Systemic Anti Cancer Therapy Protocol

Pembrolizumab, Paclitaxel and Carboplatin Squamous Non-Small Cell Lung Cancer (NSCLC)

PROTOCOL REF: MPHAPPCLU
(Version No: 1.1)

Approved for use in:

- Stage IIIB or stage IIIC or stage IV squamous NSCLC
- PD-L1 testing has been carried out and the result is available. This combination can be given in patients with a PD-L1 of 0-100%
    - If PD-L1 score is 50-100%, then the patient must require an urgent clinical response (e.g. impending major airway obstruction) to justify the use of the combination of pembrolizumab, carboplatin and paclitaxel rather than pembrolizumab monotherapy and this issue has been fully discussed with the patient.
- The patient has not received previous cytotoxic chemotherapy for advanced/ metastatic disease. Completion of treatment for earlier stage disease with chemotherapy with or without radiotherapy as part of neoadjuvant/concurrent/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of recurrent locally advanced or metastatic disease.
- No prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.
- Performance status of 0-1
- No symptomatically active brain metastases or leptomeningeal metastases

Blueteq registration required: see Blueteq for more detailed eligibility criteria

Dosage:

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg	IV infusion	3 weekly
Paclitaxel	200mg/m²		
Carboplatin	AUC 6 x (GFR + 25)*		

Given for a maximum of **4 cycles** followed by:

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg (flat dose)	IV infusion	3 weekly

Given for a further 3 cycles followed by

Drug	Dosage	Route	Frequency
Pembrolizumab	400mg (flat dose)	IV infusion	6 weekly

To be **continued until loss of clinical benefit or unacceptable** toxicity or withdrawal of patient consent or for a **maximum treatment duration of 2 years** (or a total of **35 (3-weekly) cycles** of pembrolizumab or its equivalent if 6 weekly dosing is used).

***Calvert formula for Carboplatin dosage**

Carboplatin dose (mg) = AUC 6 x (creatinine clearance + 25)

If estimated GFR is used the **Wright formula** must be used for creatinine clearance.

Creatinine clearance should be capped at 125mL/min for carboplatin.

Administration and Counselling Points:

- Paclitaxel in solution may show haziness which is attributed to the formulation of paclitaxel. Excessive shaking, agitation, or vibration of paclitaxel may induce precipitation and should be avoided.
- Premedication of chlorphenamine, dexamethasone and famotidine is given prior to paclitaxel to reduce the risk of hypersensitivity. Paclitaxel reactions commonly occur within the first few minutes of starting the infusion most likely with the first two cycles. Carboplatin risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy.
- Famotidine can be stopped after three cycles for those patients who do not experience a drug hypersensitivity reaction.

- Facilities to treat anaphylaxis must be present when administering this regime. If a patient experiences an **infusion-related reaction**, give future doses with premedication cover of IV chlorphenamine 10mg and IV hydrocortisone 100mg.

Ensure the patient is aware to contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Flu like symptoms are common, particularly during cycle 1

Emetogenic Risk:

Cycle 1-4: Moderate emetogenic

Cycle 5 onwards: Mildly emetogenic

Supportive Treatments:

Pre-Medication (Cycle 1-4):

Dexamethasone 16.5mg IV bolus 30 mins before chemotherapy

Ondansetron 16mg oral 30 mins before chemotherapy

Famotidine 20mg oral to be taken at least 60 minutes before for the first three cycles (to be discontinued after three cycles for those patients who do not experience a drug hypersensitivity reaction)

Chlorphenamine 10mg IV bolus 30 mins before chemotherapy

To take home medications (Cycle 1-4):

Dexamethasone tablets 4mg orally twice daily for three days

Domperidone 10mg tablets, three times a day when required

Extravasation risk:

Paclitaxel: Vesicant.

Carboplatin: Irritant.

Monoclonal antibody - treat symptomatically, no specific recommendations.

Refer to Clatterbridge Policy 'Prevention and Management of Extravasation Injuries' for further guidance.

Dosing in renal and hepatic impairment:

Renal dosing	Pembrolizumab	No studies have been conducted on patients with severe renal impairment. No dose adjustments are required for mild to moderate renal impairment
	Paclitaxel	No dose reductions necessary.
	Carboplatin	Patients' with CrCl<60mL/min are at increased risk of severe myelosuppression. The optimal use of carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematological nadirs and renal function. In patients with impaired renal function, dosage of carboplatin should be reduced (refer to Calvert formula). There is inadequate data on the use of carboplatin in patients with CrCl < 15mL/min.

Hepatic dosing	Pembrolizumab	No dose adjustment is needed for patients with mild hepatic impairment. Pembrolizumab has not been studied in patients with moderate or severe hepatic impairment. Please also see dose modifications and toxicity management section
	Paclitaxel	**Bilirubin /µmol/L** / **Dose in mg/m²** < 26 — 135 27 to 51 — 75 >51 — 50 If bilirubin <1.25 x ULN and transaminase < 10 x ULN, dose at 175 mg/m^2. Patients with hepatic impairment may be at increased risk of toxicity, particularly Grade 3-4 myelosuppression. This is no evidence that the toxicity of paclitaxel is increased when given as a 3 hour infusion to patients with mildly abnormal liver function. Patients should be monitored closely for the development of profound myelosuppression. There is no data on patients with severe baseline cholestasis. Patients with severe hepatic impairment must not be treated

		with paclitaxel.
	Carboplatin	No dose reductions necessary

Interactions:

- **Aminoglycosides e.g. gentamicin -** increased risk of nephrotoxicity and ototoxicity with carboplatin. Renal function should be well monitored and audiometric tests carried out as indicated.
- **Antiepileptics (CYP 3A4 inducers) -** carboplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.
- Phenytoin, carbamezapine and phenobarbital increase the clearance of paclitaxel and increase its maximum tolerated dose.
- **Ciclosporin -** levels of paclitaxel increased after oral administration of ciclosporin.
- **Fluconazole/Ketoconazole (CYP3A4 inhibitors) -** paclitaxel level may be increased
- **Quinine and Verapamil -** paclitaxel level possibly increased.
- **Steroids -** the use of systemic corticosteroids or immunosuppressants before starting pemborlizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting pembrolizumab. Further guidance can be found in the toxicity table below.
- **Warfarin -** the effects of warfarin may be increased. Monitor INR closely.

Please consult summary of product characteristics via https://www.medicines.org.uk/emc for full list of interactions.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and Rate
1	Pembrolizumab	200mg	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
1	Sodium Chloride 0.9%	50mL	IV Infusion	Flush

1	Dexamethasone	16.5mg	IV bolus	30 minutes before chemotherapy
1	Ondansetron	16mg	Oral	30 minutes before chemotherapy
1	Famotidine	20mg	Oral	At least 60 minutes before chemotherapy (for the first three cycles – can be discontinued for those patients who do not experience a hypersensitivity reaction)
1	Chlorphenamine	10mg	IV bolus	30 minutes before chemotherapy
1	Paclitaxel	200mg/m²	IV Infusion using a non-PVC giving set with a 0.22 micron filter	250-500mL sodium chloride 0.9% over 3 hours
1	Sodium Chloride 0.9%	100mL	IV Infusion	Flush
1	Carboplatin	AUC 6	IV Infusion	500mL glucose 5% over 30 to 60 minutes

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea

Pembrolizumab	The most common adverse reactions in combination with paclitaxel and carboplatin were anemia, alopecia and neutropenia. Pembrolizumab can cause immune mediated side effects such as pneumonitis, colitis, nephritis, hypophysitis, hyperthyroidism and hypothyroidism. Other non-immune adverse events include fatigue, cough, dyspnea, constipation and pruritis. Please refer to the immune-oncology toxicity specific guidance for adverse event management
Paclitaxel	Significant hypersensitivity reactions, bone marrow suppression, thrombocytopenia, anaemia, neurotoxicity (mainly peripheral neuropathy), arthralgia or myalgia or injection site reactions. The most common reactions include infection, neurotoxicity, bradycardia, hypotension, diarrhoea, vomiting, nausea and alopecia.
Carboplatin	Significant hypersensitivity reactions, bone marrow suppression, thrombocytopenia, anaemia, neurotoxicity (mainly peripheral neuropathy), arthralgia or myalgia or injection site reactions. The most common reactions include infection, neurotoxicity, bradycardia, hypotension, diarrhoea, vomiting, nausea and alopecia.

Investigations and treatment plan:

	Pre	Cycle 1+2	Pre Cycle 3	Cycle 3	Cycle 4	Cycle 5	Ongoing
Informed Consent	X						
Clinical Assessment	X		X		X		Every 12 weeks thereafter or as clinically indicated
SACT Assessment Inc. toxicity assessment	X	X		X	X	X	Every cycle
U&E & FBC & LFT (inc. ALT), Mg	X	X		X	X	X	Every cycle*
TFTs and cortisol	X	X		X	X	X	Every cycle*
CRP	X	X		X	X		As clinically indicated
CrCl/Urine output	X	X		X	X	X	Every cycle **IF** the baseline CrCl <40ml/min or creatinine increases above 1.5x upper limit of normal
Blood Glucose	X	X		X	X	X	Every cycle*
Lipid profile (cholesterol)	X						As clinically indicated
Full set of observations	X	X		X	X	X	Every cycle
CT scan	X			X			Every 12 weeks thereafter or as clinically indicated
PS recorded	X	X		X	X	X	Every cycle
Weight recorded	X	X		X	X	X	Every cycle. Height to be recorded prior to 1st cycle.
Height recorded	X						

*** Please note when dosing schedule changes to 6 weekly a mid cycle blood check is required. The treating nurse should book the patient onto the on treatment review list for these bloods to be reviewed.**

- Pregnancy test if applicable: Women of childbearing potential have to use effective contraception during and for 5 months after treatment.
- Serum samples for HIV, Hep C antibody and HBsAg are required if patient has risk factors: patients with these conditions were excluded from clinical trials.

Dose Modifications and Toxicity Management:

Grading and Management of Toxicity for Pembrolizumab:

Haematological toxicity

Proceed on day 1 of cycle if:-

Hb > 9g/L	ANC ≥ 1.0 x 10^9/L	Platelets ≥ 75 x 10^9/L

Confirm any deferrals with the prescribing oncologist.

Hepatic impairment	
AST or ALT increase to 3 to 5 times the upper limit of normal (ULN) Bilirubin increase to 1.5 to 3 times ULN	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
AST or ALT increase to greater than 5 times ULN Bilirubin increase to greater than 3 times ULN	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
In patient with liver metastasis with baseline AST or ALT at 3 to 5 times the ULN And increase by > 50% and lasting for more than one week	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Haematological Toxicity:

Proceed on day 1 if-

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Delay 1 week on day 1 if-

Plt ≤ 99 x 10^9/L	ANC ≤ 0.9 x 10^9/L

Non-haematological toxicity

Toxicity Grade	Action
Grade 1	No action. Provide symptomatic treatment
Grade 2	Withhold Pembrolizumab until resolved to <grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Grade 3 and Grade 4	Discontinue Pembrolizumab. Refer to Immuno-Oncology toxicity specific guidance for adverse event management Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisolone equivalent within 12 weeks of toxicity.

Pembrolizumab will be permanently discontinued for any Grade 3-4, severe or life-threatening adverse reaction.

Grading and Management of Toxicity for Carboplatin and Paclitaxel:

Toxicity should be grading according to the CTCAE v4.0 criteria. Following assessment, treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose or AUC 5 with prophylaxis where possible	Discontinue treatment

2nd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose or AUC 4	Interrupt treatment until resolved to grade0/1, then continue at 50% of original dose or AUC 3.5	
3rd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose or AUC 3.5	Discontinue treatment	
4th appearance	Discontinue treatment		

Peripheral Neuropathy:

Paclitaxel
CTCAE grade 2 peripheral neuropathy: withhold paclitaxel only until the neuropathy recovers to grade 1 then dose reduce to 75% of the original dose. Where the peripheral neuropathy is ≥ grade 3 omit paclitaxel from subsequent cycles.

Hypersensitivity:

As with all platinum and paclitaxel based chemotherapy, patients may experience allergic reaction during administration. The infusion should be stopped and the following should be administered

- Hydrocortisone 100 to 200mg IV
- Chlorphenamine 10mg IV

Refer to the Trusts Hypersensitivity Guidelines for further information.

It should be strongly noted that patients who have severe reactions should not be re-challenged.

References:

1. https://www.medicines.org.uk/emc
2. Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009)
3. Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)
4. BNF available via: https://bnf.nice.org.uk/
5. Keynote 407 Study. Available via: https://www.nejm.org/doi/full/10.1056/NEJMoa1810865