumab and ipilimumab	Initiate corticosteroids at a dose of 1 mg/kg/day methylprednisolone (/equivalents) Upon improvement, treatment may be resumed after corticosteroid taper.
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue both nivolumab and ipilimumab	Increase corticosteroid dose to 2 to 4 mg/kg/day methylprednisolone (/equivalents)
Grade 3 or 4	Permanently discontinue both nivolumab and ipilimumab	Initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone (/equivalents)
Immune-related colitis Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Infectious and disease-related aetiologies should be ruled out. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Consider if patient has persistent colitis despite appropriate colitis therapy.		
Grade 2 diarrhoea or colitis	Withhold both nivolumab and ipilimumab	Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone (/equivalents). Upon improvement, treatment may be resumed after corticosteroid taper.
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue both nivolumab and ipilimumab	Increase corticosteroid dose to 1 to 2 mg/kg/day methylprednisolone (/equivalents)

Grade 3 diarrhoea or colitis	Permanently discontinue both nivolumab and ipilimumab	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone (/equivalents)
Grade 4 diarrhoea or colitis	Permanently discontinue both nivolumab and ipilimumab	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone (/equivalents)
Immune-related hepatitis Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.		
Grade 2 transaminase or total bilirubin elevation	Withhold both nivolumab and ipilimumab	Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, treatment may be resumed after corticosteroid taper.
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue both nivolumab and ipilimumab	Increase corticosteroid dose to 1 to 2 mg/kg/day methylprednisolone (/equivalents)
Grade 3 or 4 transaminase or total bilirubin elevation	Permanently discontinue both nivolumab and ipilimumab	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone. (/equivalents)
Immune-related nephritis or renal dysfunction Patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.		
Grade 2 or 3 serum creatinine elevation	Withhold both nivolumab and ipilimumab	Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone. (/equivalents) Upon improvement, treatment may be resumed after corticosteroid taper.
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue both nivolumab and ipilimumab	Increase corticosteroid dose to 1 to 2 mg/kg/day methylprednisolone (/equivalents)
Grade 4 serum creatinine elevation	Permanently discontinue both nivolumab and ipilimumab	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone (/equivalents)
Immune-related endocrinopathies Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.		
Symptomatic hypothyroidism	Withhold both nivolumab and ipilimumab	Thyroid hormone replacement should be initiated as needed

Symptomatic hyperthyroidism	Withhold both nivolumab and ipilimumab	Antithyroid medication should be initiated as needed Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, treatment may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised.
Life-threatening hyperthyroidism or hypothyroidism	Permanently discontinue both nivolumab and ipilimumab	
Symptomatic Grade 2 adrenal insufficiency	Withhold both nivolumab and ipilimumab	Physiologic corticosteroid replacement should be initiated as needed.
Severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency	Permanently discontinue both nivolumab and ipilimumab	Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised
Symptomatic Grade 2 or 3 hypophysitis	Withhold both nivolumab and ipilimumab	Hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone (/ equivalents) should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, treatment may be resumed after corticosteroid taper, if needed.
Life-threatening (Grade 4) hypophysitis	Permanently discontinue both nivolumab and ipilimumab	Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.
Symptomatic diabetes	Withhold both nivolumab and ipilimumab	Insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised.
Life-threatening diabetes	Permanently discontinue both nivolumab and ipilimumab	
Immune-related skin adverse reactions		
Grade 3 rash	Withhold both nivolumab and ipilimumab	Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Rare cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), some of them with fatal outcome have been observed. If symptoms or signs of SJS or TEN appear, treatment should be discontinued and the
Grade 4 rash	Permanently discontinue both nivolumab and ipilimumab	

		patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab in combination with ipilimumab, permanent discontinuation of treatment is recommended. 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.
Other immune-related adverse reactions 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, treatment should be withheld and corticosteroids administered. Upon improvement, treatment may be resumed after corticosteroid taper. Treatment must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction. Myotoxicity: ○ Cases of myotoxicity, some with fatal outcome, have been reported with nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented. Based on the severity of myotoxicity, nivolumab in combination with ipilimumab should be withheld or discontinued., Patients with cardiac or cardiopulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day). Once a diagnosis of myocarditis is established, nivolumab in combination with ipilimumab should be withheld or permanently discontinued (see Table 1).		
Infusion reactions		
Mild or moderate infusion reaction	Caution	May receive treatment with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.
Severe or life-threatening infusion reaction	Discontinue infusion	Administer appropriate medical therapy

DRUG INTERACTIONS:

- No formal pharmacokinetic drug interaction studies have been conducted with nivolumab. Since nivolumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting nivolumab in combination with ipilimumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of nivolumab in combination with ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab in combination with ipilimumab to treat immune-related adverse reactions.
- Concomitant use of ipilumumab with anti-coagulants may increase risk of GI haemorrhage so close monitoring is required.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/USEFUL LINKS:

Please note that this is for information only and does not constitute endorsement by the NCCP

Patient Alert Card:
Nivolumab: https://www.hpra.ie/img/uploaded/swedocuments/cf83916c-1f29-46e4-a9d5-11a0e6d150d3.pdf
Ipilimumab: https://www.hpra.ie/img/uploaded/swedocuments/0781c3d7-ff8d-4cc7-9f0a-80cf9a10e59f.pdf

Patient Information Guide:
Ipilimumab: https://www.hpra.ie/img/uploaded/swedocuments/2f064c72-ccef-492b-a068-bc72d8b522cf.pdf

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Version	Date	Amendment	Approved By
1	21/08/2019		Prof Maccon Keane
2	09/10/2019	Updated adverse effects/regimen specific complications section as per SmPC update regarding CMV infection/reactivation	Prof Maccon Keane
3	23/9/2020	Addition of melanoma indication	Prof Maccon Keane
4	01/02/2021	Update reimbursement status	Prof Maccon Keane
5	22/10/2021	Added to baseline tests. Updated dose modifications for adverse events and hepatic impairment. Updated emetogenic potential. Updated adverse effects/regimen specific complications section.	Prof. Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] The administration of nivolumab 3mg/kg in combination with pilimumab 1mg/kg is an unlicensed dosing posology for this indication in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy