# Nivolumab, ipilimumab, PEMEtrexed and CARBOplatin 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 | 00713a | Nivolumab, ipilimumab ODMS 01/03/2022<br>PEMEtrexed: Hospital<br>CARBOplatin: 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 CARBOplatin 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.

**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] | 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 | 1,22 | PEMEtrexed | 500mg/m$^2$ | IV infusion | 100ml 0.9% NaCl over 10 min[5] | |
| 4 | 1,22 | CARBOplatin | AUC 5 or 6 | IV infusion | 500ml glucose 5% over 60 min | |
| | | Folic Acid or multivitamin containing 350-1000 micrograms folic acid | 350-1000micrograms[6] | 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] PEMEtrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection.

[6] 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 for further treatment required.

**Cycle 2 onwards**

| Admin. Order | Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|---|
| 1 | 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 |
| 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 |

## CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

**Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)**

- Measured GFR (e.g. nuclear renogram) is preferred whenever feasible.
- Estimation of GFR may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese and patients and those with a low serum creatinine due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended.
    - where obesity (body mass index [BMI] ≥ 30 kg/m2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered.
    - where serum creatinine is less than 63 µmol/L, the use of a creatinine value of 63umol/L or a steady pre-operative creatinine value may be considered
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

**WRIGHT FORMULA**

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

**1.** *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

**2.** *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

**COCKCROFT-GAULT FORMULA**

$$\text{GFR (ml/min)} = \frac{\text{S} \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

## 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, CARBOplatin 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
- Pre-existing neuropathies ≥ grade 2
- Significant hearing impairment/tinnitus
- Pregnancy or Breast feeding

## 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 each 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;
    - 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.

**PEMEtrexed and CARBOplatin dose modifications**

- Dose adjustments prior to treatment are based on nadir blood counts.
- 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 |
| **Immune-related endocrinopathies** | Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency<br>Grade 3 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 |
| | Grade 4 hypothyroidism<br>Grade 4 hyperthyroidism<br>Grade 4 hypophysitis<br>Grade 3 or 4 adrenal insufficiency<br>Grade 4 diabetes | Permanently discontinue treatment |
| **Immune-related skin adverse reactions** | Grade 3 rash | Withhold dose(s) until symptoms resolve and management with corticosteroids is complete |
| | Grade 4 rash | Permanently discontinue treatment |
| | Steven-Johnsons syndrome (SJS) or toxic epidermal necrolysis (TEN) | Permanently discontinue treatment |

| | | |
|---|---|---|
| **Immune-related myocarditis** | Grade 2 myocarditis<br><br>Grade 3 or 4 myocarditis | Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[b]<br><br>Permanently discontinue treatment |
| **Other immune-related adverse reactions** | Grade 3 (first occurrence)<br><br>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)<br><br>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).<br>[b]The 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 CARBOplatin**

| | Starting Dose | First Dose reduction | Second Dose Reduction | Third Dose Reduction |
|---|---|---|---|---|
| **PEMEtrexed** | 500mg/m$^2$ | 375mg/m$^2$ | 250mg/m$^2$ | Discontinue |
| **CARBOplatin** | AUC 5 or 6 | AUC 5 ( if starting dose is AUC 6) or AUC 4 (if starting dose is AUC of 5) | AUC 4 (if starting dose is AUC 6) or AUC 3 (if starting dose is AUC 5) | Discontinue |

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

| 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<br>Nivolumab must be administered with caution in patients with<br>• moderate ( total bilirubin >1.5x to 3x ULN and any AST) or<br>• 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.<br>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** | | **Aminotransferases** | |
| | ≥45 | 100% | >1.5 x ULN | and/or | > 3 x ULN (hepatic metastases absent)<br>>5 x ULN (presence of hepatic metastases | Not recommended. Clinical decision |
| | <45 | Not recommended | | | | |
| **CARBOplatin** | See note below* | | No dose modification required | | | |

***Renal dysfunction and CARBOplatin:**

- Patients with creatinine clearance values of < 60ml/min are at greater risk to develop myelosuppression.
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution.
- In case of GFR ≤ 20ml/min, CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formula are used, the dose should be adjusted per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to recalculating using Cockcroft & Gault or Wright formulae taking care this does result in a dose reduction.

## 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 CARBOplatin |
| **Neurotoxicity** Grade ≥3 | Discontinue PEMEtrexed and CARBOplatin |

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

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

Nivolumab: Minimal **(Refer to local policy)**.
Ipilimumab: Low **(Refer to local policy).**
PEMEtrexed: Low **(Refer to local policy).**
CARBOplatin 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 $B_{12}$ (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.

### 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.*

**Nivolumab and ipilimumab**

- **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.
- **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**<br>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)<br><br>If worsening or no improvement occurs despite initiation of corticosteroids | Withhold<br><br>Permanently discontinue | Initiate corticosteroids at a dose of 1 mg/kg/day methylprednisolone (/equivalents). Upon improvement, treatment may be resumed after corticosteroid taper<br><br>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**<br>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 | Withhold | Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone (/equivalents)<br><br>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 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**<br>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 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.<br><br>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 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**<br>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 | Withhold | Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone (/equivalents).<br><br>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 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**<br>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 | | |

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| 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 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**<br>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.<br><br>Myotoxicity:<br>○ 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.<br>○ 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 CARBOplatin**

- **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.

**PEMETrexed**

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

**CARBOplatin**

- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However, allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity,

such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.

## 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 ipilumumab 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 ipilumumab 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 CARBOplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use of CARBOplatin with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). When necessary perform regular audiometric testing.
- 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:

Ipilumumab:
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

## REFERENCES:


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