Pembrolizumab 2mg/kg Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
First line monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults	C43	00347a	ODMS
For the treatment of ipilimumab-refractory patients with unresectable or advanced metastatic melanoma	C43	00347b	ODMS

**If the reimbursement status[1] is not defined, the indication has yet to be assessed through the formal HSE reimbursement process.*

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 up to a maximum of 24 months.

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. Patients with confirmed complete response who have received pembrolizumab at 2mg/Kg every 3 weeks for at least 6 months could discontinue therapy at the treating physician's decision after receiving at least two doses beyond the determination of complete response.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Pembrolizumab	2mg/kg	IV infusion	100ml 0.9% NaCl over 30minutes using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.	Every 21 days for up to 24 months
Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml					

ELIGIBILTY:

- Indications as above
- ECOG status 0-1
- Adequate haematological, hepatic and renal function
- No more than one previous systemic treatment for advanced disease

EXCLUSIONS:

- Hypersensitivity to pembrolizumab or any of the excipients.
- Any medical condition that requires systemic corticosteroids or other immunosuppressive medication
- 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.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- Thyroid function tests.
- Virology Screen:Hepatitis B (HBsAg, HBcoreAb), C

Regular tests:

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

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 Grade 2 Grade ≥ 3, or recurrent Grade 2	 Permanently discontinue	 Withhold*
Colitis Grade 2 or 3 Grade 4 or recurrent Grade 3	 Permanently discontinue	 Withhold*
Nephritis Grade 2 with creatinine > 1.5-3 x ULN Grade ≥ 3 with creatinine > 3 x ULN	 Permanently discontinue	 Withhold*
Endocrinopathies Symptomatic hypophysitis with Grade > 3 hyperglycaemia (Glucose >250mg/dL or >13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3		Withhold* 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. Note: Hypothyroidism may be managed with replacement therapy without treatment interruption
Hepatitis With AST or ALT > 3-5 x ULN or total bilirubin > 1.5-3 x ULN With AST or ALT > 5 x ULN or total bilirubin > 3 x ULN 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	 Permanently discontinue Permanently discontinue	 Withhold*
Skin reactions Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) Grade 4 or confirmed SJS or TEN	 Permanently discontinue	 Withhold*
Other immune-related adverse reactions Based on severity and type of reaction (Grade 2 or Grade 3) Grade 3 or 4 myocarditis Grade 3 or 4 encephalitiis Grade 3 or 4 Guillain- Barre syndrome Grade 4 or recurrent Grade 3	 Permanently discontinue Permanently discontinue Permanently discontinue Permanently discontinue	 Withhold*
Infusion related reactions 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.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **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.

ATC CODE:

Pembrolizumab – L01XC18

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

HCP Guide

http://www.hpra.ie/img/uploaded/swedocuments/KEYTRUDA_HCP_FAQ_Oct17-2200051-23112017164639-636470524540156250.pdf

Patient Alert Card

http://www.hpra.ie/img/uploaded/swedocuments/Keytruda_Patient_Alert_Card_Oct17-2200051-23112017164740-636470524920000000.pdf

REFERENCES:

1. Robert C, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372:2521-2532.
2. 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.
3. 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.
4. KEYTRUDA® Summary of Product Characteristics Accessed May 2018 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf

Version	Date	Amendment	Approved By
1	08/06/2016		Dr Giuseppe Gullo
2	30/05/2018	Updated title, applied new NCCP regimen template, standardization of treatment table, updated guidelines for withholding or discontinuing pembrolizumab as per SmPC, updated emetogenic status	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/