Chemotherapy Protocol

BREAST CANCER

EVEROLIMUS and EXEMESTANE

Regimen

- Breast Cancer – Everolimus-Exemestane

Indication

- The first or second line treatment of post-menopausal metastatic breast cancer where the following criteria are met;

  - ER positive and HER2 negative
  - no symptomatic visceral disease
  - previous treatment with a non-steroidal aromatase inhibitor
  - no previous treatment with exemestane

- Performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Everolimus	Diarrhoea, rash, dry skin, fatigue, non-infectious pneumonitis, increased risk of infection, hyperglycaemia, hypertriglyceridaemia
Exemestane	Fractures, hot flushes, headache, increased sweating, joint and muscloskeletal pain, insomnia, fatigue, nausea

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

Monitoring

- FBC, U&Es and LFTs every 4 weeks
- Blood glucose levels at baseline and after 4 weeks of treatment. Thereafter every 4-8 weeks or as clinically indicated
- Lipids and proteinuria at baseline then as clinically indicated
- In those with osteoporosis or at risk of this disease consider bone densitometry before starting exemestane
- Hepatitis serology at baseline
- Respiratory assessment at baseline

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Consider blood transfusion or the prescription of an erythropoietin produce according to NICE TA 323 if the patient is symptomatic of anaemia or has an haemoglobin of less than 8g/dL (80g/L).

Neutrophils ($x10^9$/L)	**Dose Modifications (Everolimus)**
1 or greater	Full dose
0.5 - 1	1st Occurrence Interrupt treatment until recovery to $1x10^9$/L or greater then restart at the full dose 2nd Occurrence Interrupt treatment until recovery to $1x10^9$/L or greater then restart at 5mg once a day
less than 0.5 or NCI-CTC grade 3 febrile neutropenia	1st Occurrence Interrupt treatment until the fever has resolved and the neutrophils are $1x10^9$/L or greater then restart at 5mg once a day 2nd Occurrence Discontinue treatment permanently
NCI-CTC grade 4 febrile neutropenia	Discontinue treatment permanently
Platelets ($x10^9$/L)	**Dose Modifications (Everolimus)**
75 or greater	Full dose
50-75	1st Occurrence Interrupt treatment until recovery to $75x10^9$/L or greater then restart at the full dose 2nd Occurrence Interrupt treatment until recovery to $75x10^9$/L or greater then restart at 5mg once a day
25-50	1st Occurrence Interrupt treatment until recovery to $75x10^9$/L or greater then restart at 5mg once a day 2nd Occurrence Discontinue treatment permanently
less than 25	Discontinue treatment permanently

Hepatic Impairment

Drug	Child Pugh Class	Dose
Exemestane	Not Applicable	Use with caution
Everolimus	A	7.5mg once a day
	B	5mg once a day
	C	If benefit–risk assessment is considered favourable by the consultant, treat with a maximum daily dose of 2.5mg once a day

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Everolimus	N/A	No dose modification required
Exemestane	NA	Use with caution

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose should then be reduced to 5mg once a day or discontinued as appropriate.

Diabetes

If blood glucose is raised at baseline or the patient is a known diabetic then attempt to optimise the glycaemic control before starting everolimus.

After commencing everolimus, if the fasting glucose is between 14-27.8mmol/L or the triglycerides are in the range 5.8-11.4mmol/L then interrupt everolimus until resolved. Re-start the everolimus at 5mg once a day.

If the fasting glucose is greater than 27.8mmol/l or triglycerides are greater than 11.4mmol/L then discontinue everolimus.

Mucositis

NCI-CTC Grade	Action (Everolimus)
2	Continue the everolimus without dose adjustments if the patient can tolerate it. Alternatively interrupt until symptoms have resolved to NCI-CTC grade 1 or below and then re-challenge at the same dose
3 or recurrence of grade 2 mucositis	Interrupt treatment until symptoms have resolved to NCI-CTC grade 1 or below then restart the everolimus at 5mg once a day
4 or recurrence of grade 3 mucositis	Discontinue everolimus

Non Infectious Pneumonitis

Patients who develop non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea should be advised to report promptly. Some cases of non-infectious pneumonitis, including severe and fatal cases, were described in 12% of patients taking everolimus

For patients who develop radiological changes suggestive of non-infectious pneumonitis and have few, moderate or severe symptoms see the table below.

NCI-CTC Grade	Action (Everolimus)
1	Continue everolimus without dose adjustments
2	Interrupt therapy. Consider short term use of corticosteroids e.g. prednisolone 20mg once a day for 10-14 days. Restart everolimus at 5mg once a day when symptoms have resolved.
3	Interrupt therapy. Prescribe corticosteroids e.g. prednisolone 40mg as indicated. Restart everolimus at 5mg daily once symptoms have resolved or discontinue as appropriate.
4	Discontinue the everolimus. Treat appropriately.

Infections

Everolimus has immunosuppressant properties and may increase the risk of bacterial, fungal, viral or protozoal infections (including opportunistic, viral reactivation). Pre- existing infections should completely resolve before starting everolimus treatment; doses should be delayed if infection occurs. Avoid if possible in carriers of hepatitis B and C and monitor carefully for signs of hepatitis re-activation.

If a diagnosis of invasive systemic fungal infection is made, everolimus treatment should be promptly and permanently discontinued with appropriate antifungal therapy.

Regimen

28 day cycle continued as long as clinical benefit is observed or until unacceptable toxicity occurs (6 cycles will be set in Aria)

Drug	Dose	Days	Administration
Everolimus	10mg once a day	1-28 inclusive	Oral
Exemestane	25mg once a day	1-28 inclusive	Oral

Dose Information

- Everolimus is available as 2.5mg, 5mg and 10mg tablets.
- Exemestane is available as a 25mg tablet.

Administration Information

- For everolimus, take at the same time of day every day with or without food, but not after a high fat meal.
- For exemestane take with or just after food, or a meal.
- If a dose is missed do not take an additional but rather take the next scheduled dose

Additional Therapy

- Mouthcare for the prophylaxis or treatment of mucositis in accordance with local guidelines
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to everolimus.
- It must be made clear to all staff, including those in the community, that everolimus should only be prescribed under the supervision of an oncologist.
- Everolimus interacts with many other agents. Always check for drug interactions.

Coding

- Procurement – X71.5
- Delivery – X73.1

References

1. Baselga J, Compone M, Piccart M et al. Everolimus in post-menopausal hormone receptor positive advanced breast cancer. N Engl J Med 2012; 366 (6): 520-529.

REGIMEN SUMMARY

Everolimus-Exemestane

Day 1

1. Everolimus 10mg once a day oral
   Administration Instructions
   Swallow this medicine whole. Do not crush or chew.

2. Exemestane 25mg once a day oral
   Administration Instructions
   Take with or just after food, or a meal.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2018	None	Dr Deborah Wright Pharmacist	Dr Chern Lee Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Trust

All actions have been taken to ensure these protocols are correct. However, it remains the responsibility of the prescriber to ensure the correct drugs and doses are prescribed for patients. These protocols should be read in conjunction with other reference sources such as the Summary of Product Characteristics or published references