Carboplatin, Paclitaxel and Pembrolizumab

Indication

Previously untreated metastatic stage IIIB/C or IV squamous non-small-cell lung cancer (NSCLC) with a PD-L1 tumour proportion score of:

- 0-49% *or*
- 50-100% **and** requiring an urgent clinical response

Patients should have performance status of 0-1.

(NICE TA770)

ICD-10 codes

Codes pre-fixed with C34

Regimen details

Cycles 1-4

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion
1	Paclitaxel	200 mg/m²	IV infusion
1	Carboplatin	AUC 6*	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) a formal measurement of renal function (such as an EDTA) should be performed.
CrCl should be capped at 125mL/min.

Subsequent pembrolizumab monotherapy (cycle 5 onwards):
Three weekly regimen:

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion

or (if the patient is stable and well):

Six weekly regimen:

Day	Drug	Dose	Route
1	Pembrolizumab	400mg	IV infusion

Cycle frequency

3 weekly as combination treatment then 3 or 6 weekly as monotherapy.

Number of cycles

4 cycles, followed by pembrolizumab maintenance to continue until disease progression or unacceptable toxicity, for a maximum of 2 years treatment. Pembrolizumab should be given for a maximum of 35 3-weekly cycles including the initial 4 induction cycles of treatment or its equivalent if 6-weekly pembrolizumab monotherapy dosing is used.

Administration

Pembrolizumab should be administered in 100mL sodium chloride 0.9% over 30 minutes.

Pembrolizumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 5.0µm).

After the infusion the line should be flushed with 30mL sodium chloride 0.9%.

Patients should be monitored every 30 minutes during the infusion (blood pressure, pulse and temperature) and for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

Paclitaxel is administered in a 250-500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 3 hours. Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

Carboplatin should be administered in 250-500mL glucose 5% over 30-60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of paclitaxel or carboplatin. Facilities for the treatment of hypotension and bronchospasm **must** be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel or carboplatin and appropriate therapy initiated.

Pre-medication

The following should be administered 30 minutes prior to paclitaxel:
Chlorphenamine 10mg IV
Dexamethasone 16-20mg IV

Antiemetics as per local guidelines.

Emetogenicity

This regimen has moderate emetic potential (cycles 1-4) and low emetic potential (cycles 5 onwards).

Additional supportive medication

H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy
Loperamide should be supplied to be used if required.
Antiemetics as per local policy, if required.
GCSF is recommended as per local policy

Extravasation

Carboplatin – irritant (Group 3)
Paclitaxel - vesicant (Group 5)
Pembrolizumab – neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Cortisol	At consultant discretion

Baseline EDTA if suspected or significant renal dysfunction.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	96 hours
LFTs	96 hours
Thyroid function	6 weekly
Glucose	As clinically indicated
Calcium	As clinically indicated
Cortisol	At consultant discretion

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min
Bilirubin	See below
AST/ALT	See below
Alkaline Phosphatase	See below

Dose modifications

- **Haematological toxicity**

Combination treatment:

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Carboplatin dose**	**Paclitaxel dose**
≥ 1.5	and	≥ 100	100%	100%
< 1.5	or	50 - 100	Delay 1 week or until recovery. If longer than 3 weeks then reduce dose to AUC 4.5	Delay 1 week or until recovery. If longer than 3 weeks then reduce dose to 150mg/m^2
< 1.5	and	50 - 100	Delay 1 week or until recovery. Then reduce dose to AUC 4.5	Delay 1 week or until recovery. Then reduce dose to 150mg/m^2
Any		<25 or <50 with bleeding	Delay 1 week or until recovery. Then reduce dose to AUC 4.5	Delay 1 week or until recovery. Then reduce dose to 150mg/m^2
Febrile neutropenia			Delay 1 week or until recovery. Then reduce dose to AUC 4.5	Delay 1 week or until recovery. Then reduce dose to 150mg/m^2

If a second episode of neutropenic fever or thrombocytopenia requiring dose reduction occurs, another 25% dose reduction of carboplatin and paclitaxel is recommended. Chemotherapy should be discontinued if a third episode occurs.

If a dose reduction is required due to low neutrophils or platelets, then that dose reduction is maintained for subsequent cycles.

Pembrolizumab:
Discuss with the consultant if:
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment**

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	Consider changing to non-nephrotoxic regimen
< 20	Contra-indicated

No dose modification required for paclitaxel.

The safety and efficacy of pembrolizumab has not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment. Discuss with consultant if CrCl <30mL/min.

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Carboplatin dose**	**Paclitaxel dose**
<1.25 x ULN	and	<5	100%	100%
1.25-2.0	and		100%	75%
2.0-5.0	and		80-100%	50%
> 5.0	or	≥5	Not recommended (consultant decision)	

Pembrolizumab:
The safety and efficacy of pembrolizumab has not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. See below for management of hepatitis.

- **Other toxicities**

Carboplatin and Paclitaxel:

Toxicity	**Definition**	**Carboplatin dose**	**Paclitaxel dose**
Fatigue	Grade 3	100%	1st occurrence – 150mg/m^2, if persistent 90mg/m^2 or omit.
Neuropathy	Grade 2	100%	1st occurrence – 150mg/m^2 for all future cycles, if persistent 100mg/m^2 or omit
	Grade ≥ 3		Withhold until ≤ Grade 1, restart at 100mg/m^2.
Arthralgia/Myalgia	Grade ≥ 2	100%	Consider diclofenac +/- co-codamol or prednisolone 10mg BD for 5 days starting 24 hours post paclitaxel. If persists reduce dose to 135mg/m^2

Pembrolizumab toxicity:
Patients must be advised to seek specialist advice if they experience side effects as these can worsen rapidly.

Immune reactions may occur during or after completion of treatment.

Toxicity	Definition	Action
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4	Permanently discontinue pembrolizumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to ≤ grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue pembrolizumab
Nephritis	Grade 2 (creatinine 1.5-3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 3 (creatinine > 3 x ULN)	Permanently discontinue pembrolizumab
Endocrine	Symptomatic hypophysitis	Withhold until symptoms resolve to ≤ grade 1
	Type 1 diabetes with grade > 3 hyperglycaemia (glucose > 13.9 mmol/L) or ketoacidosis	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hyperthyroidism ≥ grade 3	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue.
	Hypothyroidism	Continue and manage with replacement therapy
Hepatitis	AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until resolves to ≤ grade 1
	AST/ALT > 5 x ULN or Bilirubin > 3 x ULN	Permanently discontinue pembrolizumab
	If liver metastasis with baseline AST/ALT 3-5 x ULN: - If AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue pembrolizumab
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis	Withhold until resolves to ≤ grade 1
	Grade 4 or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab

Pembrolizumab should be permanently discontinued if:

- Grade 4 toxicity (except for endocrinopathies that are controlled with replacement hormones)
- Corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- Treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose
- Any event occurs a second time at Grade ≥ 3 severity
- Grade 3 or 4 myocarditis
- Grade 3 or 4 encephalitis
- Grade 3 or 4 Guillain-Barré syndrome

Adverse effects - for full details consult product literature/ reference texts

- **Rare or serious side effects**

Myelosuppression
Infertility
Teratogenicity
Neurotoxicity
Hypersensitivity reactions
Pulmonary fibrosis
Pneumonitis
Colitis
Endocrinopathies
Nephritis
Hepatitis
Pancreatitis
Electrolyte disturbances
Arrhythmias
Cardiac failure

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Myelosuppression
Diarrhoea, constipation
Peripheral neuropathy
Oedema
Phlebitis
Myalgia, arthralgia
Alopecia
Fatigue
Headache, dizziness
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism
Rash, pruritis

- **Other side effects**

Elderly patients may have a higher incidence of severe neuropathy, severe myelosuppression, or cardiovascular events compared to younger patients.

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Carboplatin
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity

Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin
Pembrolizumab
Corticosteroids: use of systemic corticosteroids at baseline, before starting pembrolizumab, 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 after starting pembrolizumab to treat immune-related adverse reactions.

Additional comments

Women of child bearing potential should use effective contraception during treatment and for at least 4 months after the last dose.

Preliminary results from the follow-up of patients undergoing allogeneic HSCT after previous exposure to pembrolizumab showed a higher than expected number of cases of acute graft versus-host-disease (aGVHD) and transplant related mortality (TRM). Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case by case. Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors.

References

- National Institute for Health and Clinical Excellence TA600 accessed 13 November 2019 via www.nice.org.uk
- Summary of Product Characteristics Carboplatin (Hospira) accessed 13 November 2019 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Hospira) accessed 13 November 2019 via www.medicines.org.uk
- Summary of Product Characteristics Pembrolizumab - Keytruda® (MSD) accessed 13 November 2019 via www.medicines.org.uk
- Paz-Ares, L., et al. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer (KEYNOTE 407). N Engl J Med 2018; 379:2040-2051

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