

Pembrolizumab, CARBOplatin AUC 5 and weekly PACLitaxel 80mg/m² followed by DOXOrubicin and cycloPHOSphamide (AC 60/600) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Pembrolizumab in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early stage triple negative breast cancer at high risk of recurrence.	C50	00857a	ODMS 01/06/2024

*This applies to post 2012 indications

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

In the neoadjuvant phase, treatment is administered for eight 21 day cycles, or until disease progression that precludes definitive surgery or unacceptable toxicity. Pembrolizumab is administered at a dose of 200mg on day 1 of cycle 1-8 along with:

- Cycles 1-4: CARBOplatin day 1, PACLitaxel day 1, 8, 15
- Cycles 5-8: DOXOrubicin and cycloPHOSphamide day 1

In the adjuvant phase, pembrolizumab is either administered at a dose of 200mg on day 1 of a 21 day cycle for 9 cycles, or at a dose of 400mg on day 1 of a 42 day cycle for 5 cycles, or until disease recurrence or unacceptable toxicity occurs. **The maximum treatment duration with pembrolizumab is 12 months, beginning at cycle 1.**

Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to pembrolizumab as neoadjuvant treatment in combination with chemotherapy should not receive pembrolizumab monotherapy as adjuvant treatment.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

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Neoadjuvant phase: Cycle 1-4

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab	200mg	IV infusion	100mL 0.9% NaCl over 30 minutes ^{a, b}	Every 21 days
2	1,8,15	PACLitaxel	80mg/m ²	IV infusion	250mL 0.9% NaCl over 60 minutes ^{c, d}	Every 21 days
3	1	CARBOplatin	AUC 5	IV infusion	500mL glucose 5% over 30 minutes	Every 21 days

^a Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml.

^b Administer using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.

^c PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.

^d PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Neoadjuvant phase: Cycle 5-8

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab	200mg	IV infusion	100ml 0.9% NaCl over 30 minutes ^{a, b}	Every 21 days
2	1	DOXOrubicin ^c	60mg/m ²	IV push	N/A	Every 21 days
3	1	cycloPHOSphamide	600mg/m ²	IV infusion ^d	250mL 0.9% NaCl over 30 minutes	Every 21 days

^a Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml.

^b Administer using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.

^c Lifetime cumulative dose of DOXOrubicin is 450mg/m²

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined belowⁱ and to the age of the patient.

^d Cyclophosphamide may also be administered as an IV bolus over 5-10mins.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Adjuvant phase: Cycle 9-17 (Pembrolizumab 3 weekly schedule)

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Pembrolizumab	200mg	IV infusion	100ml 0.9% NaCl over 30 minutes ^{a, b}	Every 21 days

^a Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml.

^b Administer using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

*See alternative treatment schedule using 400mg dose below

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ALTERNATIVE TREATMENT SCHEDULE:

Adjuvant phase: Cycle 9-13 (Pembrolizumab 6 weekly schedule)

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Pembrolizumab	400mg	IV infusion	100ml 0.9% NaCl over 30 minutes ^{a, b}	Every 42 days
^a Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml.					
^b Administer using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.					

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

$$(\text{mg}) = \text{target AUC (mg/ml x min)} \times (\text{GFR ml/min} + 25)$$

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible
- **Estimation of GFR** (eGFR) can be done by using the Wright formula or using the Cockcroft and Gault formula to measure creatinine clearance
- The GFR used to calculate the AUC dosing should not exceed 125ml/min
- For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended
 - where obesity (body mass index [BMI] ≥ 30 kg/m²) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered
 - where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62micromol/L or a steady pre-operative creatinine value may be considered
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr } (\mu\text{mol/min})}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{\text{SCr } (\mu\text{mol/min})}$$

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Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indication as above
- Age > 18 years
- ECOG 0-1
- TNBC as confirmed by validated test method
- Newly diagnosed, previously untreated non-metastatic disease T1c N1-2 or T2-4 N0-2 (AJCC 7th Edition)
- Adequate haematological, hepatic and renal function

CAUTIONS:

- History of serious autoimmune disease

EXCLUSIONS:

- Hypersensitivity to pembrolizumab, CARBOplatin*, PACLitaxel, DOXOrubicin, cycloPHOSphamide or any of the excipients.
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is available [here](#)
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids)
- History of interstitial lung disease
- Untreated brain metastases
- Any active clinically significant infection requiring therapy
- Disease progression while receiving platinum based chemotherapy
- Pregnancy and lactation
- Severe hepatic impairment
- Baseline neutrophil count < 1.5x10⁹ cells/L
- Congestive heart failure (LVEF < 50%) or other significant heart disease

*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

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PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- Thyroid function tests
- Virology Screen: Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- Isotope GFR measurement (preferred) or GFR / CrCl estimation
- ECG
- MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated
- Audiometry as clinically indicated.

Regular tests:

- FBC, renal and liver profile weekly in cycles 1-4 and prior to each cycle thereafter
- Glucose prior to each cycle
- TSH every 3 to 6 weeks
- If clinically indicated, MUGA scan or echocardiogram
- Assessment of peripheral neuropathy status before each cycle (PAClitaxel only)

Disease monitoring:

Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Dose reduction is not recommended for pembrolizumab. Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of pembrolizumab therapy and institution of systemic high-dose corticosteroid
- Guidelines for withholding of doses of pembrolizumab, or permanent discontinuation are described below in Table 4
- Dose modifications for PAClitaxel, CARBOplatin, DOXOrubicin and cycloPHOSphamide are detailed in tables 1, 2, 3 and 5 below
- Any dose modification should be discussed with a Consultant

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Haematological:

Table 1: Dose modification for cycles of PACLitaxel and CARBOplatin in haematological toxicity (Cycle 2-4)

Day	ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	CARBOplatin Dose	PACLitaxel Dose
Day 1	≥1	and	≥ 75	100% Dose	100% Dose
	<1	and/or	<75	Delay treatment until recovery ^a	Delay treatment until recovery ^a
Day 8, 15	<0.5	and/or	<50		Omit day 8 and day 15 PACLitaxel dose
Day 1	Febrile Neutropenia			Decrease CARBOplatin dose by one dose level	
	<0.5 for ≥ 7 days	or	<10		
			10 to 50 with bleeding tendencies		
	Treatment delay for haematological toxicity > 1 week 1 st occurrence			Decrease CARBOplatin dose by one dose level	
	2 nd occurrence			Decrease CARBOplatin dose by one further dose level for subsequent cycles	

^aTreatment may be delayed for a maximum of 3 weeks.

Table 2: Dose modification for cycles of DOXOrubicin and cycloPHOSphamide in haematological toxicity

ANC (x10 ⁹ /L)	Platelets (x10 ⁹ /L)	Dose (Both Drugs)
≥ 1.5	> 90	100%
1 -1.49	70 to 90	*75%
< 1	< 70	Delay

*May consider using G-CSF for neutrophil support rather than dose reduction

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Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
Pembrolizumab	No dose adjustment is needed		Mild: no dose adjustment is needed			
	Haemodialysis: no need for dose adjustment is expected		Moderate and severe: no need for dose adjustment is expected			
CARBOplatin	See note below ^a		No dose modification required			
PACLitaxel	Renal impairment: No need for dose adjustment is expected		ALT		Total Bilirubin	Dose
	Haemodialysis: no need for dose adjustment is expected		< 10xULN	and	≤ 1.25xULN	80mg/m ²
			< 10xULN	and	1.26-2xULN	60mg/m ²
			< 10xULN	and	2.01-5xULN	40mg/m ²
		≥10xULN	and /or	>5xULN	Contraindicated	
cycloPHOSphamide	CrCl (mL/min)	Dose	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy			
	≥30	No dose adjustment is needed				
	10-29	Consider 75% of the original dose				
	<10	Not recommended, if unavoidable consider 50% of the original dose				
Haemodialysis	Not recommended, if unavoidable consider 50% of the original dose					
DOXOrubicin	CrCl (mL/min)	Dose	Serum Bilirubin (micromol/L)	Dose		
	>10	No dose adjustment is needed	20-50	50% of the original dose		
	<10	No need for dose adjustment is expected	> 51-86	25% of the original dose		
	Haemodialysis	Consider 75% of the original dose	>86 or Child-Pugh C	Not recommended		
Pembrolizumab: Renal and hepatic dose modifications – Giraud et al 2023 CARBOplatin: Renal and hepatic dose modifications – As previously agreed across NCCP regimens PACLitaxel: Renal and hepatic dose modifications – Giraud et al 2023 DOXOrubicin: Renal and hepatic dose modifications – Giraud et al 2023 cycloPHOSphamide: Renal and hepatic dose modifications – Giraud et al 2023						

^aRenal dysfunction and CARBOplatin

- Patients with creatinine clearance values of <60ml/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution

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- If GFR \leq 20ml/min, CARBOplatin should not be administered at all
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required on each cycle based on a serum creatinine obtained within 48 hrs of drug administration.

If isotope GFR is used, the dose can remain the same provided the serum creatinine is \leq 110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 4: Dose Modifications for Pembrolizumab for Adverse Events

Immune-related adverse reactions	Severity (NCI-CTCAE v.4 grading)	Treatment modification
Pneumonitis	Grade 2	Withhold*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine $>$ 1.5 to \leq 3 times upper limit of normal (ULN)	Withhold*
	Grade \geq 3 with creatinine $>$ 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis	Withhold*
	Type 1 diabetes associated with Grade \geq 3 hyperglycaemia (glucose $>$ 250 mg/dL or $>$ 13.9 mmol/L) or associated with ketoacidosis	For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise, treatment should be discontinued.
	Hyperthyroidism Grade \geq 3	
Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.	
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $>$ 3 to 5 times ULN or total bilirubin $>$ 1.5 to 3 times ULN	Withhold*
	Grade \geq 3 with AST or ALT $>$ 5 times ULN or total bilirubin $>$ 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases \geq 50% and lasts \geq 1 week	
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue

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Other immune-related adverse reactions**	Based on severity and type of reaction (grade 2 or Grade 3)	Withhold*
	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome Grade 4 or recurrent Grade 3	Permanently discontinue
Infusion-related reactions	Grade 3 or 4	Permanently discontinue

* Until adverse reactions recover to Grade 0-1. If treatment related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of pembrolizumab or if corticosteroid dosing cannot be reduced to $\leq 10\text{mg}$ prednisone or equivalent per day within 12 weeks, pembrolizumab should be permanently discontinued.

**Pembrolizumab should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-related adverse reactions, unless otherwise specified in Table 4.

Table 5: Dose Modification for PACLitaxel for Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥ 2 motor or sensory neuropathy First Occurrence	Decrease dose of PACLitaxel by $10\text{mg}/\text{m}^2$.
Persistent Grade ≥ 2 or 2 nd occurrence	Decrease dose of PACLitaxel by a further $10\text{mg}/\text{m}^2$
All other grade 2 non-haematological toxicity	Hold treatment until toxicity resolves to \leq grade 1. Decrease subsequent doses by $10\text{mg}/\text{m}^2$.
\geq Grade 3 reaction	Discontinue

Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue treatment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting linked [here](#)

Pembrolizumab:

Minimal (**Refer to local policy**).

CARBOplatin/PACLitaxel cycles:

High, Day 1 (**Refer to local policy**)

Low, Day 8 and 15 (**Refer to local policy**)

DOXOrubicin/cycloPHOSphamide cycles:

High (**Refer to local policy**)

For information:

Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for inclusion in NCIS (Medical Oncology) linked [here](#)
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link [here](#)

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PREMEDICATIONS:

- All patients must be premedicated with corticosteroids, antihistamines, and H₂ antagonists prior to first dose of PACLitaxel treatment.
- The H₂ antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown
 - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy
 - Where a patient experiences hypersensitivity, consider the use of alternative H₂ antagonists (**Refer to local policy**)

Table 6: Suggested premedications prior to treatment with PACLitaxel

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	DexAMETHasone	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8 ^b and thereafter	DexAMETHasone	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine ^c	20mg IV	30 minutes
^a Dose of dexAMETHasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexAMETHasone orally 12 hr and 6 hr prior to re-challenge with PACLitaxel according to consultant guidance.			
^b Dose of dexAMETHasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			
^c Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.			

OTHER SUPPORTIVE CARE:

- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered
- Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cyclophosphamide

ADVERSE EFFECTS

- For adverse effects associated with the medications in this regimen please refer to the relevant Summary of Product Characteristics (SmPC)

DRUG INTERACTIONS:

- Consult current drug interaction databases and relevant SmPC

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COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Pembrolizumab:

Patient Guide

<https://www.hpra.ie/img/uploaded/swedocuments/896369cd-ec45-4e3a-978f-bacea851002e.pdf>

Patient Alert Card

<https://www.hpra.ie/img/uploaded/swedocuments/874908fb-698e-472d-91d5-dc3a1f14a8f7.pdf>

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Version	Date	Amendment	Approved By
1	04/06/2024		Prof Maccon Keane
2	05/07/2024	Pembrolizumab 400mg adjuvant treatment option added. Amendment to table 1 to clarify dose reduction.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

ⁱCardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:

- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient

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