Pembrolizumab, PACLitaxel 175mg/m^2, CARBOplatin AUC 5 and Bevacizumab Therapy

Note: There is an option for Pembrolizumab, PACLitaxel and CARBOplatin Therapy as described in NCCP regimen 00817

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1	C53	00811a	Pembrolizumab: Reimbursement by exception[i] PACLitaxel, CARBOplatin Bevacizumab: N/A

*This is for post 2012 indications only

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.

Pembrolizumab, PACLitaxel, CARBOplatin and bevacizumab are administered on Day 1 of a 21 Day cycle and continued for 6 -8 cycles. Patients experiencing ongoing clinical benefit may continue beyond 6 cycles of PAClitaxel and CARBOplatin at the discretion of their treating clinician.

Pembrolizumab is continued as maintenance until disease progression or unacceptable toxicity occurs. Bevacizumab is continued as maintenance until disease progression or unacceptable toxicity occurs.

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

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

Pembrolizumab, PACLitaxel, CARBOplatin and Bevacizumab Therapy

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab[a]	200mg	IV infusion	100mL 0.9% NaCl over 30 minutes using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter	Every 21 days
2	1	PACLitaxel[b,c]	175mg/m^2	IV infusion	500mL 0.9% NaCl over 3 hours	Every 21 days
3	1	CARBOplatin	AUC 5	IV infusion	500mL glucose 5% over 30 minutes	Every 21 days
4	1	Bevacizumab	15mg/kg	IV infusion	100mL 0.9% NaCl over 90 minutes[d,e]	Every 21 days

[a]Pembrolizumab is diluted to a final concentration ranging from 1-10mg/mL.

[b]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.

[c]PACLitaxel should be diluted to a concentration of 0.3-1.2mg/mL.

[d]Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.

[e]The initial dose of bevacizumab should be delivered over 90 minutes as an intravenous infusion.
If the first infusion is well tolerated, the second infusion may be administered over 60 minutes.
If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
Alternatively, the unlicensed use of shorter infusion times[ii] is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance here.
It should not be administered as an intravenous push or bolus.

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

Maintenance Therapy with Pembrolizumab and Bevacizumab

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab[a]	200mg	IV infusion	100mL 0.9% NaCl over 30 minutes using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter	Every 21 days
2	1	Bevacizumab	15mg/kg	IV infusion	100mL 0.9% NaCl over 90 minutes[b,c]	Every 21 days

[a]Pembrolizumab is diluted to a final concentration ranging from 1-10mg/mL.

[b]Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.

[c]The initial dose of bevacizumab should be delivered over 90 minutes as an intravenous infusion.
If the first infusion is well tolerated, the second infusion may be administered over 60 minutes.
If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
Alternatively, the unlicensed use of shorter infusion times[ii] is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance here.
It should not be administered as an intravenous push or bolus.

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:

Dose (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** may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate 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/m^2) 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 62 micromol/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.*

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

2. *SCr measured using Jaffe assay*

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

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

ELIGIBILITY:

- Indications as above
- ECOG Status 0-1
- Adequate haematological, hepatic and renal function

CAUTION:

- History of serious autoimmune disease
- Bleeding/clotting disorders
- History of significant venous thromboembolism
- History of interstitial lung disease
- Surgical procedure/complications or an underlying condition that could lead to increased risk of fistulation or perforation
- Underlying condition that could lead to increased risk of fistulation or perforation
- Baseline neutrophil count < 1.5 x 10^9 cells/L
  Prior radiation to the chest wall or pelvic area or other serious medical illness

EXCLUSIONS:

- Hypersensitivity to pembrolizumab, PACLitaxel, CARBOplatin*, bevacizumab or any of the excipients
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is available here
- Unstable CNS metastases
- 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)
- Any active clinically significant infection requiring therapy
- Pregnancy or lactation
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Severe hepatic impairment (PACLitaxel)
- Cerebrovascular disease (e.g. TIA, CVA or cerebral haemorrhage within 6 months prior to treatment)
- Cardiovascular disease e.g. MI within 6 months prior to treatment, poorly controlled arrhythmia, congestive cardiac failure >/= Class 2

  *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
- PD-L1 expression using a validated test method
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- Blood glucose
- Thyroid function tests
- Virology Screen: Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- Audiometry if clinically indicated
- Dipstick urinalysis for protein
- Blood pressure measurement
- Cardiac assessment including history, physical exam and baseline ECG.
    - ECHO/MUGA should be considered in patients who have a history of cardiovascular disease, prior treatment with an anthracycline or other cardiotoxic drug or prior chest wall radiation
- INR if clinically indicated*
  *(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.)

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Blood glucose prior to each cycle
- Thyroid function tests every 3 to 6 weeks
- Dipstick urinalysis for protein
- Blood pressure (including post treatment)
- INR if clinically indicated*
  *(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.)

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 (See Table 3).

- Bevacizumab dose reduction for adverse events is not recommended (SmPC). If indicated,
- Bevacizumab therapy should either be permanently discontinued or temporarily suspended until toxicity resolves (Table 4 and Table 5).
- Any dose modification should be discussed with a Consultant.

Haematological:

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

ANC (x 10^9/L) (pre-treatment blood test)	
≥1.0 to <1.5	Treatment should continue if patient is clinically well, Consultant decision
0.5 to 1.0	Delay treatment until recovery
< 0.5 and/ or febrile neutropenia	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles
Platelets (x 10^9/L) (pre-treatment blood test)	
≥75 to <100	Treatment should continue if patient is clinically well, Consultant decision
50 to 75	Delay treatment until recovery
<50	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles

Renal and Hepatic Impairment:

Table 2: Recommended dose modification for pembrolizumab[a], PACLitaxel[b], CARBOplatin[c] and bevacizumab[d] in renal and hepatic impairment***

Drug	**Renal Impairment**	**Hepatic Impairment**			
Pembrolizumab[a]	No dose adjustment is needed Haemodialysis: No need for dose adjustment is expected	Mild			No dose adjustment is needed
		Moderate/Severe			No need for dose adjustment is expected
PACLitaxel[b]	No need for dose adjustment is expected Haemodialysis: No need for dose adjustment is expected	Transaminases		Bilirubin	Dose
		< 10 x ULN	and	≤ 1.25 x ULN	No dose reduction
		< 10 x ULN	and	1.26-2 x ULN	75% of original dose
		< 10 x ULN	and	2.01-5 x ULN	50% of original dose
		≥ 10 x ULN	or	> 5 x ULN	Contraindicated
CARBOplatin	See note below[c]	No dose modification required			
Bevacizumab[d]	No need for dose adjustment is expected Haemodialysis: No need for dose adjustment is expected	No need for dose adjustment is expected			

[a] Pembrolizumab (renal and hepatic - Giraud et al 2023);
[b] PACLitaxel (renal and hepatic – Giraud et al 2023),
[c] CARBOplatin (renal- See note below*, hepatic - Giraud et al 2023),
[d] Bevacizumab (renal and hepatic - Giraud et al 2023)

***See Table 3 for management of pembrolizumab in treatment related hepatitis

[c]**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.
- In case of GFR ≤ 20mL/min CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formulas are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 3: Recommended treatment modifications for pembrolizumab

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	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 3.

Table 4: Recommended dose modification for PACLitaxel, CARBOplatin and bevacizumab in adverse events

Adverse Reactions	Dose Modification
Peripheral Neuropathy	
Grade ≤ 2 which is present at the start of the next cycle	Reduce PACLitaxel by 25%; if persistent, reduce PACLitaxel by 50%
Grade ≥ 3	Omit PACLitaxel dose
Mucositis and stomatitis	
Grade 2 • 1st occurrence • 2nd occurrence • 3rd occurrence • 4th occurrence	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: No dose reduction Reduce PACLitaxel and CARBOplatin by 25% Reduce PACLitaxel and CARBOplatin by 50% Omit PACLitaxel and CARBOplatin
Grade 3 or Grade 4 • 1st occurrence • 2nd occurrence	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: Reduce PACLitaxel and CARBOplatin by 50% Omit PACLitaxel and CARBOplatin
Hypertension	
• Uncontrolled * or symptomatic hypertension on Day 1	Withhold bevacizumab treatment and start antihypertensive therapy or adjust pre-existing medication
• Grade 2-3 hypertension	Initiate antihypertensive therapy and consider interruption of bevacizumab until controlled
• Grade 4 hypertension or persisting grade 3 hypertension	Discontinue bevacizumab
Grade 4 Proteinuria	Discontinue bevacizumab
Tracheoesophageal (TE) fistula or any Grade 4 fistula	Discontinue bevacizumab
Grade 4 Thromboembolic events	Discontinue bevacizumab
Haemorrhagic event ≥ Grade 3	Discontinue bevacizumab
Gastrointestinal Perforation	Discontinue bevacizumab
*Uncontrolled hypertension for initiating bevacizumab is defined as sustained BP>150/100mmHg while receiving anti-hypertensive medication	

Table 5: Dose modifications of bevacizumab for proteinuria

Degree of proteinuria	Action
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection
24-hour urine total protein (g/24hr)	**Action**
less than or equal to 2	Proceed
greater than 2 to 4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24hour
greater than 4	Discontinue Therapy

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: High **(Refer to local policy)**
PACLitaxel: Low **(Refer to local policy)**
Bevacizumab: Minimal **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-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 outlines suggested premedications prior to treatment with PACLitaxel

Table 6: Suggested premedications prior to treatment with PACLitaxel

Drug	Dose	Administration prior to PACLitaxel
dexAMETHasone	20mg oral or IV[a,b]	For oral administration: approximately 6 and 12 hours or for IV administration: 30 minutes
Chlorphenamine	10mg IV	30 minutes
Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexAMETHasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance.		
[b]If aprepitant is added to the anti-emetic regimen, consideration should be given to reducing the dose of dexAMETHasone to 12mg on the day of treatment.		
[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.
- Anti-diarrhoeal treatment may be required with Bevacizumab **(Refer to local policy)**.

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 more information.

COMPANY SUPPORT RESOURCES/Useful Links:

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

Pembrolizumab Patient Alert Card
https://www.hpra.ie/img/uploaded/swedocuments/094590ae-1f3d-4b15-b76e-3b16bd642782.pdf

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Version	Date	Amendment	Approved By
1	17/04/2023		Prof Maccon Keane
2	05/07/2024	Reviewed. Updated exclusion criteria in line with NCCP standardisation. Updated cautions section. Updated renal and hepatic dose modifications in line with Giraud et al, 2023. Updated in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Contact oncologydrugs@cancercontrol.ie for clarification.

[ii] The rapid infusion is an unlicensed means of administration of bevacizumab for the indications described above, in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.