Chemotherapy Protocol

LYMPHOMA
ZANUBRUTINIB

Regimen

- Lymphoma - Zanubrutinib

Indication

Zanubrutinib monotherapy for the treatment of patients with previously treated Waldenstrom's macroglobulinaemia and in the absence of access to Zanubruitnib the patient would otherwise be suitable for treatment with the combination of bendamustine and rituximab where the following is met:

- Patient previously diagnosed with Waldenstrom's macroglobulinaemia
- Patient has symptomatic disease which requires systemic therapy
- Patient has been previously treated with at least 1 prior systemic therapy for Waldenstrom's macroglobulinaemia
- In the absence of access to Zanubrutinib the patient would otherwise be next treated with the combination of bendamustine and rituximab.
- The patient is treatment naïve to a Bruton's kinase inhibitor or the patient has been commenced on zanubruitnib via the manufacturer's (Beigene) early access scheme for previously treated Waldenstrom's macroglobulinaemia and all other treatment criteria on this form are fulfilled or the patient has been previously commenced on ibrutinib for previously treated Waldenstrom's macroglobulinaemia and the ibrutinib has had be discontinued solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.
- The patient has an ECOG performance status of 0, 1 or 2
- Zanubrutinib will be given as monotherapy
- Zanubrutinib will be continued until disease progression or unacceptable toxicity or patient choice to stop treatment, whichever is the sooner.

Toxicity

Drug	Adverse Effect
Zanubrutinib	Neutropenia, thrombocytopenia, upper respiratory tract infection, haemorrhage/haematoma, rash, bruising, anaemia, musculoskeletal pain, diarrhoea, pneumonia, cough

The adverse effects listed are not exhaustive. Please refer to the relevant summary of product characteristics for further details.

Monitoring

- FBC, U&Es, LFTs, bone chemistry, serum immunoglobulins and electrophoresis and glucose prior to day 1 of the cycle. This can be extended to 3 monthly for stable patients.

- Hepatitis B status prior to starting treatment as re-activation is a known adverse effect of treatment

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.

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 use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L).

Interrupt zanubrutinib for any Grade 3 or greater non-haematological, Grade 3 or greater neutropenia with infection or fever, Grade 3 thrombocytopenia with significant bleeding or any other Grade 4 haematological toxicities. Once symptoms of toxicity have resolved to Grade 1 or baseline (recovery), reinitiate zanubrutinib at the starting dose. If the toxicity reoccurs, reduce dose as per table below.

Toxicity occurance	Dose modification for ≥ Grade 3 ADRs once resolved to ≤Grade 1 or baseline	
	Once daily dosing	Twice daily dosing
First	Restart at 320mg once a day	Restart at 160mg twice a day
Second	Restart at 160mg once a day	Restart at 80mg twice a day
Third	Restart at 80mg once a day	Restart at 80mg once a day
Fourth	Discontinue zanubrutinib	Discontinue zanubrutinib

Hepatic Impairment

Dose modifications are not needed in patient with mild (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B).

The recommended dose for patients with severe hepatic impairment (Child-Pugh class C) is 80mg orally twice a day. The safety of Zanubrutinib has not been evaluated in patients with severe hepatic impairment. Monitor these patients closely for adverse events.

Renal Impairment

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

Other
Haemorrhage

Serious and fatal haemorrhagic events have occurred in patients treated with Zanubrutinib monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal haemorrhage, haematuria and haemothorax have been reported in patients. Bleeding

events of any grade including purpura and petechiae occurred in patients with haematological malignancies.

Zanubrutinib may increase the risk of haemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Dose modification may be necessary for grade 3 or greater adverse reactions as recommended.

Regimen

28 day cycle until disease progression or intolerance (6 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Zanubrutinib	320mg once a day*	1-28 (continuous)	oral

* the daily dose may be taken either as once daily (320mg) or divided into two doses of 160mg twice daily.

Dose Information

- Zanubrutinib is available as 80mg capsules

Administration Information

- 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.
- Zanubrutinib can be taken with or without food
- Zanubrutinib should be swallowed whole with water. The capsules should not be opened, broken or chewed.

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Additional Therapy

- Anti-infective prophylaxis with
  - co-trimoxazole 960mg once day on Monday, Wednesday and Friday oral
  - aciclovir 400mg twice a day
- Allopurinol 300mg once a day oral for the first cycle only

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to zanubrutinib.
- It must be made clear to all staff, including those in the community, that zanubrutinib is should only be prescribed under the supervision of a consultant haematologist or oncologist.

- There are many drug interactions associated with zanubrutinib. Please check for interactions when initiating treatment.

References

1. Beigene UK Ltd.Brukinsa 80mg hard capsules summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product.14001. Last updated 8/9/2022. Accessed 24/01/2023.
2. Tam, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. October 2020. 136(18): 2038-2050.

REGIMEN SUMMARY

Zanubrutinib

Cycle 1

Take Home Medicines

1. Zanubrutinib 320mg once a day oral
   Administration instructions:
   This may be given as 160mg twice a day
   Oral SACT
   Swallow whole

2. Aciclovir 400mg twice a day oral
   Administration instructions:
   Please supply 28 days or an original pack if appropriate

3. Co-trimoxazole 960mg once a day on Monday, Wednesday, Friday oral
   Administration instructions:
   This may be given as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice. Please supply 28 days or an original pack if appropriate.

4. Allopurinol 300mg once a day
   Administration instructions:
   Take with or after food with plenty of water. Please supply 28 days or an original pack if appropriate

Cycle 2, 3, 4, 5, 6

Take Home Medicines

5. Zanubrutinib 320mg once a day oral
   Administration instructions:
   This may be given as 160mg twice a day
   Oral SACT
   Swallow whole

6. Aciclovir 400mg twice a day oral
   Administration instructions:
   Please supply 28 days or an original pack if appropriate

7. Co-trimoxazole 960mg once a day on Monday, Wednesday, Friday oral
   Administration instructions:
   This may be given as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice. Please supply 28 days or an original pack if appropriate.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	January 2023	None	Alexandra Pritchard Pharmacist	Dr Matthew Jenner Consultant Haematologist

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 NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.