

## Nivolumab, ipilimumab, CARBOplatin and PACLitaxel Therapy

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
First-line treatment of metastatic <b>squamous</b> non-small cell lung cancer (NSCLC) in adults whose tumours have no sensitising EGFR mutation or ALK translocation.	C34	00712a	Nivolumab, ipilimumab: ODMS 01/03/2022 CARBOplatin: Hospital PACLitaxel: 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, PACLitaxel 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 systemic anti-cancer therapy (SACT) is administered.

#### Cycle 1

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,22	Nivolumab <sup>1</sup>	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 <sup>2</sup> .	Cycle 1 only
2	1	Ipilimumab <sup>1,3</sup>	1mg/kg	IV infusion Observe post infusion <sup>3</sup>	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 <sup>4</sup> .	
3	1,22	PACLitaxel	200mg/m <sup>2</sup>	IV infusion	500mL 0.9% NaCl over 3 hours <sup>5,6</sup>	
4	1,22	CARBOplatin	AUC 6	IV infusion	500mL glucose 5% over 60 minutes	
<sup>1</sup> Nivolumab or ipilimumab <b>must not</b> be administered as an intravenous push or bolus injection.						
<sup>2</sup> 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.						
<sup>3</sup> Vital signs including temperature, pulse and BP should be taken every 30 mins for the duration of the ipilimumab infusion and 1 hour following completion of the infusion.						
<sup>4</sup> The line should be flushed with 0.9% NaCl after the ipilimumab infusion has finished.						
<sup>5</sup> PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.						
<sup>6</sup> PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.						

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## 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 ongoing to progression or toxicity or up to 24 months progression
2	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 ongoing to progression or toxicity or up to 24 months progression

## CARBOplatin dose:

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

$$\text{Dose (mg)} = \text{target AUC (mg/ml x min)} \times (\text{GFR ml/min} + 25)$$

- 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 patients and those with a low serum creatinine, for example, 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]  $\geq 30 \text{ kg/m}^2$ ) 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 micromol/L, the use of a creatinine value of 62 micromol/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).

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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*

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

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

### COCKCROFT-GAULT FORMULA

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

S= 1.04 for females and 1.23 for males

### ELIGIBILITY:

- Indications as above
- Histologically confirmed Stage IV or recurrent NSCLC squamous with no prior systemic anti-cancer 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, CARBOplatin\*, PACLitaxel 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

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- Any active clinically significant infection requiring therapy
- Severe hepatic impairment (PACLitaxel)
- Baseline neutrophil count < 1.5 x 10<sup>9</sup> cells/L
- Pregnancy or Breast feeding

\*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

## PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

## TESTS:

### Baseline tests:

- FBC, renal and liver profile
- Glucose
- TFT
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- 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
- 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:

Any dose modification should be discussed with a Consultant.

### 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.

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- 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.

### PACLitaxel and CARBOplatin 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

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<b>Immune-related hepatitis</b>	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
<b>Immune-related nephritis and renal dysfunction</b>	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
<b>Immune-related endocrinopathies</b>	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency 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 Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
<b>Immune-related skin adverse reactions</b>	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
<b>Immune-related myocarditis</b>	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete <sup>b</sup>
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
<b>Other immune-related adverse reactions</b>	Grade 3 (first occurrence)	Withhold dose(s)
	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	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).

<sup>b</sup>The safety of re-initiating nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.

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**Table 2 Dose reduction levels for CARBOplatin and PACLitaxel**

	Starting Dose	First Dose reduction	Second Dose Reduction	Third Dose Reduction
<b>PACLitaxel</b>	200mg/m <sup>2</sup>	150mg/m <sup>2</sup>	100mg/m <sup>2</sup>	Discontinue
<b>CARBOplatin</b>	AUC 6	AUC 5	AUC 4	Discontinue

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

ANC (x10 <sup>9</sup> /L)	Recommended Dose	Platelets (x 10 <sup>9</sup> /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		
<b>Nivolumab</b>	Renal impairment: no dose adjustment is needed.  Haemodialysis: no need for dose adjustment is expected.	<b>Mild-Moderate</b>	No dose adjustment is needed.	
		<b>Severe</b>	No need for dose adjustment is expected.	
<b>Ipilimumab</b>	Renal impairment: no dose adjustment is needed.  Haemodialysis: No need for dose adjustment is expected.	No need for dose adjustment is expected.		
<b>PACLitaxel</b> Renal impairment: no need for dose adjustment is expected.  Haemodialysis: no need for dose adjustment is expected.		<b>ALT</b>	<b>Total bilirubin</b>	<b>Dose</b>
		< 10xULN	≤ 1.25xULN	No dose reduction
		< 10xULN	1.26-2xULN	150mg/m <sup>2</sup>
		< 10xULN	2.01-5xULN	100mg/m <sup>2</sup>
		≥10xULN	>5xULN	Contraindicated
<b>CARBOplatin</b>	See note below*	No need for dose adjustment is expected.		

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**\*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 calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration.

If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

**Management of adverse events:**

**Table 5: Dose Modification of PACLitaxel and CARBOplatin for Adverse Events**

Adverse reactions	Recommended dose modification
<b>Diarrhoea grade ≥3</b>	Withhold treatment until resolution and reduce PACLitaxel by 1 dose level.
<b>Allergic reaction <sup>a</sup> Grade ≥ 3</b>	Discontinue PACLitaxel and CARBOplatin.
<b>Neurotoxicity</b>	
Grade 2	Withhold treatment until resolution and reduce PACLitaxel by 1 dose level.
Grade ≥3	Discontinue PACLitaxel and CARBOplatin.

<sup>a</sup> 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**).
- PACLitaxel: Low (**Refer to local policy**).
- CARBOplatin: High (**Refer to local policy**).

**PREMEDICATIONS:**

- All patients must be premedicated with corticosteroids, antihistamines, and H<sub>2</sub> antagonists prior to first dose of PACLitaxel treatment.
- The H<sub>2</sub> antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.

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- Caution is advised particularly for patients receiving PAclitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.
- Where a patient experiences hypersensitivity, consider the use of alternative H<sub>2</sub> antagonists (**Refer to local policy**).

**Table 6: Suggested premedications prior to treatment with PAclitaxel**

Drug	Dose	Administration prior to PAclitaxel
dexAMETHasone	20mg oral or IV <sup>a,b</sup>	For oral administration: approximately 6 and 12 hours or for IV administration: 30 minutes
Chlorphenamine	10mg IV	30 minutes
Famotidine <sup>c</sup>	20mg IV	30 minutes
<sup>a</sup> Dose of dexAMETHasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance.		
<sup>b</sup> If aprepitant is added to the anti-emetic regimen, consideration should be given to reducing the dose of dexAMETHasone to 12mg on the day of treatment.		
<sup>c</sup> Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.		

## OTHER SUPPORTIVE CARE:

- Myalgias and arthralgias may occur with PAclitaxel. Analgesic cover should be considered.

## 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 7 for dose modifications of nivolumab and ipilimumab in combination.

**Table 7: Management of immune-related adverse reactions to nivolumab and ipilimumab**

Adverse reaction	Withhold/ discontinue	Recommended action - 1 <sup>st</sup> occurrence
<b>Immune-related pneumonitis</b> 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.		
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)

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Grade 3 or 4	Permanently discontinue	Initiate corticosteroids at a dose of 2 to 4 mg/kg/day methylprednisolone (/equivalents)
<b>Immune-related colitis</b> 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)  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)
<b>Immune-related hepatitis</b> 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.  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)
<b>Immune-related nephritis or renal dysfunction</b> 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).  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)
<b>Immune-related endocrinopathies</b>		

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<p>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.</p>		
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	
<b>Immune-related skin adverse reactions</b>		
Grade 3 rash	Withhold	<p>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.</p>
Grade 4 rash	Permanently discontinue	
<b>Other immune-related adverse reactions</b>		

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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 (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.

**PACLitaxel and CARBOplatin**

- **Neutropenia:** This is the dose limiting toxicity. Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **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.  
Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug.

**PACLitaxel**

- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare. Dose reduction or discontinuation may be necessary.
- **Arthralgia/myalgia:** May be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of PACLitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after PACLitaxel administration, and resolving within days.
- **Hepatic Dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.
- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated (**Refer to local policy**).
- **Cardiac conduction abnormalities:** If patients develop significant conduction abnormalities during PACLitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PACLitaxel. Hypotension, hypertension, and bradycardia have been observed during PACLitaxel administration; patients are

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usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of PACLitaxel infusion, is recommended.

## 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 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.
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- 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:

Ipilimumab:

<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](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	14/12/2023	Reviewed. Updated baseline tests and exclusions section. Updated renal and hepatic dose modifications and pre medications section and table for PACLitaxel.	Prof Maccon Keane

Comments and feedback welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie).

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