Pembrolizumab & Paclitaxel/Nab-Paclitaxel (Breast)

Indication

First line treatment of locally advanced unresectable or metastatic triple negative breast cancer in patients with PD-L1 expression test results of immune cell (IC) <1% and a combined positive score (CPS) of 10 or more

(NICE TA801)

ICD-10 codes

C50

Regimen details

Pembrolizumab:

Day	Drug	Dose	Route
1	Pembrolizumab	200mg every 3 weeks or 400mg every 6 weeks	IV infusion

Paclitaxel/Nab-paclitaxel

Day	Drug	Dose	Route
1, 8, 15	Paclitaxel *Or* Nab-paclitaxel	90mg/m^2 100mg/m^2	IV infusion

Cycle frequency

Pembrolizumab – 21 or 42 days as above
Paclitaxel – 28 days

Number of cycles

Pembrolizumab – until disease progression or unacceptable toxicity up to a maximum of 2 years
Paclitaxel/Nab-paclitaxel – until disease progression or unacceptable toxicity

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 1 hour.

Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

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. 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 restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel and appropriate therapy should be initiated.

Nab-paclitaxel is administered as a 5mg/mL infusion over 30 minutes.

It should be administered using an infusion set incorporating a 15µm filter.

Pre-medication

The following premedication is required 30 minutes prior to each paclitaxel infusion:
Chlorphenamine 10mg IV slow bolus
Dexamethasone 8mg IV slow bolus

Emetogenicity

This regimen has moderate emetic potential – refer to local policy

Additional supportive medication

Mouthwashes as per local policy
Proton pump inhibitor if required, as per local policy

Extravasation

N/A

Investigations – pre first cycle

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

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFT	7 days
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
Neutrophil count	≥1.0 x 10^9/L
Platelets	≥100 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min
Bilirubin	≤1.5 x ULN
ALT/AST	<2.5 x ULN
Alkaline Phosphatase	<5 x ULN

Dose modifications

- **Haematological toxicity**

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

Paclitaxel:
If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L delay for 1 week then resume at 100% dose. If delayed for > 1 week discuss with consultant.
In the case of febrile neutropenia (neutrophils < 0.5 × 10^9/L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 60mg/m^2 for all future doses.

Nab-paclitaxel:
If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L delay for 1 week then resume at 100% dose. If delayed for > 1 week discuss with consultant.
If neutrophils <0.5 x 10^9/L delay until neutrophils >1.0 x 10^9/L and reduce nab-paclitaxel dose to 80mg/m^2.
If second occurrence delay until neutrophils >1.5 x 10^9/L and reduce dose further to 60mg/m^2.

- **Renal impairment**

Pembrolizumab: 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.

Paclitaxel/Nab-paclitaxel: no need for dose adjustment is expected

- **Hepatic impairment**

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.

Paclitaxel: Paclitaxel is not recommended in severe hepatic impairment. If bilirubin < 1.5 x ULN and AST/ALT < 5 x ULN proceed with 100% dose. For more severe hepatic impairment, treatment may only proceed on consultant's decision, at a reduced dose with weekly monitoring of LFTs.

Nab-paclitaxel:

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Paclitaxel albumin dose**
< 1.5	and	< 2	100%
1.5 – 5	and/or	2 - 10	80%
> 5	and/or	> 10	Discontinue

- **Other toxicities**

Pembrolizumab:
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 or recurrent grade 3	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
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until resolves to ≤ grade 1
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome	Permanently discontinue

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 prednisolone 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

Paclitaxel/Nab-paclitaxel:

Toxicity	Definition	Paclitaxel/Nab-paclitaxel dose
Neuropathy	Grade 1-2	No dose reduction usually required.
	Grade 3	Withhold until recovery to ≤ grade 1, resume at 80% dose. If 2nd occurrence: Withhold until recovery to ≤ grade 1, resume at 60% dose.
	Grade 4	Discontinue or continue with dose reduction as above – consultant decision.

For all other grade ≥ 2 toxicities (except alopecia) withhold until grade ≤ 1 and continue with 70mg/m^2 dose. If delayed for > 1 week, discuss with consultant.

For any grade 4 toxicity (except alopecia) withhold and discuss with consultant.

Post-marketing experience of nab-paclitaxel has identified rare reports of reduced visual acuity due to cystoid macular oedema. Treatment should be discontinued.

Rare reports of congestive heart failure and left ventricular dysfunction have been observed in patients treated with nab-paclitaxel with underlying cardiac history or previous exposure to cardiotoxic products such as anthracyclines. Patients should be monitored for the occurrence of cardiac events.

If hypersensitivity reaction occurs to nab-paclitaxel, treatment should be discontinued immediately and symptomatic treatment should be initiated. The patient should not be re-challenged.

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

- **Serious side effects**

Myelosuppression
Infertility
Teratogenicity
Hypersensitivity reactions
Pneumonitis
Hepatic impairment
Cardiotoxicity
Electrolyte disturbances
Arrhythmias
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Diarrhoea, constipation
Peripheral neuropathy
Neuropathy
Myalgia, arthralgia
Alopecia
Fatigue

Anorexia
Rash
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism

- **Other side effects**

Insomnia, depression, anxiety
Headache, dizziness
Skin reactions
Nail changes
Eye problems

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.

Clozapine: increased risk of agranulocytosis

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.

Paclitaxel/Nab-paclitaxel are CYP 2C8/9 and CYP 3A4 substrates. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Additional comments

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

When reconstituted, nab-paclitaxel (Abraxane®) contains approximately 425 mg sodium per dose. This should be considered if a patient is on a controlled sodium diet.

References

- National Institute for Health and Clinical Excellence TA801 accessed 30 June 2022 via www.nice.org.uk
- Summary of Product Characteristics Pembrolizumab - Keytruda® (MSD) accessed 30 June 2022 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Accord) accessed 30 June 2022 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel albumin (Teva) accessed 30 June 2022 via www.medicines.org.uk
- Cortes, J. et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020; 396:1817-1828

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