SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

Pembrolizumab/Paclitaxel/Platinum +/- Bevacizumab

Cervical Cancer

PROTOCOL REF: MPHAPPPBCC
(Version No. 1.0)

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 localised, recurrent localised, or metastatic adenocarcinoma, adeno-squamous carcinoma, or squamous carcinoma of the cervix.
- PD-L1 positive with a CPS score ≥1
- Previous radiotherapy, including chemo-radiotherapy, permitted if it was. completed two weeks before
- No prior treatment with systemic chemotherapy or has only received chemotherapy specifically used as a radio-sensitising agent
- No prior treatment with bevacizumab or other anti-VEGF therapy
- No prior antibody treatment which targets PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4)
- ECOG performance status (PS) of 0 or 1.
- No symptomatic active brain metastases or leptomeningeal metastases

Blueteq registration required

Dosage:

Cycles 1 to 6

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg	IV infusion	3 weekly
Paclitaxel	175mg/m^2	IV infusion	3 weekly
Carboplatin	AUC 5		
+/- Bevacizumab	15mg/kg		

OR

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg	IV infusion	3 weekly
Paclitaxel	175mg/m^2	IV infusion	3 weekly
Cisplatin	50mg/m^2		
+/- Bevacizumab	15mg/kg		

In patients with a CrCl < 60ml/min carboplatin regime may be favoured.

Note: For carboplatin dosing creatinine clearance should be capped at 125mL/min. Please see renal impairment section for further details

Followed by maintenance Pembrolizumab +/- Bevacizumab

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg*	IV infusion	3 weekly
	Or		
	400mg	IV infusion	6 weekly
+/- Bevacizumab	15mg/kg	IV infusion	3 weekly

For up to a maximum of 2 years or until disease progression/unacceptable toxicity (35 x 3-weekly cycles or its equivalent if 6-weekly pembrolizumab is used).

Where risk factors for toxicity are present the 3 weekly regimen may be favoured.

Followed by maintenance Bevacizumab where appropriate

If the patient has received bevacizumab in the previous parts of the regime and is still benefiting from treatment, the patient and clinician have the option to continue with the bevacizumab as monotherapy until disease progression.

Drug	Dosage	Route	Frequency
Bevacizumab	15mg/kg	IV infusion	3 weekly

Counselling Points:

Women of childbearing potential should use effective contraception throughout treatment and for at least 4 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
- Monitor for signs of infection / sepsis

Emetogenic risk (if applicable):

Cycle 1-6: Highly emetogenic

Cycle 7 onwards: Mildly emetogenic

Supportive Treatments

Cycles 1 to 6 (chemotherapy containing cycles ONLY)

Pre-Medication:

Chlorphenamine 10mg IV bolus 30 mins before chemotherapy

Dexamethasone 20mg IV bolus 30 minutes before chemotherapy

With Carboplatin regime

- Ondansetron 16mg oral 30 minutes before chemotherapy
- Aprepitant can be added if additional risk factors

With Cisplatin regime

- Ondansetron 24mg oral 30 minutes before chemotherapy
- Aprepitant 125mg oral 60 minutes before chemotherapy

To take home medications

Dexamethasone tablets 4mg oral, twice daily for up to three days

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

Ondansetron 8mg tablets oral, twice daily for 3 days

Extravasation risk:

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

Pembrolizumab- NEUTRAL

Paclitaxel- VESICANT

Cisplatin- IRRITANT

Carboplatin- IRRITANT

Bevacizumab- NEUTRAL

Dosing in renal and hepatic impairment:

Renal	Pembrolizumab	No dose adjustment is needed for patients with mild or moderate renal impairment. Pembrolizumab has not been studied in patients with severe renal impairment
	Paclitaxel	No dose adjustment is expected
	Carboplatin	Calvert formula is utilised for Carboplatin dose calculation. *Carboplatin dose in mg = AUC x (creatinine clearance + 25)* For carboplatin Meditech calculates creatinine clearance using the Wright formula The Carboplatin Dose Calculator application for calculating creatinine is available on the Remote Citrix Web Portal - Carboplatin Dose Calculator (clatterbridgecc.nhs.uk) If estimated GFR is used the **Wright formula** must be used for creatinine clearance Any dose adjustments needed from usage of the carboplatin dose calculator see carboplatin SOP for instruction Creatinine clearance should be capped at 125mL/min for carboplatin
	Cisplatin	**GFR 50-59 ml/min**: 75% of the original dose **GFR < 50 ml/min:** not recommended, consider carboplatin
	Bevacizumab	The safety and efficacy have not been studied in patients with renal impairment No dose adjustment is expected

<table>
<tr><td rowspan="5">Hepatic</td><td>Pembrolizumab</td><td>No dose adjustment is expected</td></tr>
<tr><td>Paclitaxel</td><td>
<table>
<tr><th>ALT/AST</th><th>Bilirubin</th><th>Dose Reduction</th></tr>
<tr><td rowspan="2"><10 x ULN</td><td>>1.25 X ULN</td><td>77% of original dose (135mg/m2)</td></tr>
<tr><td>>2 x ULN</td><td>51% of original dose (90mg/m2)</td></tr>
<tr><td>≥10 x ULN</td><td>>5 x ULN</td><td>Contraindicated</td></tr>
</table>
</td></tr>
<tr><td>Carboplatin</td><td>The safety and efficacy have not been studied in patients with hepatic impairment

No dose adjustment is expected</td></tr>
<tr><td>Cisplatin</td><td>No dose adjustment is expected</td></tr>
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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.
Paclitaxel	<u>Cisplatin:</u> Paclitaxel is recommended to be administered <u>*before*</u> cisplatin. When given before cisplatin, the safety profile of paclitaxel is consistent with that reported for single agent use. Administration of paclitaxel <u>*after*</u> cisplatin treatment leads to greater myelosuppression and about a 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers. <u>Active substances metabolised in the liver:</u> The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a PK drug-drug interaction study, 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.
Carboplatin	<u>Concomitant use contraindicated</u> Yellow fever vaccine: risk of generalised disease mortality <u>Concomitant use not recommended</u> - Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an 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 which lead to a decrease in phenytoin serum levels); risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin). <u>Concomitant use to take into consideration</u> - Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymph proliferation. - Concurrent therapy with nephrotoxic or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance. - Loop diuretics: The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.
Cisplatin	<u>Nephrotoxic substances</u> Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, amphotericin B or contrast media) medicinal products will potentiate the toxic effect of cisplatin on the kidneys. During or after treatment with cisplatin caution is advised with predominantly renally eliminated substances, because of potentially reduced renal elimination. Reduction of the blood's lithium values was noticed in a few cases after treatment with cisplatin combined with bleomycin and etoposide. It is therefore recommended to monitor the lithium values.

	<u>Ototoxic substances</u> Concomitant administration of ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function. Except for patients receiving doses of cisplatin exceeding 60 mg/m^2, whose urine secretion is less than 1000 ml per 24 hours, no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity. <u>Attenuated live vaccines</u> Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease. In view of the risk of generalized illness, it is advisable to use an inactivated vaccine if available. <u>Antihistamines, Phenothiazines and others</u> Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes or trimethobenzamides may mask ototoxicity symptoms (such as dizziness and tinnitus). <u>Anticonvulsive substances</u> Serum concentrations of anticonvulsive medicines may remain at sub-therapeutic levels during treatment with cisplatin. <u>Pyridoxine + altretamine combination</u> During a randomized study of the treatment of advanced ovarian cancer, the response time was unfavorably affected when pyridoxine in combination with altretamine (hexamethylmelamine) and cisplatin. <u>Paclitaxel</u> Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33% and therefore can intensify neurotoxicity.
Bevacizumab	There are no known drug interactions with bevacizumab.

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

Treatment schedule:

Cycles 1 to 6

Day	Drug	Dose	Route	Diluent and rate
1	Pembrolizumab	200mg	IV	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
	Chlorphenamine	10mg	IV	30 mins before chemotherapy
	Dexamethasone	20mg	IV	30 mins before chemotherapy
	Ondansetron	16mg	PO	30 mins before chemotherapy
	Paclitaxel	175mg/m^2	IV	500mL sodium chloride 0.9% over 3 hours in a non-pyrogenic line with a 0.2 micron filter
	Carboplatin	AUC 5	IV	500mL glucose 5% over 30 to 60 minutes
	+/- Bevacizumab	15mg/kg	IV	100ml 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.

OR

Day	Drug	Dose	Route	Diluent and rate
1	Pembrolizumab	200mg	IV	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
	Aprepitant	125mg	PO	60 mins before chemotherapy
	Chlorphenamine	10mg	IV	30 mins before chemotherapy
	Dexamethasone	20mg	IV	30 mins before chemotherapy
	Ondansetron	24mg	PO	30 mins before chemotherapy
	Paclitaxel	175mg/m^2	IV	500mL sodium chloride 0.9% over 3 hours in a non-pyrogenic line with a 0.2 micron filter
	Furosemide	20mg	Oral	Give before cisplatin pre-hydration
	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)	IV Infusion over 90 minutes		
	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**			
	Cisplatin	50mg/m^2	IV	1000mL Sodium Chloride 0.9% over 90 minutes
	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)	IV Infusion over 90 minutes		
	+/- Bevacizumab	15mg/kg	IV	100mlsodium 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.

As with all platinum based chemotherapy, patients may experience allergic reaction during administration. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

For severe reactions, discuss with Consultant before continuing with treatment. It should be strongly noted that patients who have severe reactions should not be re-challenged

Followed by maintenance Pembrolizumab +/- Bevacizumab

Day	Drug	Dose	Route	Diluent and rate
1	Pembrolizumab	200mg (3 weekly) or 400mg (6 weekly)	IV	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
	+/- Bevacizumab	15mg/kg	IV	100ml 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.

Followed by maintenance Bevacizumab where appropriate

Day	Drug	Dose	Route	Diluent and rate
	Bevacizumab	15mg/kg	IV	100ml 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.

Main toxicities/adverse Events

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 Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia	Monitor LFTs, biochemistry, cortisol and TFTs regularly Refer to Immuno-Oncology toxicity specific guidance for adverse event management
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
Paclitaxel	
• Significant hypersensitivity reactions • Bone marrow suppression including neutropenia, thrombocytopenia and anaemia • Neurotoxicity (mainly peripheral neuropathy) • Alopecia • Cardiac conduction abnormalities • Hypotension/hypertension, and bradycardia • Arthralgia or myalgia • Cystoid macular oedema • Injection site reactions.	

Carboplatin and Cisplatin
• Significant hypersensitivity reactions • Bone marrow suppression including thrombocytopenia and anaemia • Neurotoxicity (mainly peripheral neuropathy) • Ototoxicity • Arthralgia or myalgia • Injection site reactions.
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 • Abdominal pain.

For more detailed toxicities/adverse reactions please refer to the SmPC for each agent.

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 4	Cycle 4	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**
On treatment review	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	Cycles 1 to 6 (with chemotherapy) Every cycle

						Pembrolizumab ONLY (no chemotherapy) With every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline
CT scan (or appropriate imaging)	X			X		At baseline, prior to 4 cycles of chemotherapy 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					At baseline

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.

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	<1.5 x ULN	<2.5 x ULN	<3 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

Maintenance Treatment; Pembrolizumab +/- Bevacizumab

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	<1.5 x ULN	<2.5 x ULN	<3 x ULN	Within range or no change from base line
+/- Bevacizumab	**Routine monitoring of FBC is not required. Refer to guidance below on BP and proteinuria monitoring and treatment recommendations.**						

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.

Surgery

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.

Chemotherapy agents (paclitaxel, carboplatin and cisplatin).

Toxicity Grading:

Toxicity should be grading according to the CTCAE 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:

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6. Electronic Medicines Compendium (2022, 25 November*), Keytruda 25mg/mL concentrate for solution for infusion* https://www.medicines.org.uk/emc/product/2498/smpc#gref
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9. 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.
10. Northern Cancer Alliance (2018) *Anti-emetic Guidelines for Chemotherapy Induced Nausea and Vomiting (CINV)* Newcastle Upon Tyne: NHS England

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
		Sarah Craig Advanced Pharmacist Teacher Practitioner	V1.0 New protocol