Nivolumab Monotherapy 480mg -28 days

This regimen supersedes NCCP Regimen 00349 Nivolumab Monotherapy as of May 2018 and Regimen 00573 as of Nov-2019 due to a change in the licensed dosing posology.

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults	C43	00484a	ODMS 9/10/2017
As monotherapy for the treatment of advanced renal cell carcinoma (RCC) after prior therapy in adults.	C64	00484b	ODMS 9/10/2017
As monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection	C43	00484c	ODMS 01/02/2021
As monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.[i]	C81	00484d	ODMS
As monotherapy for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.[i]	C76	00484e	ODMS
As monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults.[i]	C34	00484f	ODMS

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 is administered once every 28 days until disease progression or unacceptable toxicity develops.
For adjuvant melanoma therapy, the maximum treatment duration with nivolumab is 12 months.

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 after discontinuation of therapy

If a patient needs to be switched from the 480mg every 4 weeks schedule to the 240mg every 2 weeks schedule (See NCCP Regimen 00483 - Nivolumab Monotherapy 240mg-14 days), the first 240mg dose should be administered four weeks after the last 480mg dose.

Facilities to treat anaphylaxis MUST be present when nivolumab is administered.

Drug	Dose	Route	Diluent & Rate	Cycle
Nivolumab	480mg	IV infusion	Infuse over 60minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 micrometre	Ongoing every 28 days to progression or toxicity
Nivolumab 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 sodium chloride 9mg/mL (0.9%) solution for injection or glucose 50mg/mL (5%) solution for injection.				

ELIGIBILITY:

- Indications as above
- ECOG status
    - **ECOG 0-2:**
        - Advanced melanoma
        - RCC
    - **ECOG 0-1:**
        - Adjuvant melanoma
        - cHL
        - Head and Neck
        - NSCLC
- Aged 18 years or above
- Adequate haematological, hepatic and renal function
- Nivolumab is 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.
- **Renal cell carcinoma**
    - Histologic confirmation of advanced or metastatic renal-cell carcinoma.
    - Have received one or more prior lines of systemic therapy including at least one prior anti-angiogenic tyrosine kinase inhibitor.
- **Head and Neck**
    - Histologically confirmed recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) (oral cavity, pharynx, larynx), that is not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy)
    - Tumour progression or recurrence within 6 months of last dose of platinum-based therapy in the adjuvant (i.e. with radiation after surgery), primary (i.e., with radiation), recurrent, or metastatic setting.
- **Non-small cell lung cancer (NSCLC)**
    - Subjects must have experienced disease recurrence or progression during or after one prior platinum-containing doublet chemotherapy regimen for advanced or metastatic disease.
- **Adjuvant melanoma**
    - Stage III or completely resected Stage IV Melanoma

CAUTION:

Use with caution in:

- Patients with clinically significant autoimmune disease

EXCLUSIONS:

- Hypersensitivity to nivolumab or to any of the excipients
- Previous treatment with an anti-PD1 monoclonal antibody
- 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)
- Symptomatic interstitial lung disease
- Any active clinically significant infection requiring therapy
- **Adjuvant melanoma:**
  - Uveal melanoma
- **Head and neck**
  - Patients with carcinoma of the nasopharynx or salivary gland as primary tumour site.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist or by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- Blood, renal and liver profile
- Glucose
- TFTs
- Hepatitis B (HBV sAg) and Hepatitis C (HCV RNA)
- Serum cortisol (ideally a morning sample)

Disease specific baseline test:

- **Adjuvant and advanced Melanoma :** Determination of BRAF status

Regular tests:

- FBC, renal, liver profile and 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.

Non-small cell lung cancer (NSCLC)

- Patients should be assessed for progression prior to commencing their 8th cycle.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Dose escalation or reduction is not recommended. Any dose modification should be discussed with a Consultant.
- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of nivolumab 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 should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy.
- Guidelines for withholding of doses or permanent discontinuation are described in Table 1 below.

Table 1: Recommended Treatment Modifications for Nivolumab

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	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	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	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute

	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	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 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 prednisone or equivalent per day	Withhold dose(s) Permanently discontinue treatment

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

Renal and Hepatic Impairment:

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

Renal Impairment	Dose	Hepatic Impairment	Dose
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 >3 x ULN and any AST) hepatic impairment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**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 treatment.
- **Immune related adverse reactions:**

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	Initiate corticosteroids at a dose of 1mg/kg/day methylprednisolone (/equivalents) Upon improvement, nivolumab may be resumed after corticosteroid taper
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	Increase corticosteroid dose to 2 to 4mg/kg/day methylprednisolone (/equivalents)
Grade 3 or 4	Permanently discontinue	Initiate corticosteroids at a dose of 2 to 4mg/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	Initiate corticosteroids at a dose of 0.5 to 1mg/kg/day methylprednisolone (/equivalents) Upon improvement, nivolumab may be resumed after corticosteroid taper
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	Increase corticosteroid dose to 1 to 2mg/kg/day methylprednisolone (/equivalents)

Grade 3 diarrhoea or colitis	Withhold	Initiate corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone (/equivalents) Upon improvement, nivolumab may be resumed after corticosteroid taper
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	
Grade 4 diarrhoea or colitis	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2mg/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	Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab may be resumed after corticosteroid taper
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	Increase corticosteroid dose to 1 to 2mg/kg/day methylprednisolone (/equivalents)
Grade 3 or 4 transaminase or total bilirubin elevation	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone (/equivalents)
Immune-related nephritis and 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	Initiate corticosteroids at a dose of 0.5 to 1mg/kg/day methylprednisolone (/equivalents) Upon improvement, nivolumab may be resumed after corticosteroid taper
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	Increase corticosteroid dose to 1 to 2mg/kg/day methylprednisolone (/equivalents)
Grade 4 serum creatinine elevation	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2mg/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	Thyroid hormone replacement should be initiated as needed

Symptomatic hyperthyroidism	Withhold	Antithyroid medication should be initiated as needed Corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab 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	
Symptomatic Grade 2 adrenal insufficiency	Withhold	Physiologic corticosteroid replacement should be initiated as needed.
Severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency	Permanently discontinue	Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised
Symptomatic Grade 2 or 3 hypophysitis	Withhold	Hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2mg/kg/day methylprednisolone (/ equivalents) should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed.
Life-threatening (Grade 4) hypophysitis	Permanently discontinue	Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised
Symptomatic diabetes	Withhold	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	
Immune-related skin adverse reactions		
Grade 3 rash	Withhold	Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2mg/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, nivolumab 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, permanent discontinuation of nivolumab 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
Grade 4 rash	Permanently discontinue	
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, 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.		
Infusion reactions		
Mild or moderate infusion	Caution	May receive nivolumab with close monitoring and use of

reaction		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 should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of nivolumab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions.
- 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:
https://www.hpra.ie/img/uploaded/swedocuments/cf83916c-1f29-46e4-a9d5-11a0e6d150d3.pdf

REFERENCES:

1. Larkin J, Chiarion Sileni V et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma NEJM 2015;373:23-34.
2. Motzer Rj, Escudier B et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. NEJM 2015;373:1803-1813.
3. Younes A, Santoro A et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet 2016;17(9):1283-1294.
4. Ansell S, Armand P et al. Nivolumab in Patients (Pts) with Relapsed or Refractory Classical Hodgkin Lymphoma (R/R cHL): Clinical Outcomes from Extended Follow-up of a Phase 1 Study (CA209-039).Blood 2015;126 (23):583.
5. Ferris RL, Blumenschein G et al. Nivolumab for Recurrent Squamous Cell Carcinoma of the Head and Neck. NEJM 2016;375:1856-67.
6. Nivolumab (OPDIVO®) Summary of Product Characteristics EMA Last updated: 29/10/2021. Accessed November 2022. Available at https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf
7. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

8. Gutzmer, R. et al. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity. European Journal of Cancer; 2017, 75, 24–32. https://doi.org/10.1016/j.ejca.2016.12.038
9. Ruiz-Bañobre J et al. Development of psoriatic arthritis during nivolumab therapy for metastatic non-small cell lung cancer, clinical outcome analysis and review of the literature. Lung Cancer 2017;108:217–21. doi:10.1016/j.lungcan.2017.04.007
10. McCullar B, Alloway T, Martin M. Durable complete response to nivolumab in a patient with HIV and metastatic non-small cell lung cancer. J Thorac Dis. 2017;9(6):E540–E542. doi:10.21037/jtd.2017.05.32
11. Husnain M, Park W, Ramos JC, et al. Complete response to ipilimumab and nivolumab therapy in a patient with extensive extrapulmonary high-grade small cell carcinoma of the pancreas and HIV infection. J Immunother Cancer. 2018;6(1):66. Published 2018 Jul 9. doi:10.1186/s40425-018-0379-x
12. Borghaei et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer, N Engl J Med 2015; 373:1627-1639.
13. Zhao, Shen et al. Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumour types. Annals of Oncology, Volume 31, Issue 2, 2020, Pages 302-309

Version	Date	Amendment	Approved By
1	21/05/18		Prof. G. Gullo, Dr. D. O'Mahony, Dr. R Bambury, Dr. L Bacon, Dr E Hanrahan
2	5/02/2019	Updated thyroid function testing	Prof Maccon Keane
3	24/04/2019	Inclusion of caution for use in patients with a clinically significant history of auto-immune disease	Dr Deirdre O'Mahony Dr. S. Cuffe. Dr E Hanrahan
4	09/10/2019	Updated adverse effects/regimen specific complications section as per SmPC update regarding CMV infection/reactivation	Prof Maccon Keane
5	06/11/2019	Inclusion of adjuvant melanoma indication	Prof Maccon Keane
6	13/03/2020	Inclusion of SCC of head and neck, NSCLC and classical Hodgkin lymphoma indications.	Prof Maccon Keane
7	23/09/2020	Updated eligibility criteria for adjuvant melanoma indication	Prof Maccon Keane
8	01/02/2021	Updated reimbursement status	Prof Maccon Keane
9	12/10/2022	Reviewed. Updated dose modifications section	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] The administration of nivolumab 480mg once every 28 days 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.