Bevacizumab (Avastin®) for the first line treatment of advanced colorectal cancer with CAPIRI (or XELIRI)

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Bevacizumab</td>
<td>7.5mg/kg</td>
<td>Infusion</td>
<td>250mls 0.9% Sodium Chloride Rate see below*</td>
</tr>
<tr>
<td>Day 1</td>
<td>Glucose 5%</td>
<td>500ml</td>
<td>Infusion</td>
<td>Fast running/ Line Flush</td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral</td>
<td>Via Glucose Drip</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>8mg</td>
<td>IV bolus</td>
<td>Via Glucose Drip</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>200mg/m²</td>
<td>IV Infusion</td>
<td>250ml Glucose 5% over 2 hours</td>
</tr>
<tr>
<td>Days 1 to 14</td>
<td>Capecitabine</td>
<td>800mg/m² twice a day*</td>
<td>Oral</td>
<td>N/A</td>
</tr>
</tbody>
</table>

DOSE FREQUENCY
Treatment administered every 21 days, usually for up to 8 cycles

Capecitabine available as 500mg and 150mg tablets

RATE
Bevacizumab must be given in combination with chemotherapy every three weekly. Intravenous infusion given over 90 minutes for initial dose; if tolerated next infusion can be given over 60 minutes; can thereafter be given over 30 minutes. It can be given in 100ml Sodium Chloride provided the final solution stays within the range of 1.4-16.5 mg/ml.

EXCLUSION CRITERIA
Contraindicated in patients who have a history of hypersensitivity reaction to bevacizumab or other recombinant human or humanized antibodies
Caution in patients with:
- Untreated central nervous system metastases
- Patients incapable of managing oral chemotherapy themselves or with the assistance of a carer
- Patients with swallowing difficulties
- Uncontrolled hypertension
- History/ Risk factors for thromboembolic events e.g. history of arterial thromboembolic events
- Significant cardiac risk factors for development of CHF
- Patients with baseline renal function less than 30ml/min (Creatinine Clearance)

INVESTIGATIONS / MONITORING REQUIRED
Pre treatment:
- Assessment of renal function, FBC, Cardiac history
- Cardiac assessment incl. history and physical exam
BEVACIZUMAB (AVASTIN®) & XELIRI PROTOCOL

Cumbria, Northumberland, Tyne & Wear Area Team

Prior to each cycle
- FBC, U&E’s, LFT’s
- Tumour markers as appropriate, e.g. where CEA is elevated this should be measured before each cycle
- Monitor blood pressure every cycle and more frequently in patients who develop hypertension
- Proteinuria by dipstick analysis prior to treatment and before each dose. If protein present undertake quantitative measurement of protein in urine and if greater than 2g > 24hrs delay of bevacizumab.

APPROVED INDICATIONS

Approved for use on the National Cancer drugs Fund List for patients who meet the following criteria:

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Advanced colorectal cancer
3. 1st line indication
4. Given in combination with (a) oxaliplatin based combination chemotherapy OR (b) Given in combination with irinotecan-based combination chemotherapy
5. No previous treatment with Bevacizumab

NOTE: If excessive toxicity with oxaliplatin or irinotecan, bevacizumab can be continued with a fluoropyrimidine alone until disease progression only.

NOTE: Bevacizumab is ONLY approved for use in combination with chemotherapy and is not for use as a single agent maintenance therapy.

No treatment breaks of more than 7 weeks are allowed. Should treatment breaks be required, then an Individual Funding Request must be submitted as per CDF processes.

PREMEDICATION

*If acute cholinergic syndrome appears atropine sulphate should be administered unless clinically contraindicated. The manufacturer recommends the use of prophylactic atropine sulphate with subsequent doses of irinotecan.

Anti-emetics are not required for Bevacizumab treatment. Take home medications as per chemotherapy regimen.

RECOMMENDED TAKE HOME MEDICATION

Ondansetron 8mg twice daily for 2 to 3 days
Dexamethasone 4mg twice daily for 1 to 3 days
Metoclopramide 10 to 20mg three to four times daily as required
ASSESSMENT OF RESPONSE
Assessed radiologically after 4th cycle.
Metastatic: Tumour size and patient symptomatic response

REVIEW BY CLINICIAN
Review at each cycle as appropriate

NURSE / PHARMACIST LED REVIEW
Each cycle as applicable according to local protocols

ADMINISTRATION NOTES

XELIRI
- Irinotecan must only be given in units where clear arrangements are made to manage possible toxicity related out of hour’s admissions. Patients must be made aware of the risk of delayed diarrhoea occurring 24 hours after the administration of irinotecan and at any time before the next cycle. This means supplying information sheets to the patient and GP as appropriate.
- Early onset diarrhoea (within the first 24 hours). Can be a result of acute cholinergic syndrome and may occur in 9% of patients. Symptoms are short lasting and respond within minutes to administration of atropine (0.25 – 1mg subcutaneously).
- Delayed diarrhoea must be treated immediately with high dose Loperamide (4mg after first loose stool and 2mg every 2 hours, to a maximum of 16 (2mg) tablets in 24 hours. Hospitalise if condition not resolved in 48 hours.
- For diarrhoea lasting greater than 24 hours add ciprofloxacin 25mg twice daily. Note: many units give patients a supply of loperamide and ciprofloxacin at the start of the treatment.
- Capecitabine should start on the evening of day 1 and continue until the morning of day 15.
- Capecitabine should be omitted if Grade II toxicity occurs. It can recommence (see dose reductions) if toxicity resolves, however the treatment should still stop on day 15. (i.e. Doses are omitted not delayed).
- Note: Grade II Toxicity includes: Diarrhoea defined as an increase of 4-6 stools per day or nocturnal stools.

BEVACIZUMAB
- Hypertension is commonly observed, may be dose-related and should be managed with antihypertensives, e.g. calcium channel blockers.
- Units administering bevacizumab must have facilities available for the treatment of anaphylaxis and resuscitation.
- May not need to stop treatment for minor hypersensitivity e.g. reactions, flushing, localised rash. Must be stopped for major reactions, e.g. hypotension, dyspnoea, angioedema or generalised urticaria.
- Paracetamol can be used to treat reactions.
- Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. If elective surgery is planned, bevacizumab should be withheld and the long half-life considered.
No treatment breaks of more than 7 weeks from the start of the previous cycle are allowed. Should treatment breaks be required, then an Individual Funding Request must be submitted as per CDF processes.

**EXTRAVASATION** Follow Network and Local Trust Guidelines

**MAIN TOXICITIES**

**XELIRI**
- Acute cholinergic syndrome (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation
- Diarrhoea – risk of severed delayed diarrhoea – can be life threatening
- Nausea and Vomiting
- Stomatitis
- Palmar/ Plantar Erythrodysthesia – Can be severe, patients must be forewarned
- Pyrexia, fatigue, asthenia, anorexia
- Myelosuppression
- Hyperbilirubinemia
- Cardiotoxicity – Occasionally patients may experience coronary artery spasm. Stop treatment with fluoropyrimidinetherapy therapy if this occurs.

**BEVACIZUMAB**
- Fatigue Hypertension Proteinuria Headache
- Infusion-associated symptoms / acute hypersensitivity reactions (anaphylaxis, chills and fever, nausea, vomiting, pain, rigors, headache, asthenia etc.)
- Diarrhoea
- Abdominal pain
- Nausea and vomiting

*Less Common Toxicities that may be severe or life-threatening include:*  
- Arterial/venous thromboembolism
- GI perforation, fistulas, wound dehiscence
- Haemorrhage
- Cardiac failure
- Pneumonitis

**DOSE MODIFICATIONS**

**Haematological toxicity:**
- Delay 1 week if ANC < 1.5 and Platelets < 75 to 100
- No dose reduction for CTC grade I/II ANC
- Grade III/IV ANC → delay chemotherapy until recovered, then proceed at 25% Capecitabine and Irinotecan dose reduction
- If delay > 1 week or delay 2 weeks or greater occurs, reduce the 5FU dose (bolus & infusional) and oxaliplatin by 20%. Continue at the reduced dose for subsequent cycles unless other toxicity occurs.
- If further delay(s) for bone marrow suppression occur despite a 25% dose reduction, consider a further 25% dose reduction.
• Note: Individual prescribers will make decision to treat based on blood counts within the flexible limits for NAC and platelets listed above. Check with prescriber before proceeding if ANC and platelets below the upper limits (ANC = 1.5, platelets = 100)

• Note: In the case of asymptomatic dose delay of chemotherapy for haematological toxicity the bevacizumab may still be given if the clinician decides it is appropriate as bevacizumab does not cause significant haematological toxicity.

Non –Haematological toxicity:
CAPECITABINE
Grade 2 during course of treatment = delay until recovered and give full dose. Diarrhoea grade 3 / 4 during a course of treatment, delay until recovered and resume treatment at 25% reduced dose of capecitabine

Note CTC grading for Diarrhoea toxicity grading
• CTC Grade 1 = Diarrhoea (watery stool 2-3 times/day) OR mild increase in ostomy output compared to baseline
• CTC Grade 2 = Diarrhoea (watery stool 4-6 times/day) OR moderate increase in ostomy output compared to baseline
• CTC Grade 3/4 = Diarrhoea (watery stool >7 times/day OR severe increase in ostomy output compared to baseline

| Table of hand/ foot toxicity grading for capecitabine only |
|-----------------|-----------------|-----------------|
| Grade | Clinical | Functional |
| 1 | Numbness, dysesthesia/parasthesia, tingling, painless swelling or erythema | Discomfort but no interruption of normal activities |
| 2 | Painful erythema with swelling | Discomfort which affects activities of daily living |
| 3 | Moist desquamation, ulceration, Blistering, severe pain | Severe discomfort, unable to work or perform activities of daily living |

Table of dose adjustments according to CTC toxicity (not PPE/ hand/ foot)

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<tr>
<th>Grade 2</th>
<th>Grade3</th>
<th>Grade 4</th>
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<td>1st appearance</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose with prophylaxis where possible</td>
</tr>
<tr>
<td>2nd appearance</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose</td>
</tr>
<tr>
<td>3rd appearance</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose</td>
<td></td>
</tr>
<tr>
<td>4th appearance</td>
<td>STOP treatment</td>
<td></td>
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Expiry Date: Mar 2016
**Renal function:**
- Capecitabine is renally excreted; therefore dose requires adjustment for patients with moderate renal impairment (< 50ml/min) require a 25% dose reduction.
- Contra-indicated in severe renal failure (CrCl <30ml/min)
- Once the capecitabine dose has been reduced, it should not be increased at later time. Omitted doses are not replaced or restored, instead the patient should resume the planned treatment cycle

| CrCl > 50 | 100% | 100% |
| CrCl 30-50 | 75% | 100% |
| CrCl<30 | Cl | Not funded single agent |

**BEVACIZUMAB**
- Dose reduction for toxicity is not recommended, but dosing with bevacizumab should be omitted or discontinued for the following adverse events:
  - Uncontrollable hypertension, delayed wound healing, surgery, grade 3 proteinuria (>3g in 24hrs ref. CTCv4)
  - No information on dose adjustment. The kidneys and liver are not major organs for bevacizumab metabolism or excretion.

**TREATMENT LOCATION**
Cancer Centre or Cancer Unit where there is an Oncologist with a specialisation in Colorectal cancer patients as appropriate.

**REFERENCES**
- Bevacizumab summary of product characteristics (SPC) available at [https://www.medicines.org.uk/emc/medicine/15748/SPC/Avastin+25mg+ml+concentrate+for+solution+for+infusion/](https://www.medicines.org.uk/emc/medicine/15748/SPC/Avastin+25mg+ml+concentrate+for+solution+for+infusion/)
- Common Terminology Criteria. for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.02: Sept. 15, 2009 Available at [http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15 QuickReference_5x7.pdf](http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15 QuickReference_5x7.pdf)
- Reinacher-Schick AC et al. Activity of the combination of bevacizumab (Bev) with capecitabine/ irinotecan (CapIri/Bev) or capecitabine/ oxaliplatin (CapOx/Bev) in advanced colorectal cancer (ACRC): a randomised phase II study of the AIO Colorectal Study Group (AIO trial 0604). Am Soc Clin Oncol 2008; Abstract 4030
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