PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Zanubrutinib
Waldenstrom's Macroglobulinaemia

PROTOCOL REF: MPHAZWMAC
(Version No. 1.0)

Approved for use in:

- Waldenstrom's macroglobulinaemia in adults who have had at least 1 treatment, only if they would otherwise have treatment with bendamustine and rituximab
- **Blueteq application is required**

Dosage:

Drug	Dose	Route	Frequency
Zanubrutinib	**320mg**	oral	Once daily
OR			
Zanubrutinib	**160mg**	oral	Twice daily

Continuous. To continue until progression or unacceptable side-effects

Administration:

- If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.
- The hard capsules can be taken with or without food. Patients should be instructed to swallow the capsules whole with water, and not to open, break or chew the capsules.
- Grapefruit and Seville oranges should be used with caution during zanubrutinib treatment, as these contain moderate inhibitors of CYP3A.

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

- Allopurinol PO 300mg OD (or 100mg OD if renal dysfunction) for the first cycle
- Co-trimoxazole PO 480mg OD
- Metoclopramide PO 10mg TDS PRN
- Aciclovir is not normally recommended for this patient group but can be prescribed at the discretion of the consultant

Supportive treatments:

CYP3A	Co-administered medicinal product	Recommended dose
Inhibition	Strong CYP3A inhibitor (e.g., posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir)	80mg OD
	Moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges)	80mg BD
Induction	Strong CYP3A inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) or moderate CYP3A inducer (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin)	Avoid concomitant use; Consider alternative agents with less CYP3A induction

Avoid concomitant use of warfarin or vitamin K antagonists due to increased risk of bleeding. For more detailed interactions please refer to the SPC.

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, severe and fatal haemorrhagic events, infections, rash, musculoskeletal pain, secondary primary malignancies (especially skin cancers), dizziness, fatigue and atrial fibrillation.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment	X			X	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle (can be extended to 3 monthly in stable patients)
FBC	X	X	X	X	Every cycle (can be extended to 3 monthly in stable patients)
U&E & LFTs & Magnesium	X	X	X	X	Every Cycle (can be extended to 3 monthly in stable patients)
CrCl (Cockcroft and Gault)	X	X	X	X	Every cycle (can be extended to 3 monthly in stable patients)
CT scan**	X				At the end of treatment and if clinically indicated
ECG	X				If clinically indicated
Blood pressure measurement	X				Repeat if clinically indicated
Respiratory Rate	X				If clinically indicated
Weight recorded	X				Repeat if clinically indicated
Blood glucose	X				Repeat if clinically indicated
Hepatitis B screen (core antibody and surface antigen)	X				

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed with treatment if platelets ≥50 x10^9/L and neutrophils ≥1.0 x10^9/L.

Adverse Reaction	Adverse reaction occurrence	Dose modification (if starting dose was 320mg OD or 160mg BD)
Grade 3 febrile neutropenia (ANC <1.0 x 10^9/L and a temperature of 38.3°C or a sustained temperature of ≥38°Cfor more than one hour) Grade 3 thrombocytopenia (platelets < 50x 10^9/L) with significant bleeding Grade 4 neutropenia (ANC < 0.5) lasting > 10 consecutive days Grade 4 thrombocytopenia (platelets < 25 x 10^9/L) lasting >10 consecutive days	First	Interrupt zanubrutinib Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 320 mg once daily or 160 mg twice daily
	Second	Interrupt zanubrutinib Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 160 mg once daily or 80 mg twice daily
	Third	Interrupt zanubrutinib Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 80 mg once daily
	Fourth	Discontinue zanubrutinib

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Dosing in renal and hepatic impairment:

Renal	No dose modification is required in mild to moderate renal impairment (i.e. CrCl ≥ 30ml/min). There is limited data on patients with severe renal impairment and end-stage renal disease. Patients with severe renal impairment (i.e. CrCl < 30ml/min) or on dialysis should be monitored for adverse reactions

Hepatic	No dose modifications required for mild (Child-Pugh class A) nor moderate (Child-Pugh class B) hepatic impairment. For those with severe hepatic impairment (Child-Pugh class C) the recommended dose is 80mg BD. These patients should be monitored closely for adverse effects.

Adverse Reaction	**Adverse reaction occurrence**	**Dose modification (if starting dose was 320mg OD or 160mg BD)**
≥ Grade 3 non-haematological toxicities	First	Interrupt zanubrutinib Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 320 mg once daily or 160 mg twice daily
	Second	Interrupt zanubrutinib Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 160 mg once daily or 80 mg twice daily
	Third	Interrupt zanubrutinib Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 80 mg once daily
	Fourth	Discontinue zanubrutinib

References:

1. https://www.medicines.org.uk/emc zanubrutinib. Accessed 21/9/22. Updated 06/12/21

Circulation/Dissemination

Date added into Q-Pulse	21st December 2022
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
			To be completed by author
	1.0	**Aileen McCaughey (Advanced Pharmacist)**	**New protocol**