PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Pembrolizumab with Paclitaxel or Nab-paclitaxel as 1st line treatment for locally advanced/metastatic triple negative breast cancer

PROTOCOL REF: MPHAPPNBC
Version No. 1.0

Approved for use in:

- Previously untreated locally advanced or metastatic breast cancer, ER/PR negative, HER2 negative
- PDL1 expression test results of immune cells <1% and combined positive score (CPS) of 10 or more (for patients with immune cells >1% see atezolizumab/abraxane regimen)
- ECOG PS 0 or 1

Blueteq registration required

Exclusions

History of pneumonitis, organ transplantation, autoimmune disorders, HIV infection, active hepatitis B or C infection
Active infection requiring systemic treatment
Less than 4 weeks from major surgery
History of clinically severe autoimmune disease (can proceed with immunotherapy if well controlled autoimmune disease at the discretion of the clinical team, this needs to be documented on Meditech)
No live vaccines within 30 days of commencing treatment

Dosage:

Drug	Dosage	Route	Frequency
Pembrolizumab	400mg or 200mg	IV	6 weekly or 3 weekly
Paclitaxel	90mg/m^2	IV	Days 1, 8 and 15 of 28 day cycle

Alternatively:

Drug	Dosage	Route	Frequency
Pembrolizumab	400mg or 200mg	IV	6 weekly or 3 weekly
Abraxane (nab-paclitaxel)	100mg/m^2	IV	Days 1, 8 and 15 of 28 day cycle

Pembrolizumab continues for maximum of 2 years (equivalent to 35 x 200mg cycles)

Paclitaxel/abraxane can continue until disease progression or unacceptable toxicity.

Administration (+/- Counselling Points):

Appropriate contraceptive measures must be taken for duration of treatment and 6 months post treatment

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection / sepsis

Emetogenic risk (if applicable):

Mildly emetogenic

Supportive treatments:

Paclitaxel pre-medication:
Chlorphenamine 10mg IV bolus pre chemotherapy
Famotidine 20mg tablet pre chemotherapy for first 3 doses only
Dexamethasone 6.6mg IV as a single dose 30 mins before chemotherapy (reduce to 3.3 mg from week 2)

Extravasation risk (if applicable):

Consider insertion of PICC or port due to expected duration of treatment

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Paclitaxel/abraxane: vesicants follow trust/network policy

Dosing in renal and hepatic impairment:

Renal	Paclitaxel	All grades – no dose adjustment required
	Pembrolizumab (prior to start of treatment ONLY/Baseline)	GFR ≥ 10ml/min proceed with treatment GFR < 10ml/min- use with caution.

Hepatic	Paclitaxel	Bilirubin less than 1.25 times ULN and AST < 10 x ULN	Give 100% dose
		Bilirubin greater than 1.25 times ULN	Consider dose reduction
		ALP more than 3 times ULN	Consider dose reduction
		ALT and/or AST ≥10 x ULN or bilirubin > 5 x ULN:	Contra-.indicated
	Pembrolizumab (prior to start of treatment ONLY/ Baseline)	Administered with caution in patients with: Moderate (total bilirubin > 1.5 to 3 × ULN and any AST) or Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment. * Within normal limits or high	

Interactions:

Aminoglycosides e.g. gentamicin: Increased risk of nephrotoxicity and ototoxicity with **Antiepileptics (CYP 3A4 inducers):**. Phenytoin, carbamazepine and phenobarbital increase the clearance of paclitaxel and increase the 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.

Warfarin: The effects of warfarin may be increased. Monitor INR closely.

Treatment schedule:

To avoid additional appointments for treatment the preferred pembrolizumab dosing schedule is 400mg every 6 weeks and therefore the electronic prescription is built as a 12 week cycle

Paclitaxel and Pembrolizumab

Paclitaxel must be administered using a non-PVC giving set with a 0.22 micron filter. Pembrolizumab also requires a filter and this should be changed between treatments to ensure the products are not mixing at this point

Day	Drug	Dose	Route	Diluent and rate
1, 43	**Pembrolizumab**	400mg	IV infusion	100mL sodium chloride 0.9% over 30 minutes in a non-pyrogenic line with 0.2 micron filter **Then change the line to paclitaxel giving set**
1,8,15 29,36,43 57,64,71	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
1	Dexamethasone	6.6mg	IV Infusion	30 minutes prior to paclitaxel
8,15 29,36,43 57,64,71	Dexamethasone	3.3mg	IV Infusion	30 minutes prior to paclitaxel
1,8,15	Famotidine	20mg	Orally	60 minutes prior to paclitaxel
1,8,15 29,36,43 57,64,71	**Paclitaxel**	**90mg/m²**	**IV Infusion**	**250 to 500mL sodium chloride 0.9% over 60 minutes**

Cycle is repeated every 12 weeks

Abraxane and Pembrolizumab

Day	Drug	Dose	Route	Diluent and rate
1, 43	**Pembrolizumab**	400mg	IV infusion	100mL sodium chloride 0.9% over 30 minutes in a non-pyrogenic line with 0.2 micron filter
1	Dexamethasone	6.6mg	IV Infusion	30 minutes prior to Abraxane
8,15 29,36,43 57,64,71	Dexamethasone	3.3mg	IV Infusion	30 minutes prior to Abraxane
1,8,15 29,36,43 57,64,71	**Abraxane**	**100mg/m²**	**IV Infusion**	**Over 30 minutes**

Cycle is repeated every 12 weeks

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Chemotherapy: Paclitaxel/Abraxane	
Haematological	Neutropenia, thrombocytopenia and anaemia.
Gastrointestinal	Nausea, vomiting, stomatitis, diarrhoea, mucositis
Dermatological	Alopecia, normally reversible Skin rashes, particularly to hands and scalp Brittle, ridged and chipped nails
Ocular	Watery eyes, gritty and irritated
Hypersensitivity reactions	Reactions may occur within a few minutes following the initiation of treatment with paclitaxel or pembrolizumab facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised rash with or without pruritus do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel or carboplatin and appropriate treatment. Patients who have developed severe hypersensitivity reactions should not be re-challenged.
Nervous system	Peripheral neuropathy is very common
Musculoskeletal	Arthralgia, myalgia
Infertility	Amenorrhea, risk of premature menopause However ensure appropriate contraceptive advice is given
Immunotherapy: Pembrolizumab	
Immune-Mediated Pneumonitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Immune-Mediated Colitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other Immune-Mediated Toxicities: Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism	Monitor LFTs, biochemistry, cortisol and TFTs regularly Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia	
Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management Note: many of these overlap with chemotherapy toxicities
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Investigations and treatment plan:

	Pre	Cycle 1	C1D8	C1D15	C1D29	C1D36	C1D43	Ongoing
Informed Consent	X							
Clinical Assessment	X						X	To be reviewed prior to week 8, then as clinically indicated
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every treatment
OTR/go ahead		X					X	Each pembrolizumab and/or abraxane treatment
FBC, U&E/renal profile, Magnesium, LFTs (AST, ALT and bilirubin),	X	X	X	X	X	X	X	Every treatment
Additional immunotherapy tests: TFTs, cortisol, blood glucose, LDH, CRP, cardiac tests	X	X					X	Every day 1 and 43
CrCl (Cockcroft and Gault)	X	X					X	Every cycle day 1 and 43
Lipid profile (cholesterol)	X							Baseline and then as clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	X							Baseline and then as clinically indicated
ECG/ECHO, Trop-T, CK, pro-BNP	X							Pre-treatment
Observation (BP, RR, temp)	X	X	X	X	X	X	X	Every treatment
Weight recorded (height at pre)	X	X	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity (if required):

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Proceed with **pembrolizumab and paclitaxel** if:

Platelets ≥ 100 x 10^9/L **AND**	ANC ≥ 1.0 x 10^9/L

If parameters are outside above limits then paclitaxel is **omitted** (not deferred).

Reduce paclitaxel or abraxane dose permanently by 20% following:

Two consecutive omitted doses for thrombocytopenia
Add filgrastim daily for 3 days from day 2 if neutropenia is persistent following a dose reduction

Non- Haematological toxicity (if required):

	Grade	Adjustment to paclitaxel/abraxane
Nausea/ vomiting	1 or 2	No dose change, consider alternative antiemetics
	≥3	Hold chemotherapy until grade 1 Add aprepitant/change antiemetics If second episode then dose reduction of paclitaxel/abraxane by 20%
Mucositis	1 or 2	No adjustment
	≥3	Hold chemotherapy until grade 1 Provide supportive treatments If second episode then dose reduction of paclitaxel/abraxane by 20%
Neurotoxicity	1 or 2	No adjustment
	≥3	Hold chemotherapy until resolved to grade 1. Reduce paclitaxel/abraxane by 20% If not resolved within 3 weeks then discontinue
Hepatic	1	No adjustment
	2 or 3	Hold chemotherapy until resolved to grade 1. Discontinue if not resolved within 3 weeks
	4	Discontinue

Any grade 3 or 4 toxicity: hold all treatment
For any toxicity that is considered to be immunotherapy related please follow standard IO guidance

If deemed to be pembrolizumab toxicity then resume the chemotherapy part once resolved to grade 1 regardless of concurrent steroid dose (for example thyroid dysfunction, arthralgia)

If chemotherapy toxicity (for example, neutropenia) resume all treatment when resolved to grade 1 or 2 (see table below). If chemotherapy is not restarted proceed with pembrolizumab alone.

When treatment is delayed for 2 consecutive weeks please contact the patient's medical team to review if part of the treatment can restart

References:

https://www.medicines.org.uk/emc

Keynote 322 Cortes et al, Lancet 2020 396:1817-1828

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Version History

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