BEVACIZUMAB (7.5mg/kg) PACLITAXEL CARBOPLATIN

INDICATION (ICD10) C56, C57

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (BEV3)

1. Bevacizumab at a dose of 7.5mg/Kg In combination with 1st line paclitaxel and carboplatin AS INDUCTION TREATMENT for patients with stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma whereone of the following criteria applies to this patient:
   FIGO stage III disease and debulked but residual disease more than 1cm or
   FIGO stage III disease and unsuitable for debulking surgery or
   FIGO stage IV disease or
   FIGO stage III disease at presentation and requires neo-adjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction
   Bevacizumab is to start with:
   the 1st or 2nd cycle of chemotherapy following primary debulking surgery, or
   the 1st or 2nd cycle of chemotherapy following interval debulking surgery performed after 3–4 cycles of non-bevacizumab-containing neoadjuvant chemotherapy, or
   the 1st or 2nd cycle of chemotherapy for those patients who have inoperable stage IV disease or inoperable stage III disease or who are unable to undergo surgery due to increased risk during COVID19 or
   the 1st or 2nd cycle of neo-adjuvant chemotherapy

REGIMEN

Day 1	**BEVACIZUMAB**	7.5mg/kg	IV infusion	#ml sodium chloride 0.9%
	Premedication 30 minutes prior to paclitaxel: Chlorphenamine 10mg IV bolus Dexamethasone 20mg IV bolus			
	PACLITAXEL	175mg/m^2	IV infusion	#ml sodium chloride 0.9% over 3 hours
	CARBOPLATIN	AUC* 5	IV infusion	#ml glucose 5% over 30 minutes

*Dose calculated by EDTA GFR or calculated (CrCl + 25) x AUC.
Maximum dose when using CrCl (125+25 x AUC)mg

diluent volume for dose prescribed as per national standardised product specification

Bevacizumab - The initial dose should be administered over 90 minutes, if tolerated well 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.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days for maximum 6 cycles, then prescribe bevacizumab 7.5mg/kg maintenance if eligible (BEV10 Blueteq form needs completing)

ANTI-EMETICS

Moderate risk day 1

CONCURRENT MEDICATION REQUIRED

Carboplatin	Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously. Dexamethasone 20mg IV bolus Chlorphenamine 10mg IV bolus H_2 antagonist Carboplatin should be given at a slower rate e.g. 2-4 hours.
Paclitaxel	Ensure premedication given before paclitaxel
GCSF	Consider GCSF if treatment delays are occurring

EXTRAVASATION AND TYPE OF LINE / FILTERS

Bevacizumab – neutral
Carboplatin - irritant
Paclitaxel – vesicant

Administer paclitaxel via polyethylene lined or DEHP free administration set with ≤0.22micron filter
Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration

FBC, U&E including Mg^{++} (>0.4) and LFTs Neutrophils x 10^9/L ≥1.0 provided patient is well Platelets ≥100x10^9/L	baseline and every cycle
GFR assessed using EDTA result (BMI <19 or >30) or calculated creatinine clearance at the Consultant's discretion	baseline and every cycle
Serum creatinine	baseline and every cycle
CA125	baseline and day 1 every cycle
Blood pressure	baseline and before every bevacizumab dose
Urinalysis for proteinuria	baseline and before every bevacizumab dose
Virology	before cycle 1 if not previously checked
Weight	baseline and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Bevacizumab	Arterial thromboembolism Gastrointestinal perforation Haemorrhage Hypertension Wound healing complications
Carboplatin	Ototoxicity – monitor Neurotoxicity - monitor
Paclitaxel	(2% risk of severe hypersensitivity) Reactions range from mild hypotension (light-headedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (i.e. within 5-10 minutes), cautiously restart at a slower rate under close supervision. If further reactions occur stop treatment.

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Paclitaxel	DOACs to be used with caution, need dose modifications or to be avoided eg apixaban Clopidogrel interacts with paclitaxel Paclitaxel is catalysed, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. inhibitors (e.g. erythromycin, fluoxetine, gemfibrozil) use with caution. inducors (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) use with caution.

DOSE MODIFICATIONS
Non-haematological
Bevacizumab
Hypertension
Baseline blood pressure should be <150/100mmHg.

Diastolic increase >20mmHg above baseline or BP rises to >150/100mmHg	Antihypertensive therapy may be required.
Blood pressure >180/110mmHg	It is advised that bevacizumab therapy is withheld until blood pressure controlled.

Proteinuria

Urine dipstick result. 1+ or 2+ on dipstick (0.3–2.9g/L)	Continue with bevacizumab. No additional evaluation required.
3+ on dipstick (3-19g/L)	May have dose of bevacizumab as scheduled, but 24 hour urine to measure 24 hour protein to be done 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 re-introduce bevacizumab, with continued proteinuria monitoring via 24 hour urine.
4+ on dipstick (≥20g/L)	Withhold bevacizumab. 24 hour urine required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Wound healing
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.

Paclitaxel
If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness discuss with Consultant or Registrar before administration
If grade ≥2 neuropathy, consider paclitaxel dose reduction
If grade >3 peripheral neuropathy is >grade 3 omit further paclitaxel

Hepatic impairment
Bevacizumab
No need for dose adjustment

Carboplatin
No need for dose adjustment is expected

Paclitaxel
In the absence of Gilbert's syndrome:

Transaminase <10xULN and bilirubin ≤1.25xULN	no dose reduction
Transaminase <10xULN and bilirubin 1.26-2xULN	give 77% of original dose
Transaminase <10xULN and bilirubin 2·01-5xULN	give 51% of original dose
Transaminase ≥10xULN or bilirubin >5xULN	contraindicated

Renal impairment
Bevacizumab
No need for dose adjustment

Carboplatin

GFR/ calculated CrCl ≤20ml/min or ≤30ml/min with pre-existing severe renal impairment	contraindicated

Paclitaxel
No need for dose adjustment is expected

REFERENCES
CDF list

Assessments

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Clinical assessment	X		Pre cycle		Pre cycle	Pre-C2, then every 6 weeks (every 2 cycles), or team discretion
SACT assessment (PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E, calcium, & LFT	X	X	X	X	X	Every cycle
CrCl	X	X	X	X	X	Every cycle
Blood pressure	X	X	X	X	X	Every cycle
Urine protein	X	X	X	X	X	Every cycle
CT scan	X					At clinician's discretion, Inform consultant team if not booked
Informed consent	X					Verbal each cycle
Height	X					
Weight recorded	X	X	X	X	X	Every cycle