Bevacizumab 15mg/kg Therapy – 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
In combination with CARBOplatin and PACLitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.	C56 C57 C48	00215a	Hospital
Bevacizumab at a dose of 7.5mg/kg[i] (unlicensed indication) in combination with CARBOplatin and PACLitaxel as first line treatment has been shown to be effective in FIGO stage III debulked but residual disease more than 1cm, or FIGO stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer with respect to both progression-free and overall survival (ICON-7 trial- Reference NCCP Regimen 00620 Bevacizumab 7.5mg/kg, CARBOplatin (AUC5) and PACLitaxel 175mg/m^2 Therapy[i] for more information)			Hospital
In combination with, topotecan given on days 1-5 every 3 weeks**, for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.	C56 C57 C48	00215c	Hospital
***Reference NCCP regimen 00212 Bevacizumab 10mg/kg for details of topotecan (weekly) in combination with bevacizumab 10mg/kg.*			
In combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.	C18 C19 C20	00215d	Hospital
In combination with PACLitaxel is indicated for first-line treatment of adult patients with HER2-negative metastatic breast cancer.	C50	00215e	Hospital
In addition to platinum-based chemotherapy is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology.	C34	00215f	Hospital
In combination with erlotinib is indicated for the first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous cell lung cancer with Epidermal Growth Factor (EGFR) activating mutations	C34	00215g	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer:
Front-line treatment: Bevacizumab is administered once every 3 weeks as an intravenous infusion in addition to CARBOplatin and PACLitaxel for up to 6 cycles of treatment followed by continued use of bevacizumab as single agent until disease progression or for a maximum of 15 months (22 cycles) or until unacceptable toxicity, whichever occurs earlier. Treatment with bevacizumab commences on cycle 2.

Treatment of platinum-resistant recurrent disease: Bevacizumab is administered once every 3 weeks as an intravenous infusion in combination with topotecan (given on days 1-5, every 3 weeks), until disease progression or unacceptable toxicity.

Metastatic Breast Carcinoma and Metastatic Colorectal Carcinoma:
Bevacizumab is administered once every 21 days with chemotherapy until disease progression or unacceptable toxicity develops.

NSCLC:
First line treatment of non-squamous NSCLC in combination with platinum based chemotherapy: Bevacizumab is administered once every 21 days in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by bevacizumab as a single agent until disease progression or unacceptable toxicity occurs.

First line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib:
Bevacizumab is administered once every 21 days in addition to erlotinib until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Bevacizumab	15mg/kg	IV infusion	100ml NaCl 0.9% over 90mins*	Repeat every 21 days
Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.					
*The initial dose of bevacizumab should be delivered over 90 minutes as an intravenous infusion. 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.					

ELIGIBILITY:

- Indication as above
- ECOG status 0-2
- Adequate haematological (ANC ≥ 1.2 x 10^9/L , platelets >100 x 10^9/L) renal Creatinine ≤ 1.5 x ULN and liver status (bilirubin ≤ 26 micromol/L; AST/ Alkaline Phosphatase ≤ 5 x ULN)
- Non squamous NSCLC in combination with erlotinib : Demonstration of EGFR mutation by a validated test method

EXCLUSIONS:

- Hypersensitivity to bevacizumab or to any of the excipients
- Pregnancy
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies

USE WITH CAUTION:

Use with caution in patients with:

- Previous pelvic radiotherapy
- Pre-existing uncontrolled hypertension
- Clinically significant cardiovascular disease
- Renal disease including proteinuria
- Bleeding/Clotting disorders
- Previous anthracycline exposure
- History of significant venous thromboembolism
- Recent (less than 6 months) arterial thromboembolic events
- Prior radiation to the chest wall or other serious medical illness

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Dipstick urinalysis for protein
- Bood pressure measurement, cardiac assessment including history and physical exam
- ECHO should be considered in patients who have had chest wall radiation or prior treatment with an anthracycline
- INR if clinically indicated*

Regular tests:

- FBC, renal and liver profile, dipstick urinalysis for protein
- Blood pressure prior to each cycle and post treatment
- INR if clinically indicated*
  *(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Bevacizumab dose reduction for adverse events is not recommended (SmPC). If indicated, bevacizumab therapy should either be permanently discontinued or temporarily suspended until toxicity resolves (Table 2 and Table 3).

Renal and Hepatic Impairment:

Table 1: Dose Modification of bevacizumab in renal and hepatic impairment

Renal impairment	Hepatic Impairment
No studies have been performed in patients with renal impairment.	No studies have been performed in patients with hepatic impairment.

Management of adverse events:

Proteinuria:

Table 2: Dose modifications of bevacizumab for proteinuria

Degree of proteinuria	Action
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled.
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below.
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection.
24-hour urine total protein (g/24hr)	**Action**
less than or equal to 2	Proceed
greater than 2 to 4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24hour.
greater than 4	Discontinue Therapy

Table 3: Dose modification of bevacizumab for adverse events

Adverse reactions	Recommended dose modification
Hypertension Uncontrolled or symptomatic hypertension on Day 1 Grade 4 hypertension or persisting grade 3 hypertension	Withhold bevacizumab treatment, start antihypertensive therapy or adjust pre-existing medication. Discontinue bevacizumab
Grade 4 Proteinuria	Discontinue bevacizumab
Tracheoesophageal (TE) fistula or any Grade 4 fistula	Discontinue bevacizumab
Grade 4 Thromboembolic events	Discontinue bevacizumab
Haemorrhagic event ≥ Grade 3	Discontinue bevacizumab
Gastrointestinal Perforation	Discontinue bevacizumab

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal **(Refer to local policy).**

PREMEDICATIONS: Not usually required unless the patient has had a previous hypersensitivity.

OTHER SUPPORTIVE CARE: Anti-diarrhoeal treatment may be required **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Gastrointestinal perforations:** Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.
- **Wound healing complications:** 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. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for major elective surgery for 28 days and for 7 days for minor surgery or as directed by the prescribing Consultant.
  Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.
- **Hypertension:** An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent.
  - Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician's discretion.
  - Patients should have their blood pressure measured before each dose or more frequently if hypertension develops/worsens.
  - Any patient who develops hypertension (>150/100 mmHg) should be treated with anti-hypertensive medications, or have their pre-existing medications adjusted. Patients developing severe hypertension (>200/110 mm Hg) that is not controlled with medication should have bevacizumab discontinued.
  - It should be permanently discontinued if the patient develops hypertensive crisis or hypertensive encephalopathy.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others:

seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating therapy in patients previously experiencing PRES is not known.

- **Proteinuria:** Patients with a history of hypertension may be at increased risk for the development of proteinuria.
- **Thromboembolism:** Patients receiving bevacizumab plus chemotherapy, with a history of arterial thromboembolism or age > 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients. Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions. Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment. Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored.
- **Haemorrhage:** Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour associated haemorrhage and minor mucocutaneous haemorrhage. Bevacizumab should be used with caution in patients at risk of bleeding.
- **Aneurysms and artery dissections**: The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

DRUG INTERACTIONS:

- The safety and efficacy of concomitant administration of radiotherapy and bevacizumab has not been established.
- No interaction studies have been performed between EGFR antibodies and bevacizumab. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from the randomised phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.
- Concurrent use of bevacizumab and sunitinib can increase the risk of microangiopathic haemolytic anaemia (MAHA).
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	12/06/2015		Dr Maccon Keane
2	23/5/2017	Updated with new NCCP regimen format	Prof Maccon Keane
3	22/11/2018	Update of dose modifications of bevacizumab for proteinuria	Prof Maccon Keane
4	22/05/2019	Reviewed. Removal of 00215b as this is now regimen 00499a (GemCARBO(AUC4)Bev)	Prof Maccon Keane
5	12/02/2020	Clarification of dose modifications of bevacizumab for proteinuria	Prof Maccon Keane
6	28/04/2021	Reviewed. Clarification of dose modifications of bevacizumab for proteinuria (Table 2), updated adverse effects.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of bevacizumab (Avastin®) in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.