Nivolumab 240mg and Ipilimumab 1mg/kg Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Nivolumab in combination with ipilimumab for the first-line treatment of adult patient with unresectable or metastatic mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC).	C18	00900a	N/A

* This applies to post 2012 indications

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 a dose of 240mg every 14 days Refer to NCCP Regimen 00483) or 480mg every 28 days (Refer to NCCP Regimen 00484) until disease progression or unacceptable toxicity develops or up to 24 months in patients without disease progression, whichever comes first.

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.

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 systemic anti-cancer therapy (SACT) is administered.

Cycles 1-4

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	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 21 days for 4 cycles
2	1	Ipilimumab	1mg/kg	IV infusion Observe post infusion*	NaCl 0.9% to a concentration between 1 and 4mg/mL over 30 minutes 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 10mg/mL solution or can be diluted to as low as 1mg/mL with NaCl 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 minutes for the duration of the infusion and 1 hour following completion of the infusion.						
The line should be flushed with NaCl 0.9% after the ipilimumab infusion has finished.						

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Cycle 5 onwards

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	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 for up to 2 years
Or					
1	Nivolumab	480mg	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 28 days for up to 2 years

ELIGIBILITY:

- Indication as above
- Histologically confirmed unresectable or metastatic CRC with dMMR/MSI-H
- Adequate haematological, hepatic and renal function
- ECOG 0-1

CAUTIONS:

- Patients with clinically significant autoimmune disease
- Any active clinically significant infection requiring therapy
- Symptomatic CNS metastases
- Immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisoLONE/daily or steroid equivalent, excluding inhaled or topical steroids

EXCLUSIONS:

- Hypersensitivity to nivolumab, ipilimumab or to any of the excipients
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody Available on NCCP website
- Symptomatic interstitial lung disease
- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- Thyroid Function Tests (TFTs)

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Blood glucose prior to each cycle
- TFTs prior to each cycle
- Cortisol as clinically indicated

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 dose interruption or permanent discontinuation of nivolumab in combination with ipilimumab therapy and institution of systemic high-dose corticosteroid (see Tables 1 and 3)
- 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

Table 1: Dose modification of nivolumab and ipilimumab 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	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	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 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[a] Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence) Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10mg prednisoLONE or equivalent per day	Withhold dose(s) 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]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	No dose adjustment is needed Haemodialysis: No need for dose adjustment is expected	**Mild and moderate**	No dose adjustment is needed
		Severe	No need for dose adjustment is expected
Ipilimumab	No dose adjustment is needed Haemodialysis: No need for dose adjustment is expected	No need for dose adjustment is expected	
Renal and hepatic dose modifications from Giraud et al 2023			

Management of adverse events:

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 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
Grade 4 rash	Permanently discontinue both nivolumab and ipilimumab	

		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 (prednisoLONE 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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

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

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

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- 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

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for 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/find-a-medicine/for-human-use/authorised-medicines/details/10066#edumaterials

Ipilimumab:
https://www.hpra.ie/find-a-medicine/for-human-use/authorised-medicines/details/9440#edumaterials

Patient Information Guide:
Ipilimumab:
https://www.hpra.ie/find-a-medicine/for-human-use/authorised-medicines/details/9440#edumaterials

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Version	Date	Amendment	Approved By
1	23/04/2025		Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.