Zanubrutinib (WM/CLL)

Indication

Treatment of Waldenstrom's macroglobulinaemia in patients who have had at least one prior treatment where bendamustine plus rituximab would be a suitable alternative.

(NICE TA833)

First line treatment of chronic lymphocytic leukaemia (CLL) in patients with 17p deletion or TP53 mutation or in patients with no 17p deletion or TP53 mutation where FCR or bendamustine and rituximab are unsuitable.

Relapsed or refractory chronic lymphocytic leukaemia

(NICE TA931)

ICD-10 codes

C91, C88.0

Regimen details

Drug	Dose	Route
Zanubrutinib	320mg OD (or 160mg BD if preferred)*	Oral

* See interactions section for dose reductions required if concomitant administration with CYP3A4 inhibitors/inducers

Cycle frequency

Continuous

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

Zanubrutinib is available as 80mg hard capsules.

The dose should be taken at approximately the same time each day and may be taken with or without food. Capsules should be swallowed whole with water and not opened, broken or chewed. If a dose is not taken at the scheduled time, the dose should be omitted and the next dose taken at the normal time.

Seville oranges and grapefruit should be avoided whilst taking Zanubrutinib.

Pre-medication

Nil

Emetogenicity

This regimen has low emetic potential – refer to local policy

Additional supportive medication

Allopurinol 300mg (100mg if creatinine clearance < 20ml/min) OD for first cycle
Loperamide if required
Pneumocystis jirovecii prophylaxis as per local policy
Antiviral prophylaxis as per local policy

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U & E (including creatinine)	14 days
LFTs	14 days
Blood pressure	14 days

Other investigations it is advisable to assess before starting treatment as clinically indicated:
Clotting studies
Hepatitis B core antibody and surface antigen
Hepatitis C antibody
HIV1 and 2 status
CT staging of disease
Bone marrow biopsy
Baseline ECG +/- echocardiogram particularly if cardiac history
TP53 mutation, 17p deletion and IGHV mutation status if the treatment indication is CLL/SLL

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U & E (including creatinine)	96 hours
LFTs	96 hours
Blood pressure	Monthly or as clinically indicated
ECG	3-monthly or as clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	≥ 30ml/min
ALT/AST	< ULN
Bilirubin	<1.5 x ULN

Dose modifications

Dose level	Dose
Full dose	320mg OD (or 160mg BD)
Dose level -1	160mg OD (or 80mg BD)
Dose level -2	80mg OD

- **Haematological toxicity**

Neutrophil count		Platelet count	Action
Neutrophils <1.0 x 10^9/L with temperature >38°C Or Neutrophils <0.5 x 10^9/L for > 10 days	OR	Platelets <50 x 10^9/L with significant bleeding Or Platelets <25x 10^9/L for > 10 days	Interrupt Zanubrutinib 1st occurrence: Once toxicity has resolved to grade 1 or baseline resume at same dose level 2nd occurrence: Once toxicity has resolved to grade 1 or baseline resume at next level dose reduction

For myelosuppression, transfusions and G-CSF can be used as necessary.

- **Renal impairment**

No dose modification is required for patients with mild to moderate renal impairment (CrCl ≥ 30ml/min). There is limited data on use in patients with severe renal impairment (CrCl < 30ml/min) or on dialysis so these patients should be monitored closely for adverse reactions.

- **Hepatic impairment**

No dose modification is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. In severe hepatic impairment (Child Pugh class C) the recommended dose is 80mg BD and patients should be monitored closely for adverse reactions.

Child Pugh Classification:

Score	1	2	3
Bilirubin (µmol/L)	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
PT (s prolonged)	<4	4-6	>6
Encephalopathy	none	mild	marked
Ascites	none	mild	marked

The individual scores are summed and then grouped as:

- <7 = A
- 7-9 = B
- >9 = C

- **Other toxicities**

Interrupt Zanubrutinib for any ≥ grade 3 non-haematological toxicities. Interrupt Zanubrutinib for any ≥ grade 4 haematological toxicity. If first occurrence restart at same dose once toxicity has resolved to ≤ grade 1 or baseline. For subsequent occurrences, restart at one level dose reduction (as per the above dosing table) once toxicity has resolved to ≤ grade 1 or baseline.

Haemorrhage

Patients should be monitored for signs or symptoms of bleeding with those on antiplatelet or anticoagulant therapies at increased risk. If a patient suffers a ≥grade 3 haemorrhagic event consider dose reduction. Discontinue Zanubrutinib if intracranial haemorrhage of any grade occurs.

Infections

Infections, including opportunistic infections have occurred in patients treated with Zanubrutinib. Consider anti-infective prophylaxis and monitor for signs and symptoms of infection with prompt intervention when identified.

Second primary malignancies
Second primary malignancies, including non-skin carcinoma have occurred in patients treated with Zanubrutinib. The most common second primary malignancies were basal cell carcinoma and squamous cell carcinoma of the skin. Advise patients to use sun protection.

Cardiac arrhythmias
Atrial fibrillation and atrial flutter have occurred in patients treated with Zanubrutinib, particularly in those with cardiac risk factors, hypertension, acute infections and elderly (≥65 years). Monitor for signs and symptom of atrial fibrillation and atrial flutter and manage as appropriate.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Haemorrhage
Infections, pneumonia
Myelosuppression
Second primary malignancy
Atrial fibrillation/flutter
Tumour lysis syndrome
Viral reactivation

- **Frequently occurring side effects**

Myelosuppression
Infections
Rash, pruritis
Cough
Diarrhoea, constipation
Musculoskeletal pain
Arthralgia
Fatigue
Bruising
Dizziness
Epistaxis
Hypertension

- **Other side effects**

Peripheral oedema

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin or other vitamin K antagonists: avoid
Strong CYP3A inhibitors (e.g. posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin, indinavir, lopinavir, ritonavir, telaprevir): reduce Zanubrutinib dose to 80mg OD for the duration of inhibitor use if co-administration is unavoidable
Moderate CYP3A inhibitors (e.g. erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit juice, Seville oranges): reduce Zanubrutinib dose to 80mg BD if co-administration is unavoidable.
Strong CYP3A inducers (e.g. carbamazepine, phenytoin, rifampicin, St John's wort): avoid concomitant use of strong CYP3A inducers, consider agents with less CYP3A induction.
Moderate CYP3A inducers (e.g. bosentan, efavirenz, etravine, modafinil, nafcillin): avoid concomitant use of moderate inducers. If co-administration is unavoidable, increase Zanubrutinib dose to 320mg BD.
CYP3A substrates with narrow therapeutic index (e.g. alfentanil, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus): zanubrutinib may reduce plasma exposure of these substrates, use with caution.

CYP2C19 substrates with narrow therapeutic index: Zanubrutinib may reduce plasma exposure of these substrates, use with caution.
P-gp substrates with narrow therapeutic index (e.g. digoxin): Zanubrutinib may increase concentrations of these substrates.

Additional comments

If the patient requires surgery, consider withholding Zanubrutinib for 3-7 days pre- and post-surgery depending on type of surgery and risk of bleeding.

Zanubrutinib should not be used in pregnancy. There is no data on the use of Zanubrutinib in pregnant women and animal studies have shown reproductive toxicity.

References

- National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance TA833 accessed 18 April 2024 via www.nice.org.uk
- National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance TA931 accessed 18 April 2024 via www.nice.org.uk
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- Tam, C.S. et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUIOA): a randomised, controlled, phase 3 trial. Lancet Oncology 2022:23(8):1031-1043
- Tam, C.S. et al. A randomized phase 3 trial of Zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinaemia: the ASPEN study. Blood 2020:136(18):2038-2050

Written/reviewed by: Dr S Jen (Haematology SpR, UHBW NHS Trust), Dr L Percy (Consultant Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

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