ZANUBRUTINIB for Waldenstrom's macroglobulinaemia

Indication: Waldenstrom's macroglobulinaemia

Prior to a course of treatment

- Check FBC. Patient should have adequate bone marrow reserve, i.e neutrophils > 1.0, platelets >75 unless cytopaenia is due to disease, e.g marrow infiltration, splenomegaly
- Check eGFR - must be >30ml/min (*see dose modification),* LFTs
- Check HBsAg, anti-HBc and anti-HCV antibody
- Check baseline ECG and chest-X-ray
- Note hypertension is a common adverse event with zanubrutinib – review blood pressure control and treatment. Consider 24-hour blood pressure monitoring.
- Note that zanubrutinib is primarily metabolized by cytochrome P450 enzyme 3A4/5 and there are potentially significant drug interactions. CYP4503A4/5 inhibitors may increase zanubrutinib toxicity. Review current medications *See 'Zanubrutinib and drug interactions'.*
- Note concomitant warfarin and zanubrutinib should be avoided. Consider replacing with a NOAC. Review risk of bleeding, antiplatelet therapy – *discuss with consultant*
- Inform the patient that they must avoid grapefruit juice and Seville oranges throughout treatment
- Note any recent or planned surgical procedures - see *'Surgery and zanubrutinib'*
- If appropriate discuss possibility of pregnancy with female patients - check pregnancy test if child-bearing potential - and need for contraception with both male and female patients.
- Note that the risk of infertility with zanubrutinib is not known. Discuss risk of infertility - offer referral for semen cryopreservation/fertility preservation measures if appropriate
- Written consent for course

Prior to each cycle

- Review fitness for treatment – exclude active infection, major changes in organ function, bleeding/bruising
- Review concurrent medications noting any new medications. Evaluate for potential drug toxicities and interactions - *see 'Zanubrutinib and drug interactions'.*
- Review blood pressure control and pulse - consider 24-hour blood pressure monitoring and ECG
- Note any recent or planned surgical procedures - see *'Surgery and zanubrutinib'*
- Check FBC, eGFR, LFTs - *see dose modification*
- Plan monthly review for the first 3-6 months according to response, tolerance, then 3-monthly

Zanubrutinib	160mg bd PO [1]

Continue until disease progression or unacceptable toxicity

Prophylaxis for acute emesis	Not required
Prophylaxis for delayed emesis	Not required
Other medications	Allopurinol 300mg od (100mg od if Cr Cl <20ml/min) for cycle 1
	Cotrimoxazole 480mg od, continue for 3 months after completion
	Aciclovir 400mg bd, continue for 3 months after completion

Surgery and zanubrutinib

For any surgery or invasive procedure requiring sutures or staples zanubrutinib should be stopped for at least 7 days before and not restarted for at least 7 days after.

For minor procedures (central line placement, thoracentesis, paracentesis, needle biopsy, but not bone marrow biopsy) zanubrutinib should be stopped 3 days before and not restarted for at least 3 days after. For urgent procedures withhold post-procedure and for at least 7 days until the site is reasonably healed.

Zanubrutinib and drug interactions

- Note the lists of drugs below with potential interactions with zanubrutinib are not exhaustive. Further information on interactions is available at: *https://www.drugs.com/drug_interactions.html* or consult with Oncology Pharmacist
- Avoid strong CYP3A4/5 inhibitors e.g: indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, nefazodone. Where short term use is required consider interrupting zanubrutinib or reduce to 80mg od – *discuss with consultant*
- Use moderate CYP3A4/5 inhibitors with caution e.g: aprepitant, erythromycin, fluconazole, verapamil, diltiazem. If a moderate inhibitor must be used reduce zanubrutinib dose 80mg bd.
- Patients taking concomitant moderate or strong inhibitors of CYP3A4/5 must be monitored closely for signs of zanubrutinib toxicity
- Avoid Seville oranges and grapefruit juice throughout treatment
- Avoid use of strong CYP3A4/5 inducers e.g carbamazepine, rifampicin, phenytoin, St John's Wort.
- Any agents known to prolong the QT interval (amiodarone, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, diisopyramide, domperidone, erythromycin, flecainide, haloperidol, methadone, pentamidine, procainamide, quinidine, sotalol, terfenadine) should be used with caution and periodic monitoring of ECGs, electrolytes should be considered.

Dose modifications

Dose modifications are described for haematological, renal and liver dysfunction but note modifications may be indicated for other toxicities also. Discuss all dose reductions or delays with the relevant consultant since the approach may be different depending on the clinical circumstances and treatment intent. Note abnormal liver and renal function tests and blood counts may also be due to the disease being treated.

For neutropenia for neutropenia (unless due to disease), neutropenic sepsis, thrombocytopaenia

- Neuts < 1.0 with sepsis
- Neuts < 0.5
- Plats <25

1st occurrence	Restart at 160mg bd
2nd occurrence	Restart at 80mg bd
3rd occurrence	Restart at 80mg od
4th occurrence	Discontinue zanubrutinib

Dose modification for hepatic impairment	
• Child Pugh A (mild impairment)	No adjustment required
• Child Pugh B (moderate impairment)	No adjustment required
• Child Pugh C (severe impairment)	Note zanubrutinib has not been studies in severe liver impairment. Consider reducing to 80mg bd and monitor for toxicity
Dose modification for renal impairment	
• eGFR >30ml/min	No modification required
• eGFR < 30ml/min, on dialysis	No data available, consider risks and benefits of treatment and monitor for toxicity – *discuss with consultant*

Zanubrutinib toxicities	
Diarrhoea	Severe infection including atypical and fungal
Treatment-related hyperlymphocytosis	Haemorrhage, bleeding, bruising
Atrial fibrillation	Thrombocytopaenia, purpura
Hypertension, need for increased anti-hypertensive medications	Neutropenia
Muscle & joint pain	Rash, Stevens-Johnson syndrome
Reactivation of hepatitis B	Cardiac failure
Basal cell & squamous cell carcinoma	

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