BEVACIZUMAB (15mg/kg) PACLITAXEL CARBOPLATIN

INDICATION (ICD10) C53, C56, C57

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

Bevacizumab at a dose of 15mg/Kg in combination with 1st line chemotherapy AS INDUCTION TREATMENT patients with stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma where the following criteria have been met:

2. Bevacizumab at a dose of 15mg/Kg is to be used in combination with 1st line induction chemotherapy for previously untreated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer.
3. One of the following criteria applies to this patient:
i) FIGO stage III disease and debulked with no residual disease or residual disease less than 1cm or
ii) FIGO stage III disease and debulked with residual disease of more than 1cm or
iii) FIGO stage III disease and unsuitable for debulking surgery or
iv) FIGO stage IV disease and debulked with residual disease less than 1cm or
v) FIGO stage IV disease and debulked with residual disease of more than 1 cm or
vi) FIGO stage IV disease and unsuitable for debulking surgery or
vii) FIGO stage III disease at presentation and requires neo-adjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction or
viii) FIGO stage IV disease at presentation and requires neo-adjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction
4. Bevacizumab is to be given in combination with carboplatin and paclitaxel chemotherapy.
5. Bevacizumab is to start with:
i) the 1st or 2nd cycle of chemotherapy following primary debulking surgery, or
ii) the 1st or 2nd cycle of chemotherapy following interval debulking surgery performed after 3 – 4 cycles of non-bevacizumab-containing neoadjuvant chemotherapy, or
iii) 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
iv) the 1st or 2nd cycle of neo-adjuvant chemotherapy
6. Bevacizumab is to be given at a dose of 15mg/Kg every 3 weeks.
7. A maximum of 6 cycles of bevacizumab will be given as part of induction chemotherapy.
8. As neither bevacizumab in stage IIIA disease nor its use in the neoadjuvant setting is licensed in ovarian cancer, this use of bevacizumab must be used within the treating Trust's governance framework. Note: This policy relating to the use of bevacizumab 15mg/Kg is NOT for patients with stage I-II disease who have had optimal debulking
9. When a treatment break is needed of more than 6 weeks beyond the expected cycle length of 3-weekly treatment, I will complete a treatment break approval form to restart treatment, including as appropriate if the patient had an extended break on account of Covid-19.
10. Bevacizumab is to be otherwise used as set out in its Summary of Product Characteristics.

The first line treatment of recurrent or metastatic cervical cancer in combination with chemotherapy where all the following criteria are met:

2. Has histologically confirmed carcinoma of the cervix.
3. The indication will be for 1st line palliative chemotherapy.
4. Has primary stage IVB, recurrent, or persistent disease not amenable to curative treatment with surgery and/or radiotherapy.
5. Bevacizumab will be given with Paclitaxel and either Cisplatin or Carboplatin.
6. ECOG PS of 0 or 1.
7. Has had no previous treatment with bevacizumab or other anti-VEGF therapy.
8. Has no contraindications to the use of bevacizumab.

9. Bevacizumab dose to be 15mg/kg every 3 weeks.
10. No planned treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).
*Requests for continuation of treatment after unplanned treatment breaks over this duration should be made via the treatment break approval process.
Note: Bevacizumab is ONLY approved for use in combination with combination chemotherapy and is not approved for use as a single agent maintenance therapy.
Note: Bevacizumab should be discontinued for reasons of toxicity or disease progression, whichever occurs first.

REGIMEN

Day 1 BEVACIZUMAB 15mg/kg in 100ml sodium chloride 0.9% IV infusion
Premedication 30 minutes prior to infusion:
Dexamethasone 20 mg IV bolus
H_2 antagonist IV bolus
Chlorphenamine 10 mg IV bolus
PACLITAXEL 175mg/m^2 in 500ml* sodium chloride 0.9% IV infusion over 3 hours
CARBOPLATIN AUC 5 (maximum 700mg) in 500ml glucose 5% IV infusion over 30 minutes
Dose calculated by EDTA GFR or calculated (CrCl + 25) x AUC.

* doses 84mg to 144mg in 250ml sodium chloride 0.9%

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

Cervical - every 21 days until disease progression or loss of clinical benefit
Ovarian, fallopian tube, primary peritoneal - every 21 days for 6 cycles then prescribe bevacizumab maintenance if eligible

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

EXTRAVASATION AND TYPE OF LINE / FILTERS

Bevacizumab – neutral
Carboplatin - irritant
Paclitaxel – vesicant

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

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs, creatinine day 1
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
GFR assessed using EDTA result or calculated creatinine clearance at the Consultant's discretion.
CA125 baseline and day 1 every cycle
Blood pressure every cycle
Urinalysis for proteinuria every cycle
Baseline weight 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
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
Carboplatin

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

REFERENCES
CDF list