PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Pembrolizumab with Carboplatin/Paclitaxel and EC Neoadjuvant Breast Cancer Regimen followed by Adjuvant Pembrolizumab

PROTOCOL REF: MPHAPWCP
(Version No. 1.0)

Approved for use in:

- Neoadjuvant treatment of operable, previously untreated, clinical stage II to III invasive triple negative breast cancer (ER/PR must be ≤ 10% and HER2 negative by IHC or FISH)
- Pembrolizumab accessed through MSD scheme initially, patients must be registered
- Performance status 0 or 1

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:

Neoadjuvant treatment

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg	IV	3 weekly
Paclitaxel	80mg/m²	IV	Weekly
Carboplatin	AUC5*	IV	3 weekly
Followed by:			
Pembrolizumab	200mg	IV	3 weekly
Epirubicin	90mg/m^2	IV	3 weekly
Cyclophosphamide	600mg/m^2	IV	3 weekly

Carboplatin has maximum dose of 790mg in this combination

This is given as 4 cycles of carboplatin/pembrolizumab with 12 weeks of paclitaxel

Followed by 4 cycles of pembrolizumab with EC

Next step is surgery

Adjuvant treatment

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg	IV	3 weekly

Adjuvant treatment commences 30 to 60 days post surgery, however should hold until 2 weeks after completion of breast radiotherapy if given

For 9 cycles to complete the 17 cycles in total

***Notes: Meditech uses Wright formula to calculate estimated creatinine clearance**

For automated dose calculation this will be at AUC5

Calvert formula for Carboplatin dosage:

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

There is the option to select carboplatin within the order set where Cockroft and Gault equation can be used manually to enter a calculated dose of carboplatin using AUC6, as undertaken in the clinical trial for this regimen.

If this option is selected a **prescription note must be written at time of prescribing** detailing the parameters used to calculate the dose. Pharmacy will then adjust to the national dose bands. Without a note the prescription will not be processed.

Maximum dose of carboplatin via either method = 790mg in this protocol

Administration:

Appropriate contraceptive measures must be taken for duration of treatment and 12 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:

Moderately emetogenic

Supportive treatments:

Paclitaxel pre-medication:

Chlorphenamine 10mg IV bolus pre chemotherapy

Famotidine 20mg tablet pre chemotherapy for first 3 doses

Dexamethasone 8mg IV as a single dose 30mins before chemotherapy (reduce to 4mg from week 2)

Post carboplatin antiemetics:

Dexamethasone tablets 4mg twice daily for 3 days

Domperidone tablets 10mg three times a day as required

Post EC

Filgrastim prophylaxis – see administration details

Ondansetron tablets 8mg twice daily for 3 days

Dexamethasone tablets 4mg twice daily for 3 days

Domperidone tablets 10mg three times a day as required

Extravasation risk:

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

Paclitaxel: vesicants follow trust/network policy

Carboplatin: irritant

Cyclophosphamide: non vesicant

Epirubicin: vesicant. Erythematous streaking along the vein proximal to the site of injection has been reported, and must be differentiated from an extravasation event. This reaction usually subsides within 30 minutes.

Dosing in renal and hepatic impairment:

<table>
<tr><td rowspan="5">Renal</td><td>Cyclophosphamide</td><td><table><tr><th>CrCl</th><th>Dose (%)</th></tr><tr><td>≥ 30</td><td>100</td></tr><tr><td>10 to 29</td><td>75</td></tr><tr><td>< 10
Or
Haemodialysis (HDx)</td><td>Not recommended. If unavoidable consider 50% of the original dose</td></tr></table></td></tr>
<tr><td>Paclitaxel</td><td>All grades, including patients on HDx – no dose adjustment required</td></tr>
<tr><td>Carboplatin</td><td>Dose adjusted according to most recent results</td></tr>
<tr><td>Epirubicin</td><td>For patients on HDx – consider weekly dosing
Otherwise no adjustments required</td></tr>
<tr><td>Pembrolizumab</td><td>GFR ≥ 10ml/min proceed with treatment
GFR < 10ml/min- use with caution.</td></tr>
</table>

	(prior to start of treatment ONLY/Baseline)	

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
	EC	**LFTs**	**Dose Epirubicin** / **Dose Cyclophosphamide**
		Bil 21 to 51 µmol/L Or AST 2 to 4 x ULN	50% / 100%
		Bil 52 to 85 µmol/L Or AST > 4 x ULN	25% / 75%
		Bil > 85 µmol/L Or Child-Pugh C	Omit / Omit
	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 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, 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:

Paclitaxel and Carboplatin – cycles 1 to 4

Paclitaxel must be administered using a non-PVC giving set with a 0.22 micron filter.

Day	Drug	Dose	Route	Diluent and rate
1	**Pembrolizumab**	200mg	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	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
1	Dexamethasone	8mg	IV Infusion	30 minutes prior to paclitaxel
1	Famotidine	20mg	Orally	60 minutes prior to paclitaxel
1	Ondansetron	16mg	Orally	30 minutes prior to paclitaxel
1	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250 to 500mL sodium chloride 0.9% over 60 minutes**
1	**Carboplatin**	**AUC5**	**IV Infusion**	**500mL glucose 5% over 30 to 60 minutes**
8	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
8	Dexamethasone	4mg	IV Infusion	30 minutes prior to paclitaxel
8	Famotidine	20mg	Orally	60 minutes prior to paclitaxel
8	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250 to 500mL sodium chloride 0.9% over 60 minutes**
15	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
15	Dexamethasone	4mg	IV Infusion	30 minutes prior to paclitaxel
15	Famotidine	20mg	Orally	60 minutes prior to paclitaxel
15	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250 to 500mL sodium chloride 0.9% over 60 minutes**

Cycle is repeated every 21 days

Paclitaxel doses are omitted not delayed, with the intention of completing treatment on schedule at week 12. EC part of regimen to commence 3 weeks after the final dose of carboplatin in this section

Epirubicin and Cyclophosphamide – cycles 5 to 8

Day	Drug	Dose	Route	Diluent and rate
1	**Pembrolizumab**	200mg	IV infusion	100mL sodium chloride 0.9% over 30 minutes in a non-pyrogenic line with 0.2 micron filter **Then change the administration set**
1	Dexamethasone	12mg	Orally	30 minutes prior to chemotherapy
1	Ondansetron	24mg	Orally	30 minutes prior to chemotherapy
1	**Epirubicin**	**90mg/m^2**	**IV**	IV bolus over 10 to 15 minutes
1	**Cyclophosphamide**	**600mg/m^2**	**IV**	IV bolus over 30 minutes
3 to 9	Filgrastim	300 or 480 micrograms	S/C	Daily for 7 days starting on day 3 of cycle

Cycle is repeated every 21 days

Filgrastim dose:

For patients under 70kg: 300 micrograms subcutaneous injection daily

For patients 70kg and above: 480 micrograms subcutaneous injection daily

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: Carboplatin/Paclitaxel and EC	
Haematological	Neutropenia, thrombocytopenia and anaemia.
Gastrointestinal	Nausea, vomiting, stomatitis, diarrhoea, mucositis
Cardiotoxicity	Epirubicin - sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Congestive heart failure. Other cardiac events have been reported, included delayed toxicity.
Dermatological	Alopecia, normally reversible Paclitaxel: Brittle, chipped and ridged nails
Urological	Red colouration of urine for 1 to 2 days after administration following epirubicin Urotoxicity can occur with short-term and long-term use of cyclophosphamide. Hemorrhagic cystitis, pyelitis, ureteritis, and haematuria. Mesna can be given if required. Carboplatin is nephrotoxic
Ocular	Watery eyes, gritty and irritated Risk of cortical blindness with carboplatin (renal impairment may increase this risk)
Ototoxicity	Common when carboplatin used in high doses
Hypersensitivity reactions	Reactions may occur within a few minutes following the initiation of treatment with paclitaxel or carboplatin 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.
General disorders	Carboplatin: Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) Renal function impairment Hyperuricaemia: Serum levels of uric acid can be decreased by allopurinol.

Nervous system	Carboplatin: Paraesthesia and decreased deep tendon reflexes. Paclitaxel: peripheral neuropathy is very common
Musculoskeletal	Arthralgia, myalgia common with paclitaxel
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 Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia	Monitor LFTs, biochemistry, cortisol and TFTs regularly Refer to Immuno-Oncology toxicity specific guidance for adverse event management
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: Cycles 1 to 4

	Pre	Cycle 1	C1D8	C1D15	Cycle 2	C2d8	C2d15	Ongoing
Informed Consent	X							
Clinical Assessment	X				X			As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every treatment
On treatment review		X			X			Every cycle day 1
FBC	X	X	X	X	X	X	X	Every 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
CrCl (Cockcroft and Gault)	X	X			X			Every cycle day 1
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	X							
Blood pressure measurement	X							Repeat if clinically indicated
Respiratory Rate	X							If clinically indicated
Weight recorded	X	X	X	X	X	X	X	Every cycle
Height	X							

Investigations and treatment plan: Cycles 5 to 8

	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Comments
Clinical Assessment	X			X	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every treatment
On treatment review	X	X	X	X	Every cycle
FBC	X	X	X	X	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (AST, ALT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP, cardiac blood tests	X	X	X	X	Every cycle
CrCl (Cockcroft and Gault)	X	X	X	X	Every cycle
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 pre epirubicin					If clinically indicated
Blood pressure measurement	X				Repeat if clinically indicated
Respiratory Rate					If clinically indicated
Weight recorded	X	X	X	X	Every cycle

Investigations and treatment plan: Cycles 9 to 17

	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Comments
Clinical Assessment	X			X	As clinically indicated or at the end of treatment
SACT/IO Assessment (to include PS and toxicities)	X	X	X	X	Every treatment
On treatment review	X	X	X	X	Every cycle
FBC	X	X	X	X	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (AST, ALT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP, cardiac blood tests	X	X	X	X	Every cycle
CrCl (Cockcroft and Gault)	X	X	X	X	Every cycle
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
Blood pressure measurement	X				Repeat if clinically indicated
Respiratory Rate					If clinically indicated
Weight recorded	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity:

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.

Cycles 1 to 4

Day 1

Proceed with **carboplatin and paclitaxel** if:

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

Proceed with day 8 and day 15 **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 dose permanently by 10mg/m^2 following:

Two consecutive omitted doses for thrombocytopenia

Add filgrastim daily for 3 days from day 2 if neutropenia

Consider reducing dose or stopping weekly paclitaxel if severe febrile neutropenia

Reduce carboplatin dose permanently by 20% following:

Two week delay for thrombocytopenia

Or a single occurrence of platelets < 25 x 10^9/L

Consider reducing or stopping carboplatin if severe febrile neutropenia or two consecutive omitted doses of paclitaxel

Cycle 5 commences 3 weeks after the fourth dose of carboplatin (i.e. usually one week after week 12 of paclitaxel)

Cycles 5 to 8

Proceed with EC on day 1 if:

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

If parameters below these limits then defer for one week.

If delayed by two consecutive weeks or febrile neutropenia occurs then dose reduce both agents by 20%

Non- Haematological toxicity:

Any grade 3 or 4 toxicity: hold all treatment

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, as this is neoadjuvant treatment keeping to schedule is beneficial in terms of outcome.

Toxicity	Grade	Adjustment to carboplatin/ paclitaxel	Adjustment to epirubicin/ cyclophosphamide
	1 or 2	No dose change, consider alternative antiemetics	

Nausea/ vomiting	≥3	Hold chemotherapy until grade 1 Add aprepitant/change antiemetics If second episode then dose reduction of paclitaxel and carboplatin by 20%	Hold chemotherapy until grade 1 Add aprepitant/change antiemetics If second episode then dose reduction of epirubicin and cyclophosphamide 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 and carboplatin by 20%	Hold chemotherapy until grade 1 Provide supportive treatments If second episode then dose reduction of epirubicin and cyclophosphamide by 20%
Neurotoxicity	1 or 2	No adjustment	No adjustment, will be persisting side effect from first part of regimen
	≥3	Hold chemotherapy until resolved to grade 1. Reduce paclitaxel by 20%, consider reducing carboplatin 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	
Cardiac	1 or 2	Not applicable	No adjustment
	3	Not applicable	Discontinue epirubicin

References:

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

Keynote 522 trial protocol

Pembrolizumab for early triple negative breast cancer
Schmid et al NEJM 2020 382:810-821

Circulation/Dissemination

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Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
August 2022	1.0	**Helen Flint** **Consultant Pharmacist**	New Regimen Protocol