Pembrolizumab, PEMEtrexed and CISplatin Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Pembrolizumab is indicated in combination with PEMEtrexed and CISplatin for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumors have no EGFR or ALK positive mutations	C34	00569a	Pembrolizumab: ODMS 01/02/2021 PEMEtrexed: Hospital CISplatin: Hospital

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.

Treatment is administered every 21 days for up to 4 cycles in combination with CISplatin and then followed by maintenance therapy of pembrolizumab and PEMEtrexed every 21 days or until disease progression or unacceptable toxicity develops.

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 chemotherapy is administered.

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab[1]	200mg	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
2	1	PEMEtrexed[2]	500mg/m^2	IV infusion	100ml 0.9% NaCl over 10min	Every 21 days
3	1	CISplatin[3]	75 mg/m^2	IV infusion	1000ml 0.9% NaCl over 2 hours to start 30 min after completion of PEMEtrexed	Every 21 days **cycles 1-4**
		Folic Acid or multivitamin containing 350-1000 micrograms folic acid	350-1000 micrograms[4]	PO		
		Vitamin B_{12} (hydroxycobolamin)	1,000 micrograms[5]	IM		

[1]Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml

[2]PEMEtrexed is physically incompatible with diluents containing calcium

[3]**Pre and post hydration** therapy required for CISplatin
See local hospital policy recommendations.
Suggested **prehydration** for CISplatin therapy:

- Administer 1000ml NaCl 0.9% over 1 hour
- Administer CISplatin as described above

Post hydration:

- Administer 1000ml NaCl 0.9% with 10mmol magnesium sulphate ($MgSO_4$) and 20mmol potassium chloride (KCl) over 2 hours

Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (4, 5).

[4]At least five doses of folic acid must be taken during the seven days preceding the first dose of PEMEtrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of PEMEtrexed.

[5] Must be given in the week preceding the first dose of PEMEtrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as PEMEtrexed.

ELIGIBILITY:

- Indications as above
- Histologically or cytologically confirmed stage IV non-squamous NSCLC with no sensitizing EGFR mutations or ALK translocations
- ECOG Status 0-1
- Adequate haematological, hepatic and renal function

CAUTION:

- Use with caution in patients with history of serious autoimmune disease

EXCLUSIONS:

- Hypersensitivity to pembrolizumab, PEMEtrexed, CISplatin or any of the excipients
- Has received prior therapy with an anti-PD-1 or anti-PD-L1 antibody
- Active or unstable CNS metastases
- Creatinine clearance < 45ml/min
- 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 or pneumonitis
- Any active clinically significant infection requiring therapy
- Pre existing neuropathies ≥ grade 2
- Significant hearing impairment/tinnitus

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) and Hepatitis C
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Glucose prior to each cycle
- Thyroid function tests every 3 to 6 weeks.
- Ototoxicity and sensory neural damage should be assessed clinically prior to each cycle of platinum based chemotherapy in particular CISplatin.

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:

Pembrolizumab dose modifications:

- Dose reduction is not recommended for pembrolizumab
- 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. (See table 5)
- Any dose modification should be discussed with a Consultant.

PEMEtrexed and CISplatin dose modifications:

- Treatment may be delayed to allow sufficient time for recovery.
- Treatment should be discontinued after 2 dose reductions if toxicity >grade 3 occurs
- Any dose modification should be discussed with a Consultant.

Haematological:

Table 1: Recommended dose modification of PEMEtrexed and CISplatin in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1.5	or	≥100	100%
1-1.5	or	75-99	Consider delay until recovery
0.5-0.9	or	50-74	Delay until recovery
<0.5	or	<50	Delay treatment until recovery and consider reducing PEMEtrexed and CISplatin by 25% for subsequent cycles
<1.0 and fever >38◦C			
Any	And	<50 with bleeding	Delay treatment until recovery and consider reducing PEMEtrexed and CISplatin by 50% for subsequent cycles
Consider discontinuing therapy if a patient qualifies for a third dose reduction or a cycle is delayed by more than 21 days.			
Dose reductions should be maintained for subsequent cycles			

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment*

Drug	Renal Impairment		Hepatic Impairment			
Pembrolizumab	**Mild/Moderate**	No dose adjustment required	**Mild**	No dose adjustment required		
	Severe	Has not been studied	**Moderate/Severe**	Has not been studied		
CISplatin	**CrCl (ml/min)**	**Dose**	No dose reduction necessary			
	≥60	100%				
	45-59	75%				
	<45	Consider CARBOplatin				
PEMEtrexed	**CrCl (ml/min)**	**Dose**	**Bilirubin**		**Aminotransferases**	
	≥45	100%	>1.5 x ULN	and /or or	> 3 x ULN (hepatic metastases absent) > 5 x ULN (presence of hepatic metastases	Not recommended
	<45	Not recommended	**Clinical decision**			

***See table 3 for management of pembrolizumab in treatment-related hepatitis and table 5 for management of PEMEtrexed and CISplatin in treatment-related hepatotoxicity**

Management of immune-related adverse events:

Table 3: 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	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 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 3.

Management of adverse events:

Table 4: Dose Modification of PEMEtrexed and CISplatin for Adverse Events

Adverse reactions*	Recommended dose modification
Diarrhoea Grade ≥ 3	Withhold treatment until resolution to less than or equal to patient's pre-therapy value Resume at 75% of previous dose for both PEMEtrexed and CISplatin
Mucositis Grade ≥3	Withhold treatment until resolution to less than or equal to patient's pre-therapy value Resume at 50% of previous dose for PEMEtrexed and at 100% of previous dose for CISplatin
Neurotoxicity Grade 2 Grade ≥3	 Withhold treatment until resolution to less than or equal to patient's pre-therapy value Resume at resume at 50% of previous dose for CISplatin Withhold treatment until resolution to less than or equal to patient's pre-therapy value Resume at resume at 75% of previous dose for PEMEtrexed and discontinue CISplatin
Other Grade ≥3	Withhold treatment until resolution to less than or equal to patient's pre-therapy value Resume at resume at 75% of previous dose PEMEtrexed and CISplatin
Grade ≥3 toxicity after 2 dose reductions	Discontinue treatment

*CTCAE V4;

Treatment related hepatotoxicity

Table 5: Recommended dose modification for PEMEtrexed and CISplatin for treatment related hepatotoxicity

Bilirubin		ALT,	Dose Modification
> 3.0 x ULN	**or**	> 5 x	Withhold treatment until resolution to less than or equal to patient's pre-therapy value Resume at 75% of previous dose for both PEMEtrexed and CISplatin
>10 x ULN	or	>20 x	Discontinue

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Pembrolizumab: Minimal (**Refer to local policy)**
PEMEtrexed: Low (**Refer to local policy)**
CISplatin: High (**Refer to local policy)**

PREMEDICATIONS:

- PEMEtrexed should be pre-medicated with corticosteroid the day prior to, on the day of, and the day after PEMEtrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day
- Intramuscular injection of vitamin B_{12} (hydroxycobolamin) (1,000 micrograms) in the week preceding the first dose of PEMEtrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as PEMEtrexed.
- At least five doses of folic acid must be given during the seven days preceding the first dose of PEMEtrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of PEMEtrexed.

OTHER SUPPORTIVE CARE: None 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. **Pembrolizumab is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**

Pembrolizumab

- In view of the serious and potentially life-threatening side effects of pembrolizumab, it is mandatory that patients be carefully assessed prior to commencing on treatment. Efficacy and safety data from patient's ≥ 75 years are limited. For patients ≥ 75 years, pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis
  Patients have to be monitored regularly for hepatic, pulmonary, gastrointestinal toxicity and for endocrinopathies while on treatment
- **Immune-related adverse reactions:** Most immune-related adverse reactions occurring during treatment with pembrolizumab were 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. Immune-related adverse reactions affecting more than one body system can occur simultaneously.
  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.
- **Immune-related pneumonitis**: Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis.
- **Immune-related colitis:** Colitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 colitis. The potential risk of gastrointestinal perforation should be taken into consideration
- **Immune-related hepatitis:** Hepatitis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day (for Grade 2 events) and 1-2 mg/kg/day (for Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, pembrolizumab should be withheld or discontinued.
- **Immune-related nephritis**: Nephritis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone

or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis.

- **Immune-related endocrinopathies:** Severe endocrinopathies, including hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with pembrolizumab treatment. Long-term hormone replacement therapy may be necessary in cases of immune-related endocrinopathies.
  Hypophysitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and other causes excluded. Corticosteroids to treat secondary adrenal insufficiency and other hormone replacement should be administered as clinically indicated, and pembrolizumab should be withheld for symptomatic hypophysitis until the event is controlled with hormone replacement. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed. Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.
  Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld in cases of Grade 3 hyperglycaemia until metabolic control is achieved. Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment; therefore, patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation of pembrolizumab may be considered, after corticosteroid taper, if needed. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.
- **Immune-related skin adverse reactions:** Immune-related severe skin reactions have been reported in patients receiving pembrolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld or permanently discontinued, and corticosteroids should be administered. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients receiving pembrolizumab). For signs or symptoms of SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued. Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune stimulatory anticancer agents.
- **Other immune-related adverse reactions:** The following additional clinically significant, immune-related adverse reactions have been reported in patients receiving pembrolizumab: uveitis, arthritis, myositis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis and encephalitis. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. 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.**
- **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.

PEMEtrexed

- **Myelosuppression:** Usually the dose limiting toxicity with PEMEtrexed. PEMEtrexed should not be given to patients until absolute neutrophil count (ANC) returns to $1.5x10^9$/L and platelet count returns to $100x10^9$ /L. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematologic toxicity seen from the previous cycle.
- **Skin reactions:** Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions
- **Cardiotoxicity:** Serious cardiovascular events including MI and cerebrovascular events have been uncommonly reported usually when PEMEtrexed is given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.

CISplatin

- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Serious renal events, including acute renal failure, have been reported with PEMEtrexed alone or in association with other chemotherapeutic agents. Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with PEMEtrexed alone or with other chemotherapeutic agents. Most of these events resolved after PEMEtrexed withdrawal.
- **Neurotoxicity and Ototoxicity**: Ototoxicity and sensory neural damage should be assessed by history prior to each cycle.

DRUG INTERACTIONS:

- The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the 8harmacodynamics 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 informationIn patients with normal renal function (CrCl > 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and aspirin at higher dose (> 1.3 g daily) may decrease PEMEtrexed elimination and, consequently, increase the occurrence of PEMEtrexed adverse events.
- The concomitant administration of PEMEtrexed with NSAIDs or aspirin at higher dose should be avoided for 2 days before, on the day of, and 2 days following PEMEtrexed administration on patients with mild to moderate renal insufficiency (CrCl from 45 to 79 ml/min).
- In patients with mild to moderate renal insufficiency eligible for PEMEtrexed therapy, NSAIDs with long elimination half-lives should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following PEMEtrexed administration.
- Nephrotoxic drugs (e.g. loop diuretics and aminoglycosides) may decrease the clearance of PEMEtrexed.

- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use of CISplatin with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). When necessary perform regular audiometric testing
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Pembrolizumab - L01XC18
PEMEtrexed - L01BA04
CISplatin - L01XA01

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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3. Alimta ® (PEMEtrexed) Summary of Patient Characteristics – November 2019 Available at https://www.ema.europa.eu/en/documents/product-information/alimta-epar-product-information_en.pdf
4. CISplatin Summary of Patient Characteristics – November 2019 Available at http://www.hpra.ie/img/uploaded/swedocuments/Final%20approved%20SPC%20PA0822.199.001.pdf

Version	Date	Amendment	Approved By
1	22/11/2019		Dr Dearbhaile Collins
2	01/02/2021	Updated reimbursement status	Dr Dearbhaile Collins
3	24/06/2021	Updated CISplatin hydration protocol	Dr Dearbhaile Collins

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.