Pembrolizumab 400mg, Weekly CARBOplatin AUC 1.5 and PACLitaxel 80mg/m^2 followed by Dose Dense 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	00861a	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 as below, or until disease progression that precludes definitive surgery or unacceptable toxicity.

- Cycles 1-4 (4 x 21 day cycles) : CARBOplatin and PACLitaxel day 1, 8, 15
- Cycles 5-8 (4 x 14 day cycles): DOXOrubicin and cycloPHOSphamide day 1
- Every 6 weeks: Pembrolizumab (i.e. day 1 of cycles 1, 3, 5, and 8)

In the adjuvant phase, pembrolizumab is administered on day 1 of a 42 day cycle for 5 cycles commencing 6 weeks after day 1 of cycle 8 above, 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.

G-CSF support (using standard or pegylated form) is required with all cycles of dose dense chemotherapy.

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

Cycle 1-4 (21 day cycles)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle (21 days)
1	1	Pembrolizumab	400mg	IV infusion	100mL 0.9% NaCl over 30 minutes[a, b]	**1 and 3 only**
2	1,8,15	PACLitaxel	80mg/m^2	IV infusion	250mL 0.9% NaCl over 60 minutes[c, d]	1 – 4
3	1,8,15	CARBOplatin	AUC 1.5	IV infusion	250mL glucose 5% over 30 minutes	1 – 4
[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.

Dosing schedule: Cycle 1-4

Cycle	1			2			3			4		
Week	1	2	3	4	5	6	7	8	9	10	11	12
Pembrolizumab	✓						✓					
PACLitaxel	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CARBOplatin	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Cycle 5-8 (14 day cycles)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle (14 days)
1	1	Pembrolizumab	400mg	IV infusion	100mL 0.9% NaCl over 30 minutes[a, b]	**5 and 8 only**
2	1	DOXOrubicin[c]	60mg/m^2	IV push	N/A	5 – 8
3	1	cycloPHOSphamide	600mg/m^2	IV infusion[d]	250mL 0.9% NaCl over 30 minutes	5 – 8
[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/m^2 **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below[i] 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.

Dosing schedule: Cycle 5-8

Cycle	5		6		7		8	
Week	13	14	15	16	17	18	19	20
Pembrolizumab	✓						✓	
DOXOrubicin	✓		✓		✓		✓	
cycloPHOSphamide	✓		✓		✓		✓	

Cycle 9-13 (42 day cycles)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab	400mg	IV infusion	100mL 0.9% NaCl over 30 minutes[a, b]	9-13
[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:

(mg) = target AUC (mg/ml x min) x (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.*

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

2. *SCr measured using Jaffe assay*

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

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

COCKCROFT-GAULT FORMULA

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

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 < $1.5x10^9$ 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

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

Haematological:

Table 1: Dose modification for cycles of PACLitaxel and CARBOplatin in haematological toxicity

ANC (x 10^9/L) Pretreatment blood test	
≥1.0	100% dose
0.5 to < 1.0	Delay treatment until recovery
< 0.5	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles
Febrile neutropenia or previous delay for myelosuppression	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles
Prolonged recovery greater than two weeks delay or 3rd delay for myelosuppression	Delay treatment until recovery, consider reducing PACLitaxel and CARBOplatin by 50% for subsequent cycles or cease
Platelets (x 10^9/L) Pretreatment blood test	
≥ 100	100% dose
75 to < 100	Clinician's discretion; continue treatment if patient is clinically well.
50 to < 75	Delay treatment until recovery
< 50	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles

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

ANC (x 10^9/L)		**Platelets (x 10^9/L)**	**Dose (All Drugs)**
≥ 1.0	and	≥ 100	100%
< 1.0	and	≥ 100	Delay for 1 week (or longer if needed), then give 100% dose if ANC > 1.0 and platelets ≥ 100.
≥ 1.0	And	< 100	Delay for 1 week (or longer if needed), then give 100% dose if ANC > 1.0 and platelets ≥ 100. Dose reduce to 75% after a second delay.

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Drug	**Renal Impairment**	**Hepatic Impairment**			
Pembrolizumab	No dose adjustment is needed Haemodialysis: no need for dose adjustment is expected	Mild: no dose adjustment is needed 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 Haemodialysis: no need for dose adjustment is expected	**ALT**		**Total Bilirubin**	**Dose**
		< 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				

[a]Renal 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
- If GFR ≤ 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 ≤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 ≤ 3 times upper limit of normal (ULN)	Withhold*
	Grade ≥ 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 Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold* 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.
	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 ≥ 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 ≥ 50% and lasts ≥ 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
Other immune-related adverse reactions**	Based on severity and type of reaction (grade 2 or Grade 3)	Withhold*
	Grade 3 or4 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 ≤ 10mg 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 Persistent Grade ≥2 or 2nd occurrence	 Decrease dose of PACLitaxel by 10mg/m^2. Decrease dose of PACLitaxel by a further 10mg/m^2
All other grade 2 non-haematological toxicity	Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m^2.
≥ 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: Moderate **(Refer to local policy).**
PACLitaxel: Low **(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 information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here

PREMEDICATIONS:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment
- The H_2 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 H_2 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

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

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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13. cycloPHOSphamide (Endoxana®) Injection 500mg Powder for Solution for Injection Summary of Product Characteristics. Accessed March 2024. Last updated Dec 2018. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-001_21122018112107.pdf

Version	Date	Amendment	Approved By
1	14/06/2024		Prof Maccon Keane
1a	18/07/2024	Update to the reimbursement status section	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Cardiotoxicity 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