# Nivolumab Monotherapy 240mg-14 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 | HSE approved reimbursement status* |
|---|---|---|---|
| As monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. | C43 | 00483a | ODMS 09/10/2017 |
| As monotherapy for the treatment of advanced renal cell carcinoma (RCC) after prior therapy in adults. | C64 | 00483b | ODMS 09/10/2017 |
| 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. | C81 | 00483c | ODMS 09/10/2017 |
| As monotherapy for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy. | C76 | 00483d | ODMS 01/05/2018 |
| As monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. | C34 | 00483e | ODMS 03/09/2018 |
| As monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. | C43 | 00483f | ODMS 01/02/2021 |
| As monotherapy for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction (GEJ) cancer who have residual pathologic disease following prior neo-adjuvant chemo-radiotherapy. | C15/C16 | 00483g | ODMS 01/09/2023 |
| As monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥1%, who are at high risk of recurrence after undergoing radical resection of MIUC, providing patients are unsuitable for adjuvant treatment with platinum based chemotherapy. | C67 | 00483h | ODMS 01/12/2024 |

* This is for post 2012 indications only.

## 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.*

For adjuvant melanoma and muscle invasive urothelial carcinoma (MIUC), nivolumab is administered once every 14 days for the maximum treatment duration of **12 months (26 cycles).**

For adjuvant oesophageal or gastro-oesophageal junction (GEJ) cancer, nivolumab is administered at a dose of 240mg once every 14 days or 480mg once every 28 days for the first 16 weeks, followed by nivolumab 480mg every 28 days, beginning at week 17 for a **total duration of 12 months.** Please refer to NCCP Regimen 00484 - Nivolumab Monotherapy 480mg-28 days.

For all other indications nivolumab is administered once every 14 days until disease progression or unacceptable toxicity develops.

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 melanoma, RCC, oesophageal cancer, GEJ cancer or MIUC (adjuvant treatment) patients need to be switched from the 240mg every 2 weeks schedule to the 480mg every 4 weeks schedule (See NCCP Regimen 00484 - Nivolumab Monotherapy 480mg-28 days), the first 480mg dose should be administered two weeks after the last 240mg dose.

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

| 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 | Ongoing every 14 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. | | | | |

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

## ELIGIBILITY:

- Indications as above
- ECOG status
    - **Advanced melanoma** and **RCC**: 0-2
    - **cHL**: 0-1
    - **Head and Neck**: 0-1
    - **NSCLC**: 0-1
    - **Adjuvant melanoma**: 0-1
    - **Adjuvant oesophageal / GEJ:** 0-1
    - **Adjuvant MIUC:** 0-1
- 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
- **Adjuvant oesophageal / GEJ:**
  - Stage II or Stage III carcinoma of the oesophagus or GEJ and histologically confirmed predominant adenocarcinoma or squamous cell carcinoma
  - Have completed neo-adjuvant platinum-based chemo-radiotherapy followed by surgery (nivolumab should commence within 16 weeks post-surgery)
- **Adjuvant MIUC:**
  - Radical surgical resection within 4 months of the start date for adjuvant nivolumab therapy
  - MIUC at high risk of recurrence, as defined by either:
    a. pathological stage pT3-pT4a or pT0/x-pT4a/N+ for patients not eligible/declined adjuvant cisplatin-based chemotherapy or
    b. pathological stage pT2-pT4a or pT0/xpT4a/N+ for patients who received neoadjuvant cisplatin
  - Confirmation of PD-L1 expression on ≥1% of tumour cells as demonstrated by a validated test method on the tumour tissue
  - Disease free status as determined by imaging within 4 weeks of expected date of start date for adjuvant nivolumab therapy

## CAUTION:

Use with caution in:

- Patients with clinically significant autoimmune disease
- 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)
- Any active clinically significant infection requiring therapy

## EXCLUSIONS:

- Hypersensitivity to nivolumab or any of the excipients
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is Available on the NCCP website
- Symptomatic interstitial lung disease
- **Head and neck:**
  - Patients with carcinoma of the nasopharynx or salivary gland as primary tumour site.
- **Adjuvant melanoma:**
  - Uveal melanoma
- **MIUC:**
  - Partial cystectomy or partial nephrectomy
  - Adjuvant systemic or radiation therapy for MIUC following radical surgery

## 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
- Blood 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
- **MIUC:** PD-L1 testing with the DAKO autostainer using the 28-8 Pharm DX antibody on the request of a Consultant Medical Oncologist or following a tumour conference recommendation where there is an intention to treat with nivolumab in line with this licensed indication

**Regular tests:**

- FBC, renal, liver profile and blood glucose prior to each cycle
- TFTs once a month and as indicated based on clinical evaluation

**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.

**NSCLC**

- Patients should be assessed for progression prior to commencing their 8$^{th}$ 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<br><br>Grade 3 or 4 pneumonitis | Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete<br><br>Permanently discontinue treatment |
| **Immune-related colitis** | Grade 2 diarrhoea or colitis<br><br>Grade 3 diarrhoea or colitis<br><br>Grade 4 diarrhoea or colitis | Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete<br><br>Withhold dose(s) until symptoms resolve and management with corticosteroids is complete<br><br>Permanently discontinue treatment |
| **Immune-related hepatitis** | Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin<br><br>Grade 3 or 4 elevation in AST, ALT, or total bilirubin | Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete<br><br>Permanently discontinue treatment |
| **Immune-related nephritis and renal dysfunction** | Grade 2 or 3 creatinine elevation<br><br>Grade 4 creatinine elevation | Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete<br><br>Permanently discontinue treatment |
| **Immune-related endocrinopathies** | Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis,<br>Grade 2 adrenal insufficiency<br>Grade 3 diabetes<br><br>Grade 4 hypothyroidism<br>Grade 4 hyperthyroidism<br>Grade 4 hypophysitis<br>Grade 3 or 4 adrenal insufficiency<br>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<br><br>Permanently discontinue treatment |

| | | |
|---|---|---|
| **Immune-related skin adverse reactions** | Grade 3 rash<br><br>Grade 4 rash<br><br>Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) | Withhold dose(s) until symptoms resolve and management with corticosteroids is complete<br><br>Permanently discontinue treatment<br><br>Permanently discontinue treatment |
| **Immune-related myocarditis** | Grade 2 myocarditis<br><br>Grade 3 or 4 myocarditis | Withhold dose(s) until symptoms resolve and management with corticosteroids is complete<br><br>Permanently discontinue treatment |
| **Other immune-related adverse reactions** | Grade 3 (first occurrence)<br><br>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)<br><br>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** | | **Hepatic Impairment** | |
|---|---|---|---|
| No dose adjustment is needed | | **Mild/moderate** | No dose adjustment is needed |
| **Haemaodialysis** | No need for dose adjustment is expected | **Severe** | No need for dose adjustment is expected |
| Renal and hepatic dose modifications as per Giraud et al, 2023. | | | |

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

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

Minimal (**Refer to local policy).**

**For information:**

**Within NCIS regimens, antiemetics have been standardised by 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:** No specific recommendations

## 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:**
https://www.hpra.ie/img/uploaded/swedocuments/c02753be-51a5-44fd-8117-123823bdcff8.pdf

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| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 21/05/2018 | | Prof. G. Gullo, Dr. D. O'Mahony, Dr. R Bambury, Dr. L Bacon, Dr E Hanrahan, Prof. F Kelleher |
| 2 | 27/08/2018 | Inclusion of indication for second line treatment of non small cell lung cancer | Dr. D. O'Mahony, Dr. S. Cuffe. |
| 3 | 05/02/2019 | Updated thyroid function testing | Prof Maccon Keane |
| 4 | 24/04/2019 | Inclusion of caution for use in patients with clinically significant history of auto-immune disease | Dr Deirdre O'Mahony<br>Dr. S. Cuffe.<br>Dr E Hanrahan |
| 5 | 09/10/2019 | Updated adverse effects/regimen specific complications section as per SmPC update regarding CMV infection/reactivation | Prof Maccon Keane |
| 6 | 06/11/2019 | Inclusion of adjuvant melanoma indication. | 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 |
| 10 | 01/09/2023 | Addition of new indication for adjuvant oesophageal / gastro-oesophageal junction (GEJ) cancer (00483g) | Prof Maccon Keane |
| 11 | 25/11/2024 | Addition of new indication for MIUC. Updated Treatment, Eligibility, Exclusions and Baseline testing sections. Updated dose modifications in renal and hepatic impairment to align with Giraud et al. Updated Emetogenic potential, Adverse effects, Regimen specific complications and Drug interactions sections to align with NCCP standardisation. | Dr Dearbhaile O' Donnell |
| 11a | 28/11/2024 | Update to HSE reimbursement status of 00483h | NCCP |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.