# Pembrolizumab 400mg Monotherapy

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement Status |
|---|---|---|---|
| First-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR mutations or ALK translocations. | C34 | 00558a | ODMS 01/04/2018 |
| As monotherapy for the treatment of adults with unresectable or advanced melanoma | C43 | 00558b | ODMS June 2016 |
| For the treatment of ipilimumab-refractory patients with unresectable or advanced metastatic melanoma | C43 | 00558c | ODMS June 2016 |
| As monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who are transplant-ineligible and have failed brentuximab vedotin | C81 | 00558d | ODMS 12/11/2018 |
| As monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy | C67 | 00558e | ODMS 01/02/2021 |
| As monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy whose tumours express PD-L1 with a combined positive score (CPS) ≥10 | C67 | 00558f | ODMS 01/02/2021 |
| As monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection | C43 | 00558g | ODMS 01/5/2021 |

## 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.*

Pembrolizumab is administered once every 42 days (6 weeks) until disease progression or unacceptable toxicity develops. **For adjuvant melanoma therapy, the maximum treatment duration with pembrolizumab is 12 months.**

For patients who achieve a satisfactory objective response according to the treating clinician's judgement and who have no signs of progression at 24 months of treatment, the discontinuation of the treatment should be taken into consideration.

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

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

| Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|
| 1 | Pembrolizumab | 400mg | IV infusion | 100ml 0.9% NaCl over 30 minutes using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter. | Every 42 days (6 weeks) |
| Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml | | | | | |

## ELIGIBILITY:

- Indications as above
- ECOG Status 0-1
- Adequate haematological, hepatic and renal function
- **First line Non-Small Cell Lung Cancer**
    - Histologically or cytologically confirmed stage IV NSCLC with no sensitizing EGFR mutations or ALK translocations
    - Confirmation of PD-L1 tumour proportion score of 50% or greater by a validated test
    - No previous systemic therapy for metastatic disease
- **Melanoma**
    - Advanced : No more than one previous systemic treatment for advanced disease
    - Adjuvant: melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
- **Classical Hodgkin Lymphoma**
    - Consider the benefit of treatment with pembrolizumab versus the risk of possible GVHD in patients with a history of allogeneic HSCT
- **Urothelial carcinoma second- line:**
    - Histologically or cytologically confirmed urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra that shows predominantly transitional-cell features on histologic testing
    - ECOG 0-2
    - Have had progression or recurrence of urothelial cancer following receipt of a firstline platinum-containing regimen (CISplatin or CARBOplatin)
- **Urothelial carcinoma first-line**
    - Histologically- or cytologically-confirmed diagnosis of advanced/unresectable (inoperable) or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra (transitional cell and mixed transitional/non-transitional cell histologies)
    - Ineligible for CISplatin therapy
    - ECOG 0-2
    - PD-L1 with a combined positive score (CPS) >10 as demonstrated by a validated assay method

## CAUTION:

Use with caution in patients with:

- History of serious autoimmune disease

## EXCLUSIONS:

- Hypersensitivity to pembrolizumab or any of the excipients.
- Has received prior therapy with an anti-PD-1 or anti-PD-L1 antibody
- Untreated brain 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)
- History of interstitial lung disease
- Any active clinically significant infection requiring therapy

## PRESCRIPTIVE AUTHORITY:

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

## TESTS:

**Baseline tests**:

- FBC, renal and liver profile
- Glucose
- Thyroid function tests.
- Virology Screen:Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- NSCLC and 1L urothelial cancer: PD-L1 expression using a validated test method

**Regular tests**:

- FBC, renal and liver profile prior to each cycle
- Glucose prior to each cycle
- Thyroid Function Tests every 3 to 6 weeks.

**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.
- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of pembrolizumab therapy and institution of systemic high-dose corticosteroid.
- Dose reduction is not recommended.
- Guidelines for withholding of doses or permanent discontinuation are described below in Table 1.

**Table 1: Guidelines for withholding or discontinuation of pembrolizumab**

| Immune-related adverse reaction | Discontinuation | Treatment Modification |
|---|---|---|
| **Pneumonitis**<br>Grade 2<br>Grade ≥ 3, or recurrent Grade 2 | <br><br>Permanently discontinue | <br>Withhold* |
| **Colitis**<br>Grade 2 or 3<br>Grade 4 or recurrent Grade 3 | <br><br>Permanently discontinue | <br>Withhold* |
| **Nephritis**<br>Grade 2 with creatinine > 1.5-3 x ULN<br>Grade ≥ 3 with creatinine > 3 x ULN | <br><br>Permanently discontinue | <br>Withhold* |
| **Endocrinopathies**<br>Grade 2 adrenal insufficiency and hypophysitis<br>Grades 3 or 4 adrenal insufficiency or Symptomatic hypophysitis | | <br>Withhold treatment until controlled by hormone replacement<br>Withhold* |

| | | |
|---|---|---|
| Type 1 diabetes associated with Grade > 3 hyperglycaemia (Glucose >250mg/dL or >13.9 mmol/L) or associated with ketoacidosis<br><br>Hyperthyroidism Grade ≥ 3 | | For patients with Grade ≥ 3 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed.Otherwise treatment should be discontinued.<br>Note: Hypothyroidism may be managed with replacement therapy without treatment interruption |
| **Hepatitis**<br>With AST or ALT > 3-5 x ULN or total bilirubin > 1.5-3 x ULN<br>With AST or ALT > 5 x ULN or total bilirubin > 3 x ULN<br>In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥50% and lasts ≥1 week | <br><br>Permanently discontinue<br><br>Permanently discontinue | Withhold* |
| **Skin reactions**<br>Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)<br>Grade 4 or confirmed SJS or TEN | <br><br>Permanently discontinue | Withhold* |
| **Other immune-related adverse reactions**<br>Based on severity and type of reaction (Grade 2 or Grade 3)<br>Grade 3 or 4 myocarditis<br>Grade 3 or 4 encephalitis<br>Grade 3 or 4 Guillain-Barre syndrome<br>Grade 4 or recurrent Grade 3 | <br><br>Permanently discontinue<br>Permanently discontinue<br>Permanently discontinue<br>Permanently discontinue | Withhold* |
| **Infusion related reactions**<br>Grade ≥ 3 | Permanently discontinue | |

NCI-CTCAE v 4.0 *Until adverse reactions recover to Grade 0-1

**Pembrolizumab should be permanently discontinued:**

- For Grade 4 toxicity except for endocrinopathies that are controlled with replacement therapy
- If corticosteroid dosing cannot be reduced to ≤10mg prednisolone or equivalent per day within 12 weeks
- It treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks from last dose of pembrolizumab.
- If any event occurs a second time at Grade ≥ 3 severity.

**Renal and Hepatic Impairment:**

**Table 2: Dose modification of pembrolizumab in renal and hepatic impairment**

| Renal Impairment | | Hepatic Impairment | |
|---|---|---|---|
| **Mild/Moderate** | No dose adjustment required | **Mild** | No dose adjustment required |
| **Severe** | Has not been studied | **Moderate/Severe** | Has not been studied |

## SUPPORTIVE CARE:

**EMETOGENIC POTENTIAL:** Minimal (**Refer to local policy).**

**PREMEDICATIONS:** Not usually required

**OTHER SUPPORTIVE CARE**: Not usually required

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Immune-mediated adverse reactions:** Most immune-related adverse reactions occurring during treatment with pembrolizumab are reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab.
  For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month.
  Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.
  Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.
  Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones
  Specific guidelines for management of Immune Mediated Adverse Events are available.
- **Infusion-related reactions:** Severe infusion-related reactions have been reported in patients receiving pembrolizumab. For severe infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued. Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

## DRUG INTERACTIONS:

- No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be

avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab 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

**HCP Guide**

https://www.hpra.ie/img/uploaded/swedocuments/FAQs-2204092-30042018155540-636607005460937500.pdf

**Patient Alert Card**

https://www.hpra.ie/img/uploaded/swedocuments/Patient_Alert_Card_-2204092-30042018155421-636607004747656250.pdf

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| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 10/04/2019 | | Dr Deirdre O'Mahony<br>Prof Michaela Higgins |
| 2 | 10/07/2019 | Update of indication for 00558b | Prof Maccon Keane |
| 3 | 21/08/2019 | Addition of first line and second line indications for urothelial cancer | Prof Maccon Keane |
| 4 | 23/9/2020 | Updated management of adverse events in line with SmPC update.<br>Addition of adjuvant melanoma indication. | Prof Maccon Keane |
| 5 | 01/02/2021 | Updated reimbursement status | Prof Maccon Keane |
| 6 | 30/4/2021 | Updated indication for 00558g<br>Updated reimbursement status | Prof Maccon Keane |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.