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	HSE approved 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	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
As monotherapy for the treatment of recurrent, or metastatic cervical cancer with disease progression on or after chemotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1[i]	C53	00455j	Reimbursement by exception[ii]
First-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) in adults.	C18	00455k	ODMS 01/04/2023
As monotherapy for the adjuvant treatment of adults with Stage IIB or IIC melanoma and who have undergone complete resection.	C43	00455l	ODMS 01/12/2024
For the adjuvant treatment of adult patients with renal cell carcinoma (RCC) at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.	C64	00455m	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.

Pembrolizumab is administered once every 21 days until disease progression or unacceptable toxicity develops.
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.

For adjuvant treatment of melanoma and renal cell carcinoma (RCC), the maximum treatment duration with pembrolizumab is 12 months.

- Please note, for patients with IIIB melanoma who are eligible for treatment in the adjuvant setting[iii]: At physicians' discretion, 3 cycles of neo-adjuvant pembrolizumab can be administered, followed by 15 cycles post operatively

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	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.					

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

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
        - ECOG Status 0-1
    - Adjuvant Stage III:
        - Melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
        - ECOG Status 0-1

- Adjuvant Stage IIB/IIC:
  - Confirmed new diagnosis of Stage IIB or IIC cutaneous melanoma per American Joint Committee (AJCC) on Cancer 8th edition guidelines
  - Adjuvant pembrolizumab should start within 12 weeks of surgery
  - 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
  - PD-L1 with a combined positive score (CPS) ≥1 as demonstrated by a validated assay method
- **Cervical:**
  - ECOG 0-2
  - PD-L1 with a combined positive score (CPS) ≥1 as demonstrated by a validated test method
- **Metastatic colorectal cancer:**
  - ECOG 0-2
  - Histologically confirmed dMMR/MSI-high CRC as demonstrated by a validated test method
- **Renal cell carcinoma:**
  - Histologically confirmed diagnosis of clear cell RCC
  - ECOG 0-2
  - Treatment should start within 12 weeks of surgery

CAUTION:

- History of serious autoimmune disease
- 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
- Untreated brain metastases

EXCLUSIONS:

- Hypersensitivity to pembrolizumab 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
- History of interstitial lung disease
- 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
- Blood glucose
- Thyroid function tests
- Virology Screen: Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- NSCLC, 1L urothelial cancer, HNSCC, cervical cancer : PD-L1 expression using a validated test method

Regular tests:

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

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 Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold* 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	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

Other immune-related adverse reactions**	Based on severity and type of reaction (grade 2 or Grade 3)	Withhold*
	Grade 3 or4 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 ≤ 10mg 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**	
No dose adjustment is needed		**Mild**	No dose adjustment is needed
Haemodialysis	No need for dose adjustment is expected	**Moderate/Severe**	No need for dose adjustment is expected
Renal and hepatic recommendations: Giraud et al, 2023			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer 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:

- Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab.

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics(SmPC) for full 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 Guide
https://www.hpra.ie/img/uploaded/swedocuments/896369cd-ec45-4e3a-978f-bacea851002e.pdf
Patient Card
https://www.hpra.ie/img/uploaded/swedocuments/094590ae-1f3d-4b15-b76e-3b16bd642782.pdf

REFERENCES:

1. Bellmunt, J et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017; 376:1015-26.
2. Balar, A et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol 2017; 18: 1483–92
3. Reck M, Delvys R-A et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-1833.
4. Robert C, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015; 372:2521-2532.
5. Ribas A, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncology 2015; 16 ;(8)908-918.
6. Robert C, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial**.** Lancet Oncol 2014; 384:1109-17.
7. Chen R et al. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. J Clin Oncol 2017;35:2125-2133
8. Gutzmer, R. et al. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and pre-existing autoimmunity or ipilimumab-triggered autoimmunity. European Journal of Cancer; 2017, 75, 24–32. https://doi.org/10.1016/j.ejca.2016.12.038
9. Eggermont, A. et al. 2018. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med 378(19):1789-1801.
10. Burtness B, et al Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet; Available from: http://www.ncbi.nlm.nih.gov/pubmed/31679945

11. Marabelle A, et al. Efficacy of Pembrolizumab in Patients with Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results from the Phase II KEYNOTE-158 Study. J Clin Oncol 2020;38(1):1-10.
12. Andre T, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med 2020; 383:2207-2218.
13. Patel SP, et al. Neoadjuvant-adjuvant or Adjuvant Only Pembrolizumab in Advanced Melanoma. N Engl J Med 2023: 388: 813-823.
14. Luke J et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double blind, phase 3 trial. Lancet 2022 Apr 30;399(10336):1718-1729
15. Luke JJ, Ascierto PA, Khattak MA, et al. Pembrolizumab Versus Placebo as Adjuvant Therapy in Resected Stage IIB or IIC Melanoma: Final Analysis of Distant Metastasis-Free Survival in the Phase III KEYNOTE-716 Study. *J Clin Oncol*. 2024;42(14):1619-1624.
16. Choueiri TK et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N Engl J Med 2021;385:683-694
17. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
18. Pembrolizumab (Keytruda®) Summary of Product Characteristics. Last updated: 14/07/2021. Accessed Aug 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

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	23/09/2020	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	30/04/2021	Updated indication for 455g	Prof Maccon Keane

		Updated reimbursement status	
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
12	26/01/2022	Updated: deactivation of 00455d and inclusion of indication 00455i. Updated reimbursement status.	Prof Maccon Keane
13	01/04/2023	Addition of cervical and mCRC indications. Updated treatment section to include option for neoadjuvant administration schedule in melanoma.	Prof Maccon Keane, Prof Fergal Kelleher
14	13/08/2024	New indication added (00455l). Exclusions section updated with regard to previous PD-1/PD-L1 treatment. Renal and hepatic dose modifications aligned to Giraud et al 2023 recommendations. Regimen updated as per NCCP standardisation.	Prof Fergal Kelleher
15	12/09/2024	Adjuvant RCC indication added. Cautions and exclusions sections amended.	Prof Maccon Keane
15a	29/11/2024	HSE Reimbursement status updated of indications 00455l and 00455m.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of pembrolizumab in Ireland. Patients 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" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

[ii] Contact oncologydrugs@cancercontrol.ie for clarification

[iii] This is an unlicensed dosing posology for the use of pembrolizumab in Ireland. Patients 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" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.