Nivolumab, ipilimumab, PEMEtrexed and CISplatin Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved Reimbursement Status*
First-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumours have no sensitising EGFR mutation or ALK translocation.	C34	00714a	Nivolumab, ipilimumab: ODMS 01/03/2022 PEMEtrexed: N/A CISplatin: N/A

*This applies to post 2012 indications

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.

Nivolumab, PEMEtrexed and CISplatin are administered on day 1 and 22; ipilimumab is administered on day 1. After completion of cycle 1 treatment is continued with nivolumab administered on day 1 and 22, ipilimumab on day 1 until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Each cycle is 42 days.

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

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Cycle 1

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,22	Nivolumab[1]	360mg	IV infusion	Infuse over 30 minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm[2].	Cycle 1 only
2	1	Ipilimumab[1,3]	1mg/kg	IV infusion Observe post infusion[3]	0.9% NaCl to a concentration between 1 and 4mg/mL over 30 minutes using a 0.2-1.2 µm low-protein binding in-line filter[4].	
3	1,22	PEMEtrexed	500mg/m^2	IV infusion	100mL 0.9% NaCl over 10 minutes[5]	
4	1,22	CISplatin	75mg/m^2	IV infusion	1000mL 0.9% NaCl over 60 minutes to start 30 minutes after completion of PEMEtrexed[6]	
		Folic Acid or multivitamin containing 3501000 micrograms folic acid	350-1000micrograms[7]	PO		

[1] Nivolumab or Ipilimumab **must not** be administered as an intravenous push or bolus injection.

[2] Nivolumab can be infused directly as a 10 mg/mL solution or can be diluted to as low as 1 mg/mL with NaCl 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection.

[3] Vital signs including temperature, pulse and BP should be taken every 30 mins for the duration of the infusion and 1 hour following completion of the infusion.

[4] The line should be flushed with 0.9% NaCl after the ipilimumab infusion has finished.

[5] PEMEtrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection.

[6] **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 10mmol magnesium sulphate (MgSO4) and 20mmol potassium chloride (KCl) in 1000 mL 0.9% NaCl over 2 hours.

Mannitol 10% may be used 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.

[7] 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.
See Premedications section for further treatment required.

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

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Cycle 2 onwards

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1,22	Nivolumab	360mg	IV infusion	Infuse over 30 minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm.	Every 42 days
1	Ipilimumab	1mg/kg	IV infusion Observe post infusion	0.9% NaCl to a concentration between 1 and 4mg/mL over 30 minutes using a 0.2-1.2 µm low-protein binding in-line filter.	Every 42 days

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

ELIGIBILITY:

- Indications as above
- Histologically confirmed Stage IV or recurrent NSCLC with no prior systemic anticancer therapy
- ECOG 0-1
- Adequate organ function
- Nivolumab and ipilimumab are not recommended during pregnancy and in women of childbearing potential not using effective contraception unless prescribing consultant deems clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab

CAUTION:

Use in caution in:

- Patients with clinically significant autoimmune disease
- 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
- Any active clinically significant infection requiring therapy
- Active or unstable CNS metastases

EXCLUSIONS:

- Hypersensitivity to nivolumab, ipilimumab, PEMEtrexed and CISplatin or to any of the excipients
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody Available on the NCCP website
- Creatinine clearance < 45mL/min
- Pre-existing neuropathies ≥ grade 2
- Significant hearing impairment/tinnitus
- Pregnancy or Breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

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TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- TFT
- Hepatitis B (HBV sAg) and Hepatitis C (HCV RNA)
- Serum cortisol (ideally a morning sample)
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC, renal and liver profile prior to treatment
- Blood glucose prior to each cycle
- TFTs 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:

Nivolumab and ipilimumab dose modifications:

- Dose escalations and reductions are not recommended for nivolumab and ipilimumab. Dosing delay or discontinuation may be required based on individual safety and tolerability
- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of nivolumab in combination with ipilimumab therapy and institution of systemic high-dose corticosteroid
- If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use. Nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy
- Nivolumab in combination with ipilimumab must be permanently discontinued for;
    - Any severe immune-related adverse reaction that recurs
    - Any life-threatening immune-related adverse reaction
    - Any grade 4 or recurrent grade 3 adverse reactions, persistent grade 2 or 3 adverse reactions despite management

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- When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or nivolumab monotherapy could be resumed based on the evaluation of the individual patient
- Guidelines for permanent discontinuation or withholding of doses are described in Table 1.
- Any dose modification should be discussed with a Consultant

Table 1: Dose Modification of nivolumab and ipilimumab for adverse events

Immune-related adverse reaction	Severity	Treatment Modification
Immune-related pneumonitis	Grade 2 pneumonitis Grade 3 or 4 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis Grade 3 diarrhoea or colitis Grade 4 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete Permanently discontinue treatment Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation Grade 4 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present Permanently discontinue treatment

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Immune-related skin adverse reactions	Grade 3 rash Grade 4 rash Steven-Johnsons syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete Permanently discontinue treatment Permanently discontinue treatment
Immune-related myocarditis	Grade 2 myocarditis Grade 3 or 4 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[b] Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence) Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10mg prednisoLONE or equivalent per day	Withhold dose(s) Permanently discontinue treatment
Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4). [b]The safety of re-initiating nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.		

Haematological:

PEMEtrexed and CISplatin dose modifications

- Any dose modification should be discussed with a Consultant
- After the treatment, growth factors may be used to assist recovery **(Refer to local policy)**

Table 2: Dose reduction levels for PEMEtrexed and CISplatin

	Starting Dose	First Dose reduction	Second Dose Reduction	Third Dose Reduction
PEMEtrexed	500mg/m^2	375mg/m^2	250mg/m^2	Discontinue
CISplatin	75mg/m^2	56mg/m^2	38mg/m^2	Discontinue

Table 3. Dose modification for haematological toxicity induced by PEMEtrexed and CISplatin

ANC x 10^9 /L	Comment	Platelets x 10^9 /L	Comment
≥ 1.5	100%	≥ 100	Continue
1.0 to < 1.5	Consult with team, if clinically well, continue treatment	75 - < 100	Consult with team, if clinically well treatment, consider continuation
0.5 to < 1.0	Delay until treatment recovery	50 - < 75	Delay until treatment recovery
< 0.5	Delay until treatment recovery and reduce by 25%	< 50	Delay until treatment recovery and reduce by 25%
Febrile neutropenia	Delay until treatment recovery and reduce by 25%	< 50 with bleeding	Delay until treatment recovery and reduce by 50%

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Renal and Hepatic Impairment:

Table 4: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Nivolumab	No dose adjustment is needed Haemodialysis: no need for dose adjustment is expected		**Mild-Moderate**	No dose adjustment is needed.
			Severe	No need for dose adjustment is expected
Ipilimumab	No dose adjustment is needed Haemodialysis: No need for dose adjustment is expected		No need for dose adjustment is expected	
PEMEtrexed	**CrCl (mL/min)**	**Dose**		
	≥45	No dose adjustment is needed.	**Mild and moderate**: No need for dose adjustment is expected	
	<45 and haemodialysis	Not recommended	**Severe:** Not recommended, based on the risk of PEMEtrexed induced liver dysfunction	
CISplatin	**CrCl (mL/min)**	**Dose**	No need for dose adjustment is expected	
	≥60	100%		
	50-59	75%		
	40-49	50%		
	<40	Not recommended		
	Haemodialysis	50% of the original dose may be considered		
Renal and hepatic dose modifications from Giraud et al 2023				

Management of adverse events:

Table 5: Dose Modification of PEMEtrexed and CISplatin for Adverse Events

Adverse effect	Recommended dose modification
Diarrhoea Grade ≥ 3 and any diarrhoea irrespective of grade requiring hospitalisation	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 or any recurrence of neurotoxicity	Withhold treatment until resolution to less than or equal to patient's pre-therapy value. Resume at 100% dose for PEMEtrexed and reduce CISplatin by 50% Discontinue
Other Grade ≥3	Withhold treatment until resolution to less than or equal to patient's

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	pre-therapy value. Resume at resume at 75% of previous dose PEMEtrexed and CISplatin
Grade ≥3 toxicity after 2 dose reductions	Consider discontinuation of both drugs. Discuss with consultant.
Allergic reactions: Grade 3 ≥	Clinician decision. Consider discontinuation of whichever drug caused the allergy.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting- Available on the NCCP website

Nivolumab: Minimal **(Refer to local policy)**.
Ipilimumab: Low **(Refer to local policy).**
PEMEtrexed: Low **(Refer to local policy).**
CISplatin: High (**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:

- A corticosteroid should be given 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
- Hydration pre and post CISplatin administration **(Reference local policy or see recommendations above)**

OTHER SUPPORTIVE CARE:

None usually required.

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ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details

REGIMEN SPECIFIC COMPLICATIONS:

Nivolumab and ipilimumab:

- **Immune and infusion related adverse reactions:** Please see Table 6 for dose modifications of nivolumab and ipilimumab in combination.

Table 6: Management of immune-related adverse reactions to nivolumab and ipilimumab

Adverse reaction	Withhold/ discontinue	Recommended action - 1st occurrence
Immune-related pneumonitis Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.		
Grade 2 (symptomatic) If worsening or no improvement occurs despite initiation of corticosteroids	Withhold Permanently discontinue	Initiate corticosteroids at a dose of 1 mg/kg/day methylPREDNISolone (/equivalents). Upon improvement, treatment may be resumed after corticosteroid taper Increase corticosteroid dose to 2 to 4 mg/kg/day methylPREDNISolone (/equivalents)
Grade 3 or 4	Permanently discontinue	Initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylPREDNISolone (/equivalents)
Immune-related colitis Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Infectious and disease-related aetiologies should be ruled out. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Consider if patient has persistent colitis despite appropriate colitis therapy		
Grade 2 diarrhoea or colitis If worsening or no improvement occurs despite initiation of corticosteroids	Withhold Permanently discontinue	Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylPREDNISolone (/equivalents) Upon improvement, treatment may be resumed after corticosteroid taper Increase corticosteroid dose to 1 to 2 mg/kg/day methylPREDNISolone (/equivalents)
Grade 3 diarrhoea or colitis	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone (/equivalents)
Grade 4 diarrhoea or colitis	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylPREDNISolone (/equivalents)
Immune-related hepatitis Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.		
Grade 2 transaminase or total	Withhold	Persistent elevations in these laboratory values should be

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bilirubin elevation If worsening or no improvement occurs despite initiation of corticosteroids	 Permanently discontinue	managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylPREDNISolone equivalents. Upon improvement, treatment may be resumed after corticosteroid taper. Increase corticosteroid dose to 1 to 2 mg/kg/day methylPREDNISolone (/equivalents)
Grade 3 or 4 transaminase or total bilirubin elevation	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylPREDNISolone (/equivalents)
Immune-related nephritis or renal dysfunction Patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.		
Grade 2 or 3 serum creatinine elevation If worsening or no improvement occurs despite initiation of corticosteroids	Withhold Permanently discontinue	Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylPREDNISolone (/equivalents). Upon improvement, treatment may be resumed after corticosteroid taper. Increase corticosteroid dose to 1 to 2 mg/kg/day methylPREDNISolone (/equivalents)
Grade 4 serum creatinine elevation	Permanently discontinue	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylPREDNISolone (/equivalents)
Immune-related endocrinopathies Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.		
Symptomatic hypothyroidism	Withhold	Thyroid hormone replacement should be initiated as needed.
Symptomatic hyperthyroidism	Withhold	Antithyroid medication should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylPREDNISolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised.
Life-threatening hyperthyroidism or hypothyroidism	Permanently discontinue	
Symptomatic Grade 2 adrenal insufficiency	Withhold	Physiologic corticosteroid replacement should be initiated as needed.
Severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency	Permanently discontinue	Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilized.
Symptomatic Grade 2 or 3 hypophysitis	Withhold	Hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylPREDNISolone (/ equivalents) should also be considered if acute inflammation of the pituitary gland is suspected. Upon

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		improvement, nivolumab may be resumed after corticosteroid taper, if needed.
Life-threatening (Grade 4) hypophysitis	Permanently discontinue	Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.
Symptomatic diabetes	Withhold	Insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised.
Life-threatening diabetes	Permanently discontinue	
Immune-related skin adverse reactions		
Grade 3 rash	Withhold	Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylPREDNISolone equivalents. Rare cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), some of them with fatal outcome have been observed. If symptoms or signs of SJS or TEN appear, treatment should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab in combination with ipilimumab, permanent discontinuation of treatment is recommended. Caution should be used when considering the use of treatment in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.
Grade 4 rash	Permanently discontinue	
Other immune-related adverse reactions For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, treatment should be withheld and corticosteroids administered. Upon improvement, treatment may be resumed after corticosteroid taper. Treatment must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction. Myotoxicity: ○ Cases of myotoxicity some with fatal outcome, have been reported with nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented. Based on the severity of myotoxicity, nivolumab in combination with ipilimumab should be withheld or discontinued, and appropriate treatment instituted. ○ Patients with cardiac or cardiopulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisoLONE 1 to 2 mg/kg/day or methylPREDNISolone 1 to 2 mg/kg/day). Once a diagnosis of myocarditis is established, nivolumab in combination with ipilimumab should be withheld or permanently discontinued (see Table 1).		
Infusion reactions		
Mild or moderate infusion reaction	Caution	May receive treatment with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.
Severe or life-threatening infusion reaction	Discontinue infusion	Administer appropriate medical therapy.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

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COMPANY SUPPORT RESOURCES/Useful Links:

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

Patient Alert Card:
Ipilumumab:
https://www.hpra.ie/img/uploaded/swedocuments/0781c3d7-ff8d-4cc7-9f0a-80cf9a10e59f.pdf

Nivolumab:
https://www.hpra.ie/docs/default-source/3rd-party-documents/educational-materials/1506ie1600061-03-ire-opdivo-patient-alert-card_final.pdf?sfvrsn=2

Patient Information Guide:
Ipilimumab:
https://www.hpra.ie/img/uploaded/swedocuments/2f064c72-ccef-492b-a068-bc72d8b522cf.pdf

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Version	Date	Amendment	Approved By
1	25/01/2022		Prof Maccon Keane
2	09/12/2024	Reviewed. Updated infusion time for CISplatin. Updated exclusions and cautions sections. Updated renal and hepatic dose modifications section to align with Giraud et al 2023. Updated adverse events, regimen specific complications and drug interactions sections in line with NCCP standardisation.	Prof Maccon Keane
3	13/05/2025	Updated wording of indication and eligibility – removed non-squamous	Prof Maccon Keane
4	04/09/2025	Updated wording in exclusions section regarding prior PD-L1 therapy.Updated Table 4**:** Dose Modification of PEMEtrexed and CISplatin for Adverse Events. Updated haematological dose modifications – removed nadir blood counts.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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