

Nivolumab, ipilimumab, PEMEtrexed and CISplatin Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
First-line treatment of metastatic non-squamous 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: 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.

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 the chemotherapy is administered.

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Cycle 1

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,2,2	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	1mg/kg	IV infusion Observe post infusion ³	0.9% sodium chloride to a concentration between 1 and 4mg/ml over 30 min using a 0.2-1.2 µm low-protein binding in-line filter ⁴ .	
3	1,2,2	PEMExred	500mg/m ²	IV infusion	100ml 0.9% NaCl over 10 min ⁵	
4	1,2,2	CISplatin	75mg/m ²	IV infusion	1000ml 0.9% NaCl over 2 hours to start 30 min after completion of PEMExred ⁶	
		Folic Acid or multivitamin containing 350-1000 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 sodium chloride 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 30mins for the duration of the infusion and 1 hour following completion of the infusion.

⁴ The line should be flushed with 0.9% sodium chloride after the ipilimumab infusion has finished.

⁵ PEMExred 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 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.

⁷ At least five doses of folic acid must be taken during the seven days preceding the first dose of PEMExred, and dosing must continue during the full course of therapy and for 21 days after the last dose of PEMExred.

See Premedications for further treatment required.

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Cycle 2 onwards

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,2,2	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
2	1	Ipilimumab	1mg/kg	IV infusion Observe post infusion	0.9% sodium chloride to a concentration between 1 and 4mg/ml over 30 min using a 0.2-1.2 µm low-protein binding in-line filter.	Every 42 days

ELIGIBILITY:

- Indications as above
- Histologically confirmed Stage IV or recurrent non-squamous 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

EXCLUSIONS:

- Hypersensitivity to nivolumab, ipilimumab, PEMetrexed and CISplatin or to any of the excipients
- Previous treatment with an anti-PD1/PD-L1 monoclonal antibody
- Symptomatic CNS metastases
- 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)
- Symptomatic interstitial lung disease
- Any active clinically significant infection requiring therapy
- Creatinine clearance < 45ml/min
- Pre-existing neuropathies ≥ grade 2
- Significant hearing impairment/tinnitus
- Pregnancy or Breast feeding

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PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- 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
- Glucose prior to each cycle
- TFT's 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;

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- 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.
- 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.

PEMtrexed and CISplatin dose modifications

- Dose adjustments are based on nadir blood counts following the baseline dose of therapy.
- After the treatment, growth factors may be used to assist recovery (**Refer to local policy**).
- 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	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis	Permanently discontinue treatment
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment

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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
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 prednisone 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).
^bThe safety of re-initiating nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.

Haematological:

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

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

ANC (x10 ⁹ /L)	Recommended Dose	Platelets (x 10 ⁹ /L)	Recommended Dose
≥ 0.5	100%	≥ 50	100%
<0.5	Delay treatment until recovery and reduce by one dose level	≥ 50	Delay treatment until recovery and reduce by one dose level
		25 - <50	Delay treatment until recovery and reduce by one dose level
		<25	Delay treatment until recovery and reduce by one dose level

Renal and Hepatic Impairment:

Table 4: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
Nivolumab	Mild-Moderate	No dose adjustment necessary	Mild	No dose adjustment necessary		
	Severe	Has not been studied	Moderate-Severe	Has not been studied Nivolumab must be administered with caution in patients with <ul style="list-style-type: none"> • moderate (total bilirubin >1.5x to 3x ULN and any AST) or • severe (total bilirubin >3 x ULN and any AST) 		
Ipilimumab	No specific dose adjustment is necessary in patients with mild to moderate renal dysfunction.		No specific dose adjustment is necessary in patients with mild hepatic impairment. Administer with caution in patients with transaminase levels ≥5 x ULN or bilirubin levels >3 x ULN at baseline.			
PEMEtrexed	CrCl (ml/min)	Dose	Bilirubin	and/or	Aminotransferases	Not recommended. Clinical decision
	≥45	100%			>1.5 x ULN	
	<45	Not recommended			>5 x ULN (presence of hepatic metastases)	
CISplatin	CrCl (ml/min)	Dose	No dose reduction necessary			
	≥60	100%				
	45-59	75%				
	<45	Discontinue				

Management of adverse events:

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

Adverse reactions	Recommended dose modification
Diarrhoea grade ≥3	Withhold treatment until resolution and reduce PEMEtrexed by 1 dose level.
Allergic reaction^a Grade ≥ 3	Discontinue PEMEtrexed and CISplatin
Neurotoxicity	
Grade 2	Reduce dose of CISplatin by one dose level
Grade ≥3	Discontinue PEMEtrexed and CISplatin

^a Only the drug(s) causing the hypersensitivity reaction or acute infusion reaction (≥Grade 3) require(s) discontinuation. All other drugs may be continued

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

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 B₁₂ (hydroxycobolamin) (1,000 micrograms) in the week preceding the first dose of PEMEtrexed and once every three cycles thereafter. Subsequent vitamin B₁₂ 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.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Cardiac adverse events and pulmonary embolism:** Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during combination treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions. Serious cardiovascular events including myocardial infarction 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.

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 - 1 st 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 infiltrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.		

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Grade 2 (symptomatic)	Withhold	Initiate corticosteroids at a dose of 1 mg/kg/day methylprednisolone (/equivalents). Upon improvement, treatment may be resumed after corticosteroid taper
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	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)
<p>Immune-related colitis</p> <p>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</p>		
Grade 2 diarrhoea or colitis	Withhold	Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone (/equivalents)
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	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)
<p>Immune-related hepatitis</p> <p>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.</p>		
Grade 2 transaminase or total bilirubin elevation	Withhold	Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents.
If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	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)
<p>Immune-related nephritis or renal dysfunction</p> <p>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.</p>		
Grade 2 or 3 serum creatinine elevation	Withhold	Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone (/equivalents).
		Upon improvement, treatment may be resumed after

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If worsening or no improvement occurs despite initiation of corticosteroids	Permanently discontinue	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 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
Grade 4 rash	Permanently discontinue	

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		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.
<p>Other immune-related adverse reactions</p> <p>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.</p> <p>Myotoxicity:</p> <ul style="list-style-type: none"> ○ 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 (prednisone 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.

PEMETrexed and CISplatin

- **Myelosuppression:** Usually the dose limiting toxicity with PEMETrexed. PEMETrexed should not be given to patients until absolute neutrophil count (ANC) returns to $1.5 \times 10^9/L$ and platelet count returns to $100 \times 10^9 /L$. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematologic toxicity seen from the previous cycle.
- **Renal Toxicity:** Nephrotoxicity is common with PEMETrexed and 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. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).

PEMETrexed

- **Skin reactions:** Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions

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CISplatin

- **Neurotoxicity and ototoxicity:** Ototoxicity and sensory neural damage should be assessed by history prior to each dose.

DRUG INTERACTIONS:

- No formal pharmacokinetic drug interaction studies have been conducted with nivolumab. Since nivolumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting nivolumab in combination with ipilimumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of nivolumab in combination with ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab in combination with ipilimumab to treat immune-related adverse reactions.
- Concomitant use of ipilimumab with anti-coagulants may increase risk of GI haemorrhage so close monitoring is required.
- In 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.
- Concomitant administration of substances that are also tubularly secreted (e.g. probenecid, penicillin) could potentially result in delayed 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.
- 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 Alert Card:

Ipilimumab:

<https://www.hpra.ie/img/uploaded/swedocuments/0781c3d7-ff8d-4cc7-9f0a-80cf9a10e59f.pdf>

Nivolumab:

<https://www.hpra.ie/img/uploaded/swedocuments/cf83916c-1f29-46e4-a9d5-11a0e6d150d3.pdf>

Patient Information Guide:

Ipilimumab:

<https://www.hpra.ie/img/uploaded/swedocuments/2f064c72-ccef-492b-a068-bc72d8b522cf.pdf>

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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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