

Pembrolizumab 200mg Monotherapy

This regimen supersedes NCCP Regimen 00347 Pembrolizumab 2mg/kg Monotherapy as of September 2018 due to a change in the licensed dosing posology.

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 $\geq 50\%$ tumour proportion score (TPS) with no EGFR mutations or ALK translocations.	C34	00455a	ODMS 01/04/2018
As monotherapy for the treatment of adults with unresectable or advanced melanoma	C43	00455b	ODMS June 2016
For the treatment of ipilimumab-refractory patients with unresectable or advanced metastatic melanoma	C43	00455c	ODMS June 2016
As monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy	C67	00455e	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	00455f	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	00455g	ODMS 01/05/2021
As monotherapy for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1	C76	00455h	ODMS 20/12/2021
As monotherapy for the treatment of adult patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.	C81	00455i	ODMS 01/02/2022

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 patient's individual clinical circumstances.

Pembrolizumab is administered once every 21 days 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.

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Tumour Group: Lung/Skin Melanoma/Lymphoma/Genitourinary/Head and Neck NCCP Regimen Code: 00455	ISMO Contributor: Prof Michaela Higgins, Dr Giuseppe Gullo, Dr Deirdre O'Mahony, Prof Maccon Keane, Dr Cliona Grant	Page 1 of 8
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Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Pembrolizumab	200mg	IV infusion	100ml 0.9% NaCl over 30 minutes	Every 21 days
Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml.					
Administer using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.					

ELIGIBILITY:

- Indications as above
- 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
 - ECOG Status 0-1
 - 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
 - ECOG Status 0-1
- **Classical Hodgkin Lymphoma**
 - Consider the benefit of treatment with pembrolizumab versus the risk of possible GVHD in patients with a history of allogeneic HSCT
 - ECOG Status 0-1
- **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 first line 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 valid assay method
- **Head and neck squamous cell carcinoma (HNSCC)**
 - Histologically or cytologically-confirmed recurrent or metastatic head and neck squamous cell carcinoma considered incurable by local therapies
 - Primary HNSCC tumour excluding cancers of the nasopharynx
 - ECOG 0-2

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- PD-L1 with a combined positive score (CPS) ≥ 1 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 $>10\text{mg}$ prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids)
- History of interstitial lung disease
- Any active clinically significant infection requiring therapy
- HNSCC: Progressive disease within six months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC

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, 1L urothelial cancer and HNSCC : PD-L1 expression using a validated test method

Regular tests:

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

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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: Recommended treatment modifications for pembrolizumab

Immune-related adverse reactions	Severity (NCI-CTCAE v.4 grading)	Treatment modification
Pneumonitis	Grade 2	Withhold*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis	Withhold*
	Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis	For patients with Grade 3 or Grade 4 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.
	Hypothyroidism Grade ≥ 3	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	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	
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue

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Other immune-related adverse reactions**	Based on severity and type of reaction (grade 2 or Grade 3)	Withhold*
	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome Grade 4 or recurrent Grade 3	Permanently discontinue
Infusion-related reactions	Grade 3 or 4	Permanently discontinue

* Until adverse reactions recover to Grade 0-1. If treatment related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of pembrolizumab or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, pembrolizumab should be permanently discontinued

**Pembrolizumab should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-related adverse reactions, unless otherwise specified in Table 1

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,

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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

Patient Guide

<https://www.hpra.ie/img/uploaded/swedocuments/896369cd-ec45-4e3a-978f-bacea851002e.pdf>

Patient Alert Card

<https://www.hpra.ie/img/uploaded/swedocuments/874908fb-698e-472d-91d5-dc3a1f14a8f7.pdf>

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Version	Date	Amendment	Approved By
1	21/03/2018		Prof Michaela Higgins
2	04/09/2018	Change in licensed dosing posology for melanoma. Standardisation of treatment table to 100ml NaCl 0.9%. Clarification on the use of systemic steroids in exclusion criteria	Prof Michaela Higgins Dr Giuseppe Gullo
3	08/11/2018	Inclusion of indication for Hodgkin Lymphoma. Updated treatment section and inclusion /exclusion criteria	Dr Deirdre O'Mahony
4	09/04/2019	Inclusion of caution for use in patients with history of serious auto-immune disease	Dr Deirdre O'Mahony Prof Michaela Higgins
5	10/07/2019	Update of indication for 00455b	Prof Maccon Keane
6	21/08/2019	Addition of first line and second line indications for urothelial cancer	Prof Maccon Keane
7	23/9/2020	Updated management of adverse events in line with SmPC update. Addition of adjuvant melanoma indication.	Prof Maccon Keane
8	01/02/2021	Updated reimbursement status	Prof Maccon Keane
9	30/4/2021	Updated indication for 455g Updated reimbursement status	Prof Maccon Keane
10	09/09/2021	Reviewed. Amended Table 1 (symbols re nephritis and endocrinopathies). Updated company support resources.	Prof Maccon Keane
11	22/12/2021	Updated indication for 00455h Updated reimbursement status Updated table 1 in line with SmPC.	Dr Cliona Grant

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12	26/01/2022	Updated: deactivation of 00455d and inclusion of indication 00455i Updated reimbursement status	Prof Maccon Keane
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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