

# Pembrolizumab carboplatin paclitaxel EC/AC for early breast cancer

## Indication

Triple negative breast cancer (neoadjuvant), stage cT1c N1-2 or cT2-4d N0-2

## Regimen details

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg	IV	3-weekly
	<b>Or</b> 395mg	SC	3-weekly
Paclitaxel	80mg/m <sup>2</sup>	IV	Weekly
Carboplatin	AUC5 (Max dose 790mg)	IV	3-weekly
For 4 cycles, followed by:			
Pembrolizumab	200mg	IV	3-weekly
	<b>Or</b> 395mg	SC	3-weekly
Doxorubicin*	60mg/m <sup>2</sup>	IV	3-weekly
Cyclophosphamide	600mg/m <sup>2</sup>	IV	3-weekly
For 4 cycles, followed by:			
Pembrolizumab	400mg	IV	6-weekly
	<b>Or</b> 790mg	SC	6-weekly
For a further 5 cycles			

\*or epirubicin 90mg/m<sup>2</sup>

## Cycle frequency

As above

## Number of cycles

As above

## Administration

### Pembrolizumab subcutaneous

Inject into the subcutaneous tissue of the thigh or abdomen, avoiding the 5 cm area around the navel. Do not inject into skin that is damaged, sore, bruised, scarred, scaly, or has red patches. Rotate injection sites for subsequent injections.

- Inject 395mg over 1 minute
- Inject 790mg over 2 minutes

### Pembrolizumab intravenous

Pembrolizumab is to be given before chemotherapy, via a 0.2µm in-line filter in 100ml 0.9% sodium chloride over 30 minutes

### Paclitaxel

Paclitaxel is to be given after pembrolizumab and before carboplatin. See below for pre-medication

Paclitaxel is given via a 0.2µm in-line filter in 250ml 0.9% sodium chloride over 1 hour

Carboplatin is given in 500ml 5% glucose over 1 hour

Patients must be monitored for infusion reactions

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Systemic Anticancer Treatment Protocol

Epirubicin/doxorubicin and cyclophosphamide are given into the side port of a fast flowing drip

### Pre-medication

30 minutes before paclitaxel

Chlorphenamine 10mg	I.V. bolus
Ranitidine 50mg (or other H <sub>2</sub> antagonist)	50mls 0.9% sodium chloride
Dexamethasone 10mg	100mls 0.9% sodium chloride

For subsequent weeks reduce dexamethasone dose to 8mg then 4mg then stop dexamethasone.

Continue to give dexamethasone 8mg as anti-emetic pre-med for carboplatin day 1.

If patient experiences any hypersensitivity reaction do not reduce the dexamethasone dose further but continue the same or increased dose of dexamethasone. If severe reaction, change regimen/remove offending agent

Stop H<sub>2</sub> antagonist after 3 doses if paclitaxel tolerated

### Emetogenicity

Carboplatin/paclitaxel day 1: moderate

Carboplatin/paclitaxel day 8 & 15: minimal

Doxorubicin (or epirubicin) & cyclophosphamide: high

Pembrolizumab alone: minimal

### Additional supportive medication

Pegfilgrastim 6mg subcutaneous 24 hours after chemotherapy on cycles 5-8

### Extravasation

Pembrolizumab – neutral

Paclitaxel – vesicant

Carboplatin – irritant

Doxorubicin/epirubicin – vesicant

Cyclophosphamide - neutral

### Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT inc AST	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Cortisol	Baseline
Luteinising hormone	Baseline
Follicle stimulating hormone	Baseline
Testosterone	Baseline
MUGA/echocardiogram	Before doxorubicin/epirubicin

### Investigations –pre subsequent cycles

FBC U&Es and LFTs – before each dose of chemotherapy

Magnesium once a month, random glucose or BM once a month

TFTs every 6 weeks

Consultation every three weeks

### Standard limits for administration to go ahead

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

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Systemic Anticancer Treatment Protocol

Investigation	Limit
Neutrophil count (day 1)	$\geq 1.0 \times 10^9/L$
Neutrophil count (day 8 & 15)	$\geq 0.8 \times 10^9/L$
Platelet count (day 1)	$\geq 100 \times 10^9/L$
Platelet count (day 8 & 15)	$\geq 75 \times 10^9/L$
Creatinine clearance	$\geq 60 \text{ mL/min}$
Bilirubin	$\leq 1.5 \times \text{ULN}$
AST	$< 1.5 \times \text{ULN}$

## Dose modifications

### Haematological toxicity:

#### Cycles 1-4

In the event of haematological toxicity, delay day 1 treatment for 7 days. Paclitaxel should be omitted on day 8 or 15, not delayed

If treatment is delayed for 2 weeks, or if platelets fall below 25, reduce carboplatin dose by 25%

#### Cycles 5-6

In the event of haematological toxicity, delay day 1 treatment for 7 days

If treatment is delayed for 2 weeks, or if febrile neutropenia occurs, reduce dose of doxorubicin (or epirubicin) and cyclophosphamide by 25%

### Non-haematological toxicity:

<b>Renal</b>	<b>Carboplatin:</b> review serum creatinine result at each cycle, recalculate carboplatin dose if creatinine has increased by >20%		
<b>Hepatic</b>		<b>Epirubicin/Doxorubicin</b>	<b>Cyclophosphamide</b>
	<b>Bilirubin</b> $\mu\text{mol/L}$	<b>Dose</b>	<b>Dose</b>
	24 to 50	50%	100%
	51 to 85	25%	75%
	Above 85	Omit	Omit
	<b>Paclitaxel</b>		
	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		
Alk Phos more than 3 times ULN	Consider dose reduction		
<b>Peripheral Neuropathy</b>	NCI-CTC grade 2 peripheral neuropathy withhold paclitaxel only until the neuropathy recovers to grade 1 then dose reduce by 10mg/m <sup>2</sup> If NCI-CTC grade 3 peripheral neuropathy occurs, discontinue paclitaxel and proceed to EC part of regimen		
<b>Myalgia/Arthralgia</b>	Often co-exist, usually grade 1 or 2. Manage with reassurance that the condition is self-limiting. NSAIDs may be considered but they may be ineffective		

<b>Infusion reactions</b>	<p>Carboplatin &amp; paclitaxel: Consult network guidelines for managing hypersensitivity reactions and rechallenge</p> <p>Pembrolizumab: Discontinue pembrolizumab in the event of a grade 3 or 4 infusion reaction</p>
<b>Mucositis</b>	Reduce epirubicin/doxorubicin by 20% in the event of grade 3 or 4 mucositis

### Immunotherapy related toxicities

Immunotherapy toxicities should be aggressively managed as can cause permanent and life-threatening complications. Refer to UKONS and ESMO guidance for treatment of immune related toxicities. Available at:

<https://www.healthierlsc.co.uk/canceralliance/chemotherapy-protocols/immunotherapy-toxicity-guidelines>

### Adverse effects –

for full details consult product literature/ reference texts

Nausea  
 Alopecia  
 Anemia  
 Neutropenia  
 Fatigue  
 Diarrhoea  
 Elevated liver enzymes  
 Vomiting  
 Asthenia  
 Constipation  
 Rash  
 Peripheral neuropathy  
 Infusion reactions  
 Hypothyroidism  
 Hyperthyroidism  
 Skin reaction  
 Adrenal insufficiency

### 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.

**Phenytoin:** requires close monitoring if using concurrently.

### Cyclophosphamide

**Amiodarone:** increased risk of pulmonary fibrosis – avoid if possible

**Azathioprine:** increased risk of hepatotoxicity

**Clozapine:** increased risk of agranulocytosis – avoid concomitant use

**CYP2B6 and CYP3A4 inhibitors (Nevirapin, Ritonavir):** co-administration may reduce the efficacy of cyclophosphamide

**Digoxin tablets:** reduced absorption – give as liquid form

**Indapamide:** prolonged leucopenia is possible - avoid

**Itraconazole:** may increase adverse effects of cyclophosphamide

**Grapefruit juice:** decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose

### 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

**Yellow fever vaccine:** contraindicated

**Paclitaxel:**

**Clozapine:** increased risk of agranulocytosis.

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.

### Additional comments

### References

Schmid et al. Pembrolizumab for Early Triple-Negative Breast Cancer N Engl J Med 2020; 382:810-821

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**THIS PROTOCOL HAS BEEN DIRECTED BY DR HOGG, LEAD ONCOLOGIST FOR BREAST CANCER**

**RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE**

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