Nivolumab, ipilimumab, CARBOplatin and PACLitaxel Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
First-line treatment of metastatic **squamous** 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: N/A PACLitaxel: N/A

*This applies to post 2012 indications

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Nivolumab, 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[1]	360mg	IV infusion	Infuse over 30 minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm[2]	Cycle 1 only
2	1	Ipilimumab[1,3]	1mg/kg	IV infusion Observe post infusion[3]	0.9% NaCl to a concentration between 1 and 4mg/mL over 30 minutes using a 0.2-1.2 µm low-protein binding in-line filter[4]	
3	1,22	PACLitaxel	200mg/m^2	IV infusion	500mL 0.9% NaCl over 3 hours[5,6]	
4	1,22	CARBOplatin	AUC 6	IV infusion	500mL glucose 5% over 30 minutes	

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

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

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

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

[5]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.

[6]PACLitaxel should be diluted to a concentration of 0.3-1.2mg/mL.

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

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

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

CARBOplatin dose:

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

Dose (mg) = target AUC (mg/mL x minute) x (GFR mL/minute +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/minute
- 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] ≥ 30 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).

1. *SCr measured using enzymatic assay.*

GFR (mL/minute) = (6230 - 32.8 x Age) x BSA x (1 - 0.23 x Sex)
SCr (micromol/minute)

2. *SCr measured using Jaffe assay*

GFR (mL/minute) = (6580 - 38.8 x Age) x BSA x (1 - 0.168 x *Sex*)
SCr (micromol/minute)

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

COCKCROFT-GAULT FORMULA

GFR (mL/minute) = S x (140 - age in years) x wt (kg)
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 0-2
- 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
- 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

EXCLUSIONS:

- Hypersensitivity to nivolumab, ipilimumab, CARBOplatin*, PACLitaxel or to any of the excipients
- Previous treatment with an anti-PD1/PD-L1 monoclonal antibody
- Baseline neutrophil count < 1.5 x 10^9 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
- Blood glucose
- TFT
- Isotope GFR measurement (preferred) or GFR / CrCl estimation
- Hepatitis B (HBV sAg) and Hepatitis C (HCV RNA)
- Audiology and creatinine clearance if clinically indicated
- Assessment of peripheral neuropathy status as clinically indicated

Regular tests:

- FBC, renal and liver profile prior to treatment
- Blood glucose prior to each cycle
- TFTs prior to each cycle
- Serum cortisol as clinically indicated
- Assessment of peripheral neuropathy status as clinically indicated

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.
- 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.

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 Grade 4 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency Grade 3 diabetes Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash Grade 4 rash Steven-Johnsons syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete Permanently discontinue treatment Permanently discontinue treatment
Immune-related myocarditis	Grade 2 myocarditis Grade 3 or 4 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[b] Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence) Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10mg prednisoLONE or equivalent per day	Withhold dose(s) Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).
[b]The safety of re-initiating nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known.

PACLitaxel and CARBOplatin dose modifications

- Day 1 of each cycle treatment may proceed on if: ANC ≥1.5 x10^9/L and platelet ≥100 x10^9/L
- 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 2 Dose reduction levels for CARBOplatin and PACLitaxel

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

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

ANC (x10^9/L)	Recommended Dose	Platelets (x 10^9/L)	Recommended Dose
≥ 1.0	100% If patient feeling unwell, defer until recovery	≥ 100	100% If patient feeling unwell, defer until recovery
0.5 - < 1.0	Delay treatment until recovery	≥ 50	Delay treatment until recovery
< 0.5	Delay treatment until recovery and reduce by one dose level	<50	Delay treatment until recovery and reduce by one dose level

Note: Patients who cannot tolerate treatment after 2 dose reductions should be discussed with treating clinician regarding continuation of treatment.

Renal and Hepatic Impairment:

Table 4: Dose modification in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment		
Nivolumab	Renal impairment: no dose adjustment is needed. Haemodialysis: no need for dose adjustment is expected.	**Mild-Moderate**	No dose adjustment is needed.	
		Severe	No need for dose adjustment is expected.	
Ipilimumab	Renal impairment: no dose adjustment is needed. Haemodialysis: No need for dose adjustment is expected.	No need for dose adjustment is expected.		
PACLitaxel	Renal impairment: no need for dose adjustment is expected. Haemodialysis: no need for dose adjustment is expected.	**ALT**	**Total bilirubin**	**Dose**
		< 10xULN	≤ 1.25xULN	No dose reduction
		< 10xULN	1.26-2xULN	150mg/m^2
		< 10xULN	2.01-5xULN	100mg/m^2
		≥10xULN	>5xULN	Contraindicated
CARBOplatin	See note below*	No need for dose adjustment is expected.		

Nivolumab: Renal and hepatic: Giraud et al 2023
Ipilumumab: Renal and hepatic: Giraud et al 2023
PAClitaxel: Renal and hepatic: Giraud et al 2023
CARBOplatin: Renal and hepatic: Giraud et al 2023

***Renal dysfunction and CARBOplatin:**

- Patients with creatinine clearance values of <60mL/minute are at greater risk to develop myelosuppression.
- If GFR between 20 to ≤ 30mL/minute, CARBOplatin should be administered with extreme caution.

- In case of GFR ≤ 20mL/minute, 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
Diarrhoea grade ≥3	Withhold treatment until resolution and reduce PACLitaxel by 1 dose level.
Allergic reaction [a] Grade ≥ 3	Discontinue PACLitaxel and CARBOplatin.
Neurotoxicity	
Grade 2	Withhold treatment until resolution and reduce PACLitaxel by 1 dose level.
Grade ≥3	Discontinue PACLitaxel 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:

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

Nivolumab: Minimal **(Refer to local policy)**.
Ipilimumab: Low **(Refer to local policy).**
PACLitaxel Low **(Refer to local policy).**
CARBOplatin High (**Refer to local policy).**

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment
- The H_2 antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown

- 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_2 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[a,b]**	**For oral administration: approximately 6 and 12 hours or for IV administration: 30 minutes**
Chlorphenamine	**10mg IV**	**30 minutes**
Famotidine[c]	**20mg IV**	**30 minutes**
[a]Dose of dexAMETHasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance.		
[b]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.		
[c]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:

Please refer to the relevant Summaries of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for 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/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
3	19/05/2025	Regimen reviewed. Amended typographical error in indication. Updated exclusions criteria. Updated CARBOplatin infusion time. Updated baseline and regular tests sections. Updated haematological dose modifications section. Regimen updated in	Prof Maccon Keane

		line with NCCP standardisation.	

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.