PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Platinum/paclitaxel /Pembrolizumab +/- Bevacizumab Compassionate Access Scheme

Cervical Cancer

PROTOCOL REF: MPHAPPPCC

Version No: 1.1

Approved for use in:

Pembrolizumab in combination with platinum- based chemotherapy, **with or without bevacizumab** is indicated for the first line treatment of adults with cervical cancer where all of the following criteria are met:

- Persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous-cell carcinoma of the cervix.
- PD-L1 positive (≥1%)
- Previous radiotherapy, including chemoradiotherapy, permitted if it was. completed two weeks before
- No prior treatment with bevacizumab or other anti-VEGF therapy is permitted
- (ECOG) PS score 0 or 1.

For the individual patient request: approval must be confirmed by Merck Sharp & Dohme (MSD) prior to prescribing

Blueteq registration required for Bevacizumab

Exclusions

- History of pneumonitis, organ transplantation, autoimmune disorders, HIV infection, myocarditis, 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)
- Patient with active CNS disease or carcinomatosis meningitis
- Pregnancy or breast feeding

Dosage:

Cycles 1 to 6 (patients with ongoing clinical benefit who were receiving chemotherapy without unacceptable side effects could continue beyond 6 cycles at the discretion of the clinical team)

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg	IV infusion	3 weekly
Paclitaxel	175mg/m²		
Carboplatin	AUC 5		
+/- Bevacizumab	15mg/kg		

OR

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg	IV infusion	3 weekly
Paclitaxel	175mg/m²		
Cisplatin*	50mg/m²		
+/- Bevacizumab	15mg/kg		

NOTE: Cisplatin is not recommended in patients with a Creatinine Clearance (CrCl) calculated using Cockroft and Gault (C&G) formula < 60ml/min or in case of deafness. Therefore Carboplatin regimen to be considered- discuss with clinical team. **If clinical team make decision to proceed with cisplatin, provided CrCl ≥ 50 ml/min, then dose will need to be adjusted accordingly (refer 'Dosing in renal and hepatic impairment' section).**

Followed by maintenance Pembrolizumab (3 or 6 weekly)

Drug	Dosage	Route	Frequency	Duration
Pembrolizumab	200mg*	IV infusion	3 weekly	**For up to a maximum of 2 years** *(to complete 35 x 3-weekly cycles or its equivalent if 6-weekly dosing is used)*
OR				
Pembrolizumab	400mg	IV infusion	6 weekly	

Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 3 weekly regimen may be used.

Carboplatin

Calvert formula for Carboplatin dosage

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

Meditech calculates creatinine clearance using the Wright formula, the Carboplatin Dose Calculator application for calculating creatinine is available on the Remote Citrix Web Portal. If estimated GFR is used the **Wright formula** must be used for creatinine clearance.

Creatinine clearance should be capped at 125mL/min for carboplatin

Avoid the use of Cockcroft and Gault formulae as it is less accurate.

Cisplatin

Check renal function before commencing cisplatin using Cockcroft and Gault Creatinine Clearance (CrCl) equation:

Calculate creatinine clearance using Cockcroft and Gault equation:

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{}$

Serum Creatinine (micromol/L)

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

CrCl must be ≥ 50 mL/min for cisplatin based treatment. Please ensure the dose has been adjusted if renal function is between 50 and 60 ml/min, refer 'Dosing in renal and hepatic impairment' section.

Bevacizumab

Should be withheld for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

Patient Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 5 months following the last dose of Pembrolizumab and 6 months after the last dose of Bevacizumab.

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
- Flu like symptoms are common, particularly during cycle 1
- Monitor for signs of infection / sepsis as this regimen is associated with neutropenia

Emetogenic Risk:

Cycle 1-6: Highly emetogenic

Cycle 7 onwards: Mildly emetogenic

Extravasation risk:

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

Cisplatin- IRRITANT

Carboplatin- IRRITANT

Paclitaxel- VESICANT

Pembrolizumab- NEUTRAL

Bevacizumab- NEUTRAL

Supportive Treatments:

Cycles 1 to 6 (prior to chemotherapy containing cycles ONLY)

Dexamethasone tablets 4mg orally twice daily for three days

Metoclopramide tablets 10mg oral, up to 3 times a day or as required for a maximum of 5 consecutive days.

Aprepitant capsules 125mg oral 1 hour before chemotherapy then 80mg as a single dose on day 2 and 3 of treatment cycle (for use with cisplatin regimen and as 2nd line anti-emetic for carboplatin containing regimen)

Dosing in renal and hepatic impairment:

Renal dosing	Pembrolizumab (prior to start of treatment ONLY/Baseline)	GFR ≥ 10ml/min proceed with treatment GFR < 10ml/min- use with caution.
	Bevacizumab	There is no data for bevacizumab in patients with impaired renal function.

<table>
<tr><td rowspan="3"></td><td>Paclitaxel</td><td>All grades including patients on haemodialysis - no dose adjustment required.</td></tr>
<tr><td>Carboplatin</td><td rowspan="2">Both cisplatin and carboplatin are eliminated primarily in the urine and are themselves nephrotoxic. If there is any significant renal toxicity discuss with consultant before proceeding.
Ahead of each cycle of treatment calculate CrCl/GFR using (refer to ‘Administration’ Section):
• C&G formula prior to treatment with cisplatin.
• Wright formula prior to treatment with carboplatin.</td></tr>
<tr><td>Cisplatin</td></tr>
</table>

GFR (mL/min)	Cisplatin dose	Carboplatin dose
≥ 60	100%	100%
50 to 59	75% OR Consider switching to carboplatin	
30 to 49	Switch to carboplatin	**If CrCl ≤ 20ml/min Discuss with clinical team prior to administration**
< 30		

<table>
<tr><td rowspan="3">Hepatic dosing</td><td>Pembrolizumab (prior to start of treatment ONLY/Baseline)</td><td>Administered with caution in patients with:
Moderate (total bilirubin > 1.5 -3 × ULN and any AST)
or
Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment.
* Within normal limits or high</td></tr>
<tr><td>Bevacizumab</td><td>There is no data for bevacizumab in patients with impaired liver function.</td></tr>
<tr><td>Paclitaxel</td><td></td></tr>
</table>

Bilirubin		ALT and/or AST	Dose

		≤ 1.25x ULN	AND	< 10 x ULN	175mg/m^2
		1.26 to 2xULN			135mg/m^2
		2.01 to 5xULN			90mg/m^2
		> 5xULN	OR	≥10 x ULN	**NOT TO BE GIVEN**
	Carboplatin	No dose reductions necessary			
	Cisplatin				

Interactions:

Pembrolizumab
No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
Bevacizumab
There are no known drug interactions with bevacizumab.

Carboplatin and cisplatin

Concomitant use contraindicated

Yellow fever vaccine: risk of generalized disease mortality.

Concomitant use not recommended

- Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease. This is increased in subjects who are already immunosuppressed by their underlying disease. Use inactivated vaccine where this exist (poliomyelitis).
- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).

Concomitant use to take into consideration

- Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.
- Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to Carboplatin induced changes in renal clearance.
- Loop diuretics (e.g. furosemide, indapamide): The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.

Paclitaxel
Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures. Studies in Kaposi's Sarcoma patients, who were taking multiple concomitant medicinal product, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

For more detailed interactions please refer to the SmPC for each agent.

Administration:

Cycles 1 to 6 (chemotherapy containing cycles ONLY)

Pembrolizumab, Paclitaxel, Carboplatin +/- Bevacizumab

Day	Drug	Dose	Route	Diluent and Rate
1	Pembrolizumab	200mg (3 weekly)	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic

				line with a 0.2 micron filter
1	+/- Bevacizumab	15mg/kg	IV Infusion	100ml-250ml sodium chloride 0.9% over 90 minutes. 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.
1	Dexamethasone	16.5mg	IV bolus	30 minutes before chemotherapy
1	Ondansetron	16mg	Oral	30 minutes before chemotherapy
1	Famotidine	20mg	Oral	At least 60 minutes before chemotherapy **(can be discontinued after 3 cycles for those patients who do not experience a hypersensitivity reaction)**
1	Chlorphenamine	10mg	IV bolus	30 minutes before chemotherapy

1	Paclitaxel	175mg/m²	IV Infusion using a non-PVC giving set with a 0.22 micron filter	500mL sodium chloride 0.9% over 3 hours
1	Carboplatin	AUC 5	IV Infusion	500mL glucose 5% over 30 to 60 minutes

OR

Pembrolizumab, Paclitaxel, Cisplatin +/- Bevacizumab

Day	Drug	Dose	Route	Diluent and Rate
1	Pembrolizumab	200mg (3 weekly)	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
1	+/- Bevacizumab	15mg/kg	IV Infusion	100ml-250ml sodium chloride 0.9% over 90 minutes. 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.

1	Dexamethasone	16.5mg	IV bolus	30 minutes before chemotherapy
1	Famotidine	20mg	Oral	At least 60 minutes before chemotherapy **(can be discontinued after 3 cycles for those patients who do not experience a hypersensitivity reaction)**
1	Chlorphenamine	10mg	IV bolus	30 minutes before chemotherapy
1	Paclitaxel	175mg/m²	IV Infusion	500mL sodium chloride 0.9% over 3 hours using a non-PVC giving set with a 0.22 micron filter
1	Aprepitant	125mg	Oral	60 minutes before chemotherapy
1	Ondansetron	24mg	Oral	30 minutes before chemotherapy
1	Furosemide	20mg	Oral	Give before cisplatin pre-hydration
1	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)		IV Infusion over 90 minutes	
1	Measure urine output volume and record If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes			
1	Cisplatin	50mg/m²	IV Infusion	1000mL

				Sodium Chloride 0.9% over 90 minutes
1	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)		IV Infusion over 90 minutes	

- Paclitaxel must be administered using a non-PVC giving set with a 0.22 micron filter.
- Paclitaxel should be administered prior to carboplatin
- Paclitaxel in solution may show haziness which is attributed to the formulation of paclitaxel.
- Excessive shaking, agitation, or vibration of paclitaxel may induce precipitation.
- The patient should be asked to drink 2 litres of fluid in the 24hrs following treatment with cisplatin.
- **Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. Therapy should also be withheld for at least 28 – 60 days before elective surgery.**
- For minor surgery, including port placement, it is recommended that bevacizumab is withheld for 7 days after surgery.

Cycle 7 onwards

Maintenance single agent pembrolizumab (3 or 6 weekly)

Pembrolizumab	400mg	IV infusion	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter	6 weekly to complete 2 years**
Pembrolizumab	200mg*	IV infusion		3 weekly to complete 2 years**

Where risk factors for toxicity are present e.g. pre-existing autoimmune disease or previous toxicity, the 3 weekly regimen may be used.

**To continue until disease progression or unacceptable toxicity or after 2 years of treatment (to complete 35 x 3-weekly cycles or its equivalent if 6-weekly dosing is used) whichever is first.

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.). Please refer to the CCC Hypersensitivity; Management Prevention Policy

Main Toxicities:

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Pembrolizumab	
Immune-Mediated Pneumonitis Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%).	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Immune-Mediated Colitis Colitis occurred in 1% of patients (including G3 in 0.5%).	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other Immune-Mediated Toxicities: Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism	Monitor LFTs, biochemistry, cortisol and TFTs regularly Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia	
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
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Pembrolizimab	The most common adverse reactions in combination with bevacizumab, paclitaxel and carboplatin were anaemia, alopecia, nausea, diarrhoea, fatigue, constipation, arthralgia, peripheral neuropathy, vomiting, hypertension.

Bevacizumab	The most serious adverse reactions were gastrointestinal perforations, haemorrhage, including pulmonary haemorrhage/haemoptysis, arterial thromboembolism. The most frequently observed adverse reactions across clinical trials in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.
Paclitaxel	Significant hypersensitivity reactions, bone marrow suppression, thrombocytopenia, anaemia, neurotoxicity (mainly peripheral neuropathy), arthralgia or myalgia or injection site reactions. The most common reactions include infection, neurotoxicity, bradycardia, hypotension, diarrhoea, vomiting, nausea and alopecia.
Carboplatin and cisplatin	Significant hypersensitivity reactions, bone marrow suppression, thrombocytopenia, anaemia, neurotoxicity (mainly peripheral neuropathy), ototoxicity, arthralgia or myalgia or injection site reactions. The most common reactions include infection, neurotoxicity, bradycardia, hypotension, diarrhoea, vomiting, nausea and alopecia.

Investigations and treatment plan

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 2	Prior to cycle 3	Cycle 3	Ongoing
Informed Consent	x					
Clinical Assessment	x			x		Every 12 weeks thereafter or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x		x	Every cycle**
OTR	x	x	x		x	Every cycle prior to pembrolizumab treatment
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (AST, ALT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x	x		x	Every cycle
Lipid profile (cholesterol)	x					At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x					At baseline then if clinically indicated
Full set of observations (*BP, heart rate, temperature, respiratory rate and O_2 sats*)	x	x	x	x	x	Every cycle
Urinalysis		x	x		x	Required prior to each cycle of treatment with **bevacizumab**
Creatinine Clearance (Cockcroft and Gault)	x	x	x		x	<u>Cycles 1 to 6 (with chemotherapy)</u> Every cycle <u>Pembrolizumab ONLY (no chemotherapy)</u> With every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline
CT scan	x					At baseline then every 12 weeks or if clinically indicated

Trop-T, CK, pro-BNP	x					At baseline and thereafter as clinically indicated (ECG to be reviewed by clinical team)
ECG	x					
Weight recorded	x	x	x		x	Every cycle
Height recorded	x					

Dose Modifications and Toxicity Management:

- Dose modifications due to toxicity are ONLY permitted on chemotherapy agents (paclitaxel, carboplatin and cisplatin).
- Only dosing delay or discontinuation due to toxicity are permitted for pembrolizumab and/or bevacizumab based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of pembrolizumab doses are contained in 'Treatment Threshold' section below.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Treatment Threshold

Pembrolizumab, Paclitaxel, Carboplatin or Cisplatin +/- Bevacizumab (Cycles 1 to 6)
Administer treatment on day 1 if:

SACT	Platelets	Neutrophils	Serum Creatinine	Bil	AST/ ALT	ALP	TSH and Free T4
Pembrolizumab	≥ 100 x 10^9/L **(Must be within normal range prior to cycle 1*)**	≥ 1.0 x 10^9/L	≤1.5 x ULN or baseline	<3 x ULN	<5 x ULN	<5 x ULN	Within range or no change from base line
Paclitaxel and carboplatin/ cisplatin			**Refer to 'Dosing in renal and hepatic impairment' section for recommended dose modifications for carboplatin, cisplatin and paclitaxel based on individual renal and hepatic function**				

Bevacizumab	**Routine monitoring of FBC is not required. Refer to guidance below on BP and proteinuria monitoring and treatment recommendations.**	

ULN = upper limit of normal

*****If platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need assessment and chemotherapy dose reduction

Pembrolizumab ONLY (Cycle 7 onwards)
Administer on day 1 if:

	Platelets	Neutrophils	Serum Creatinine	Bil	AST/ ALT	ALP	TSH and Free T4
Pembrolizumab	≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≤1.5 x ULN or baseline	<3 x ULN	<5 x ULN	<5 x ULN	Within range or no change from base line

Pembrolizumab

Dose reduction NOT permitted. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.

Grade 2 Moderate	Withhold treatment until resolved to ≤ grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold treatment. Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

Bevacizumab:

Dose reduction NOT permitted. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Hypertension:

Baseline blood pressure should be < 150/100mmHg. Pre-existing hypertension should be adequately controlled (usually by GP) before starting bevacizumab treatment.

If diastolic increase > 20mmHg above baseline or blood pressure rises to >150/100mmHg, antihypertensive therapy may be required. Treatment, and initial monitoring until stabilized, is usually best managed via the patient's GP.

If blood pressure > 180/110mmHg, it is advised that bevacizumab therapy is withheld until blood pressure controlled.

For "white coat syndrome" induced hypertension, please contact patient's GP for monitoring of blood pressure in between cycles.

Proteinuria:

1+ or 2+ on dipstick (0.3 – 2.9g/L)	**3+ on dipstick (3 - 19g/L):**	**4+ on dipstick (≥20g/L)**

Continue with bevacizumab. No additional evaluation required	May have dose of bevacizumab as scheduled, but will need 24 hour urine collection to measure protein a few days before next cycle due. If 24hr protein result < 2g, continue with bevacizumab. With continued proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein level falls to < 1g/24hr, return to dipstick analysis. If ≥2g, withhold bevacizumab until repeat 24 hour urine collection shows < 2g protein. Then reintroduce bevacizumab, with continued proteinuria monitoring via 24 hour urine.	**Withhold bevacizumab**. 24 hour urine collection required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Non Haematological Toxicity:

Toxicity should be grading according to the CTCAE v4.0 criteria. Following assessment, treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible	Interrupt treatment until resolved to at least grade 1, then continue at 75-80% of original dose or AUC 5 with prophylaxis where possible	Discontinue treatment
2nd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose or AUC 4	Interrupt treatment until resolved to grade0/1, then continue at 50% of original dose or AUC 3.5	

3rd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose or AUC 3.5	Discontinue treatment	
4th appearance	Discontinue treatment		

Peripheral Neuropathy:

Paclitaxel
CTCAE grade 2 peripheral neuropathy: withhold paclitaxel only until the neuropathy recovers to grade 1 then dose reduce to 75% of the original dose. Where the peripheral neuropathy is ≥ grade 3 omit paclitaxel from subsequent cycles.

References:

Bevacizumab 25 mg/mL concentrate for solution for infusion SmPC, Zentiva. Available from www.medicines.org.uk/emc/medicine. Last updated 15th October 2021

Carboplatin 10 mg/ml concentrate for solution for infusion SmPC, Accord Healthcare Ltd, Middlesex. Available from www.medicines.org.uk/emc/medicine. Last updated 31st August 2018.

Cisplatin 1 mg/ml Concentrate for Solution for Infusion SmPC, Accord Healthcare Ltd, Middlesex. Available from www.medicines.org.uk/emc/medicine. Last updated 25th June 2021.

Paclitaxel 6 mg/ml concentrate for solution for infusion SmPC Hospira UK Ltd, Warwickshire Available from www.medicines.org.uk/emc/medicine. Last updated 27th April 2020.

Keytruda 25mg/mL, Summary of Product Characteristics, Merck Sharp & Dohme (UK) Limited. Available from www.medicines.org.uk/emc/medicine. Last updated 21st September 2021

Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.

Colombo, N., et al. (2021). Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. New England Journal of Medicine, 385(20), 1856-1867.

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
July 2022	1.0	Hala Ghoz Lead Protocols Pharmacist	New regimen protocol
October 2022	1.1	Hala Ghoz Lead Protocols Pharmacist	Review and update