PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Paclitaxel, Carboplatin and Bevacizumab Gynaecological Cancer

PROTOCOL REF: MPHAGYNBEV

Version No: 1.3

Approved for use in:

- International Federation of Gynaecology and Obstetrics (FIGO) Stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma
- In combination with first line chemotherapy as INDUCTION TREATMENT followed by single agent Bevacizumab as MAINTENANCE TREATMENT.

Blueteq registration required

SEPARATE BLUETEQ REGISTRATION REQUIRED FOR INDUCTION AND MAINTENANCE BEVACIZUMAB TREATMENT

Dosage:

Cycles 1 to 6 (INDUCTION TREATMENT)

Drug	Dosage	Route	Frequency
Paclitaxel	175mg/m²	IV INFUSION	3 weekly
Carboplatin	AUC 5		
Bevacizumab	15mg/kg	IV INFUSION	3 weekly
OR			
Bevacizumab	7.5mg/kg*	IV INFUSION	3 weekly

***Unlicensed dose**

Cycle 7 Onwards (MAINTENANCE TREATMENT)

Drug	Dosage	Route	Frequency
Bevacizumab	7.5mg/kg	IV infusion	3 weekly

For up to a maximum of 18 cycles (including the number of cycles given with induction treatment) or until disease progression/unacceptable toxicity

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

Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 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:

Cycle 1-6: Highly emetogenic

Cycle 7: 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

Ondansetron 16mg oral 30 minutes before chemotherapy

Aprepitant can be added if additional risk factors

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**'.

Carboplatin- IRRITANT

Paclitaxel- VESICANT

Bevacizumab- NEUTRAL

Dosing in renal and hepatic impairment:

Renal	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

<table>
<tr><td></td><td>Bevacizumab</td><td>The safety and efficacy have not been studied in patients with renal impairment

No dose adjustment is expected</td></tr>
<tr><td rowspan="3">Hepatic</td><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>Bevacizumab</td><td>The safety and efficacy have not been studied in patients with hepatic impairment

No dose adjustment is expected</td></tr>
</table>

Interactions:

Paclitaxel	<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

	Concomitant use not recommended - 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). Concomitant use to take into consideration - 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.
Bevacizumab	There are no known drug interactions with bevacizumab.

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

Administration:

Cycles 1 to 6 (INDUCTION TREATMENT)

Day	Drug	Dose	Route	Diluent and Rate
1	Bevacizumab	7.5mg/kg Or 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.
	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

Cycle 7 onwards (MAINTANANCE TREATMENT)

Day	Drug	Dose	Route	Diluent and rate
1	Bevacizumab	7.5mg/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.

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.

Main Toxicities:

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
• 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:

	Pre	Cycle 1	Cycle 2	Prior to cycle 3	Cycle 3	Ongoing
Informed Consent	x					
Clinical Assessment	x			x		Every 3 cycles or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x		x	Every cycle**
FBC	x	x	x		x	<u>Cycles 1 to 6 (with chemotherapy)</u> Every cycle <u>Cycle 7 onwards</u> Every 3 months
U&E/Magnesium/renal profile/bone profile		x	x		x	
LFTs	x	x	x		x	
Full set of observations (*BP, heart rate, temperature, respiratory rate and O_2 sats*)	x	x	x		x	Every cycle
Urinalysis		x	x		x	Required prior to each cycle of treatment with **bevacizumab**
Creatinine Clearance via the Wright formula	x	x	x		x	<u>Cycles 1 to 6 (with chemotherapy)</u> <u>Every cycle</u> <u>Cycle 7 onwards every 3 months</u>
CA125						Every cycle Ovarian patients only
CT scan	x					if clinically indicated
Trop-T, CK, pro-BNP	x					At baseline and thereafter if clinically indicated
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).
- Patients on the higher dose of bevacizumab (15mg/kg) can be dropped to the lower dose (7.5mg/kg) due to toxicity.
- Only dosing delay or discontinuation due to toxicity are permitted for bevacizumab based on individual safety and tolerability.

Treatment Threshold

Administer treatment on day 1 if:

<table>
<tr><th>Cycles</th><th>SACT</th><th>Platelets</th><th>Neutrophils</th><th>Creatinine Clearance</th><th>LFTs</th></tr>
<tr><td rowspan="2">1 to 6</td><td>Paclitaxel and/or carboplatin</td><td>≥ 100 x 10^9/L (Must be within normal range prior to cycle 1*)</td><td>≥ 1.0 x 10^9/L</td><td colspan="2">Refer to ‘Dosing in renal and hepatic impairment’ section for recommended dose modifications for carboplatin and paclitaxel based on individual renal and hepatic function</td></tr>
<tr><td>Bevacizumab</td><td colspan="4">Routine monitoring of FBC, creatinine clearance and LFTS is not required. Refer to ‘Investigations’ table and guidance below on BP and proteinuria monitoring and treatment recommendations.</td></tr>
<tr><td>7 onwards</td><td>Bevacizumab</td><td colspan="4">Routine monitoring of FBC creatinine clearance and LFTS is not required. Refer to ‘Investigations’ table and guidance below on BP and proteinuria monitoring and treatment recommendations.</td></tr>
</table>

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

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	**Withhold bevacizumab**. 24 hour urine collection required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

	bevacizumab, with continued proteinuria monitoring via 24 hour urine.	

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 and carboplatin).

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:

1. Burger, R. A., et al. (2011). Incorporation of bevacizumab in the primary treatment of ovarian cancer. *NEJM*, 365(26), 2473-2483.
2. Electronic Medicines Compendium (2023, 17 March), *Alymsys 25 mg/mL concentrate for solution for infusion.* https://www.medicines.org.uk/emc/product/12588/smpc
3. Electronic Medicines Compendium (2022, 07 December), *Avastin 25 mg/mL concentrate for solution for infusion* https://www.medicines.org.uk/emc/product/3885/smpc
4. Electronic Medicines Compendium (2022, 30 September*), Carboplatin 10mg/ml intravenous infusion* https://www.medicines.org.uk/emc/product/3787/smpc#gref

5. Electronic Medicines Compendium (2023,10 February), *Paclitaxel 6mg/mL concentrate for solution for infusion* https://www.medicines.org.uk/emc/product/3891/smpc#gref
6. Joint Formulary Committee. *British National Formulary (onlin*e) London: BMJ Group and Pharmaceutical Press
7. 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.
8. Northern Cancer Alliance (2018) *Anti-emetic Guidelines for Chemotherapy Induced Nausea and Vomiting (CINV)* Newcastle Upon Tyne: NHS England
9. Oza AM, et al. (2015). Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *The Lancet Oncology*, 16(8):928-936.

Circulation/Dissemination

Date added into Q-Pulse	17th August 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
May 2023	1.3	Sarah Craig Advanced Pharmacist Teacher Practitioner	Slight updates (mainly supportive meds and renal function) to align with other gynae protocols and blueteq requirements