RESEARCH PROTOCOL

(BRAMble) Brukinsa Real-world Analysis in Marginal zone Lymphoma

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1) RESEARCH TEAM & KEY CONTACTS

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2) INTRODUCTION

The marginal zone lymphomas (MZL), broadly comprising extranodal MZL (ENMZL), splenic MZL (SMZL) and nodal MZL (NMZL), collectively represent the second most common indolent non-Hodgkin lymphoma (iNHL) (Cheah et al., 2022). In the UK, MZL represents 17% of all new lymphoma diagnoses and has a 10-year prevalence of 23.8 cases per 100,000 people. The disease most commonly affects older people, with a median age at presentation of 72 years (Smith et al., 2015). Advanced-stage MZL is incurable, although disease typically follows an indolent course and median survival exceeds 5-10 years depending on subtype. The majority of patients treated with first-line immuno(chemo)therapy are expected to relapse, at which point treatment options include surveillance, chemotherapy and novel approaches.

Zanubrutinib is an irreversible, next-generation, covalent Bruton's tyrosine kinase (BTK) inhibitor with enhanced BTK specificity and improved safety compared to the first-generation drug ibrutinib. In July 2024, zanubrutinib (Brukinsa®) received NICE approval for treatment of patients with relapsed/refractory MZL after at least one prior line of antiCD-20-containing therapy based on results of the pivotal MAGNOLIA trial(Opat et al., 2023). In this study, overall and complete response rates (ORR/CR) were 68.2% and 25.8% respectively, with 2-year duration of response 72.9%. Two-year progression-free and overall survival were 70.9% and 85.9% respectively. Prior to NICE approval, zanubrutinib was available to patients in England between January 2022- July 2024 via a Pre-reimbursement Access Programme (PRAP).

BRAMbLe (**B**rukinsa **R**eal-world **A**nalysis in **M**arginal zone **L**ymphoma) is a UK Lymphoma Research Group multicentre, non-interventional, retrospective, observational study aimed at collecting clinical outcome data for patients with relapsed/refractory MZL who were treated with zanubrutinib within the PRAP in England. The study will evaluate patient characteristics and outcome data for real-world patients and report longer-term treatment outcomes to support the use of Zanubrutinib in MZL and widened patient access in other countries.

3) BACKGROUND

In many cases, MZL can be managed via a 'watch and wait' programme of surveillance after initial diagnosis in patients presenting with low tumour burden or asymptomatic advanced stage disease. When indicated, treatment options for disseminated disease include rituximab monotherapy (especially for splenic and extranodal subtypes) or rituximab with chemotherapy such as rituximab and/or chlorambucil; bendamustine (BR); or rituximab plus cyclophosphamide, vincristine and prednisolone (R-CVP). Response rates and progression free survival (PFS) are typically high; after first line therapy, PFS is 72% at 5 years for rituximab-chlorambucil in ENMZL and 90% at 3 years for BR in SMZL (Iannitto et al., 2018; Zucca et al., 2017). Maintenance therapy with rituximab has been shown to improve PFS but not overall survival (OS) and use is variable (Pirosa et al., 2021).

Despite the typically indolent clinical course of MZL and the long PFS associated with first line therapy, most patients undergo relapse. For those requiring treatment, historical approved treatment options in England were limited to immuno(chemo)therapy for advanced stage

disease and/or radiotherapy for local disease control. An optimal therapy at relapse was not established and many older patients (who make up the majority of patients with relapsed/refractory MZL) could not tolerate combination or intensified immunochemotherapy approaches leading to disappointing clinical outcomes in real-world practice.

The phase 2 MAGNOLIA trial established zanubrutinib as a safe and effective therapy in 68 patients with relapsed/refractory MZL (R/R MZL) dosed at 160mg twice daily until disease progression or toxicity (Opat et al., 2023). At final analysis, the primary endpoint of overall response rate (ORR) was 68.2% and CR was 25.8% by PET and/or CT response assessment. Two-year duration of response rate (DoR) was 72.9%, and 2-year PFS and OS were 70.9% and 85.9%, respectively. Treatment was well tolerated; adverse events were mostly low grade and included diarrhoea (22.1%), contusion (20.6%) and constipation (14.7%)(Opat et al., 2021). The most common grade ≥3 adverse events of special interest were infections (22.1%, including covid-19 in 5.9%) and neutropenia (11.8%), with no reported cases of neutropenic sepsis. Any grade atrial fibrillation, major bleeding and hypertension were rare, occurring in 2.9%, 1.5% and 4.4% of patients, respectively. Efficacy and safety outcomes were consistent across subgroups, suggesting broad utility for this treatment but subsets were small due to the small overall sample size, and older/frailer patients typically encountered in real-world practice were under-represented in the trial in which only one-quarter (27.9%) were ≥75 years and >90% were ECOG 0-1.

National Institute for Clinical Excellence (NICE) approval was granted to zanubrutinib in July 2024 for the treatment of patients with relapsed or refractory MZL after at least one prior line of anti-CD20 based therapy based on results of the MAGNOLIA trial (National Institute for Clinical Excellence, 2024). Prior to NICE approval, zanubrutinib was delivered in England via a PRAP to approximately 160 patients, more than double the number treated within the pivotal trial, with less stringent eligibility criteria. The current study will evaluate clinical outcomes in this larger, real-world cohort, serving as a confirmatory study and more robust evidence-base for outcomes in high-risk subsets, older and frailer patients, in turn to inform clinical decision-making, future research and international reimbursement approvals.

4) STUDY OBJECTIVES

4.1 Primary Question/Objective

To validate the effectiveness and safety of zanubrutinib in a real-world setting in England, reporting progression free survival outcomes and building upon findings from the Phase II MAGNOLIA trial.

4.2 Secondary Question/Objective

Secondary endpoints:

- Overall & complete response rates
- Duration of response & complete response
- Time to next treatment

- Overall survival
- Rate of grade 3-5 adverse events
- Rates of grade 1-5 adverse events of special interest (bleeding, cardiovascular toxicity, second primary malignancies including skin cancer)
- Discontinuation rates
- Mutation profiles (if done)

5) STUDY DESIGN & PROTOCOL

5.1 Participants

Adult patients with R/R MZL treated with zanubrutinib via the PRAP between January 2022 – July 2024. Approximately 160 patients are expected to be eligible for inclusion.

5.2 Study Intervention and/or Procedures

This is a multicentre, retrospective, real world observational study in patients with relapsed or refractory MZL treated with zanubrutinib on the Pre-Reimbursement Access Programme. Sites that treated at least one patient on the scheme will be identified and approached for permission to share investigator contact details with the study team to facilitate site set-up. Data will be collected at sites and uploaded in a pseudonymised format to a secure online platform (Medidata RAVE). Data will be cleaned, checked and analysed at the Southampton Clinical Trials Unit.

Data will be collected from initial diagnosis until death or last follow up at the time of data-lock. In addition to demographic and disease characteristics data, basic data will be collected on prior therapy for MZL including details of systemic therapies and response rates. Details of zanubrutinib treatment will be collected including start date, dosing (including delays and dose reductions), discontinuation reason. Efficacy and safety data will be collected including initial and best response, dates of progression, last follow-up and death, details of grade 3-5 adverse events (AEs) and grade 1-5 adverse events of special interest (AESI; cardiovascular toxicity and bleeding). Limited data on subsequent therapy will be collected.

No patient intervention is planned and data collection is expected to take 12 months.

5.3 End of study

The end of the study is defined as the date of completion of data analysis and publication.

6) STUDY PARTICIPANTS

6.1 Inclusion Criteria

1. Histologically confirmed MZL (any subtype)
2. Relapsed/refractory disease after at least one line of CD20-directed systemic therapy

3. Patient was treated with zanubrutinib on the BeiGene PRAP, for which the inclusion criteria were as follows (note that it is not necessary to reconfirm eligibility of each of the following points):
   a) ECOG PS = 0-2
   b) Patient is aged ⩾18 years
   c) Patient's disease is serious or life threatening
   d) All other alternative therapies have been exhausted
   e) There is no alternative chemotherapeutic option
   f) A rechallenge with a prior treatment not possible
   g) There is a strong rationale that the patient may benefit from the treatment with zanubrutinib
   h) Efficacy and safety data for zanubrutinib is available and of sufficient strength to assess whether likely benefits outweigh potential risks for the patient
   i) Clinical data in similar patients available
   j) A clinical study is not available, either because the patient is ineligible or because there is no access to a trial
   k) The patient cannot be enrolled in an existing expanded access cohort program
   l) Patient does not have access to ibrutinib, or ibrutinib is contraindicated
   m) Patient does not have access to acalabrutinib, or acalabrutinib is contraindicated.
   n) Female patients of childbearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception in combination throughout the period of taking Zanubrutinib and for at least 1 month after last dose. Male patients must use a condom during treatment and for 3 months after the last dose when having sexual intercourse with a pregnant woman or with a woman of childbearing potential
   o) The patient is not under active treatment for another hemato-oncological or oncological disease

6.2 Exclusion Criteria

1. A significant proportion of MZL treatment data is unavailable for collection
2. Excluded from the BeiGene zanubrutinib PRAP due to one or more of the following criteria:
   a) The patient is actively participating in a clinical trial
   b) If female, the patient is pregnant or breast feeding
   c) Patient has clinically significant cardiovascular disease (e.g., unstable angina, New York Heart Association (NYHA) class II or IV congestive heart failure, clinically significant arrhythmias (e.g., sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
   d) Patient has a history of bleeding disorder, stroke or intracranial haemorrhage within the last 180 days
   e) Patient has severe pulmonary disease, active infection requiring systemic therapy
   f) Patient has known central nervous system involvement by leukaemia? or lymphoma
   g) Patient has known infection with HIV or hepatitis B or C, moderate or severe hepatic impairment

h) Patient has ongoing need for systemic corticosteroid other than systemic adrenal replacement therapy
i) Patient has had ongoing alcohol or drug addiction
j) Patient requires treatment with a strong CYP3A inhibitor or inducer

6.3 Recruitment

Investigators at participating sites will identify suitable patients from hospital records. Identifiable personal information (name, date of birth, hospital or NHS number) will only be accessible to site staff. Eligible subjects will be assigned a unique study number by Medidata RAVE for pseudonymised data collection by the direct clinical team onto the study database. No identifiable personal information will be stored on the study database or provided to any person outside of the patient's existing clinical care team. Explicit patient consent is not required for this study as the research is limited to the use of pseudonymised data, in line with the Information Commissioners Office (ICO) guidance document - Anonymisation: managing data protection risk code of practice.

7) OUTCOME MEASURES

Primary outcome:

- Progression free survival (PFS) - defined as time in months from the first dose of zanubrutinib to disease progression or death from any cause. Patients who do not progress or die will be censored at their date of last clinical follow up.

Secondary outcome measures:

- Best overall & complete response rates
- PET assessed overall & complete response rates (if available)
- Duration of response (DoR) – defined as time from first PR or CR to disease progression or death from any cause. Patients who do not progress or die will be censored at their date of last clinical follow up.
- Duration of complete response (DoCR) - defined as time from first CR to disease progression or death from any cause. Patients who do not progress or die will be censored at their date of last clinical follow up.
- Time to next treatment (TTNT) - defined as time from the start of zanubrutinib to the start of any new anti-lymphoma therapy (NALT), including radiotherapy but excluding corticosteroids or other supportive care, or death date whichever is earliest. Patients who do not start another NALT or die will be censored at their date of last clinical follow up.
- Overall survival (OS) – defined as time in months from first dose of zanubrutinib to death from any cause. Patients who do not die will be censored at their last known alive date.

- Rate of grade 3-5 adverse events graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), and coded using Medical Dictionary for Regulatory Activities terminology (MEDRA v24)
- Rates of grade 1-5 adverse events of special interest (neutropenia, infections, bleeding, cardiovascular toxicity including arrythmias, hypertension, second primary malignancies including skin cancer)
- Zanubrutinib treatment delivery including duration and frequency of Zanubrutinib (once daily versus twice daily), dose delays and reductions and reason for discontinuation.

8) DATA COLLECTION, SOURCE DATA AND CONFIDENTIALITY

Southampton Clinical Trials Unit will be responsible for data management. Pseudonymised patient data will be entered onto an electronic data capture tool, Medidata RAVE (Rave Electronic Data Capture (EDC) System | Medidata Solutions [medidata.com]), a system familiar to most sites and used by pharmaceutical companies for many trials. Sites will access the system directly and will be able to add and edit their own data, in accordance with the current Data Protection Regulations.

The participant data is pseudonymised by assigning each participant a unique identifier code which is used to identify the participant during the trial and for any participant-specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff. Personal data and the participant identifier code will be stored on NHS computers for 15 years to allow scope for updated analysis. Any updated analysis will be preceded by an ethical amendment to extend the study. After this time-point all personal data collected expressly for the purposes of this study will be deleted from NHS computers. No persons outside of the patients existing clinical care team will have access to identifiable patient information. The participant identifier code will be stored on secure NHS servers by the site staff. Only the direct clinical team (site staff) will have access to the key for their participants.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). eCRF completion guidelines will be provided to the investigator sites to aid data entry of participant information. Only the Investigator and personnel authorised by them should enter or change data in the eCRFs.

The system will be programmed to automatically flag to sites any missing data or common-sense mistakes / data queries within the system itself. The study statistician will also perform a number of checks on the data looking for dates which are inconsistent in order /data which don't make sense and other general consistency checks. These will then be added into Medidata RAVE and flagged automatically to sites for them to address directly in the system. A data coordinator will oversee these tasks and in turn be overseen by a data manager who will also be responsible for designing the Medidata RAVE system. Once answered, the data queries will be closed or re-raised within Medidata RAVE and resolved prior to data lock, download and analysis. Sites will be responsible for accuracy, completeness and timelines of data entered to the patient record.

There will be no source data verification performed for this study. The confidentiality of each participant will be guaranteed by the local study investigator, who will be a member of the participant's direct clinical team. This means that the clinical investigator must respect patient confidentiality concerning all data collected. Only the direct clinical care team will have access to the participant's medical records. These individuals are bound by professional secrecy and confidentiality agreements. None of these individuals will transfer participants name or other personal identifiers to anyone else. Participants personal data will be processed in the strictest confidentiality.

Pseudonymised data may be looked at by individuals from the Sponsor (University of Manchester), Southampton Clinical Trials Unit, regulatory authorities or from the NHS trust for monitoring and auditing purposes, however no one outside of the clinical care team will review patient identifiable information.

The pseudonymised data will only be analysed within the UK by authorised project researchers at the Sponsor site (University of Manchester) and the Southampton Clinical Trials Unit. Fully anonymised data may be shared with other researchers subject to conditions as described in section 15.

Southampton Clinical Trials Unit will be responsible for storing and archiving its copies of study data according to University of Southampton data policies for 15 years. Access to archived and pseudonymised data is controlled by a designated representative within the Southampton Clinical Trials Unit. All applicable Data Protection legislation will be abided by.

Adverse events (AEs)

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE): any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

AE Reporting Requirements

Adverse events experienced by the patient from the start of zanabrutinib up to 30 days after the last administration, of grade 3, 4 or 5 (per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0), should be recorded in the relevant eCRF and submitted to SCTU. Each AE must be recorded with the highest grade experienced. Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AE unless the conditions worsened during the zanabrutinib administration.

Please Note: As the study involves retrospective data collection SCTU will not need to notify REC or the MHRA of any Suspected Unexpected Serious Adverse Events and will not be required to submit a Development Safety Update Report.

Adverse events of special interest (AESI)

An AESI is an AE of scientific and medical interest specific to understanding of the Investigational Medicinal Product. An AESI may be serious or non-serious. The database will be designed to identify adverse events of special interest.

AESI of ANY grade experienced by the patient from the start of zanabrutinib up to 30 days after the last administration should be recorded in the relevant eCRF and submitted to SCTU. Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AE unless the conditions worsened during the zanabrutinib administration. Any questions in relation to an event being an AESI should be referred to the SCTU.

Adverse events of special interest include:

- Neutropenia - including the terms “neutropenia” and “neutrophil count decreased.”
- Infections
- Bleeding including major haemorrhage defined as any serious or grade $\geqslant$3 bleed at any site, or central nervous system bleed of any grade
- Atrial fibrillation/flutter
- Ventricular arrhythmia (e.g. ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.)
- Hypertension
- Second primary malignancies including skin cancer

Grade to be assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

9) STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis

A detailed statistical analysis plan will be produced prior to analysis and brief details of the planned analyses are provided below. Reporting will follow STROBE guidelines.

Analysis populations

Efficacy analyses will be performed using the efficacy analysis set, defined as all patients enrolled in the study who received at least 1 dose of zanubrutinib and had a confirmed diagnosis of MZL.

Analyses on adverse event data will be performed using the safety analysis set, defined as all patients enrolled in the study who received at least 1 dose of Zanubrutinib.

Statistical Analyses

Time to event data (including primary endpoint PFS and secondary endpoints DoR, DoCR, TTNT and OS) will be presented using Kaplan-Meier curves and median and 12 and 24 month event-free rates will be estimated from these together with 95% confidence intervals (CIs). Reverse Kaplan-Meier analyses will be used to determine follow-up times. A treatment policy approach will be used for all intercurrent events for these endpoints except for duration or response where disease assessment after the initiation of any new anti-lymphoma therapy will not be included.

The number and proportion of patients who have a complete response and overall response (CR or PR) will be summarised together with a Clopper-Pearson exact 95% confidence interval for the proportion. Response will be assessed regardless of the following inter-current event, premature discontinuation of any component of study treatment. Disease assessment after the initiation of any new anti-lymphoma therapy will not be included. Complete and overall response rates by PET scan will also be summarised in the same way for patients who have this information available.

The median duration of Zanubrutinib treatment patients received and median number of cycles will be summarised together with the inter-quartile range. Reasons for discontinuation of Zanubrutinib, dose delays and reductions will be summarised using frequency counts and percentages.

Summary statistics will be used to describe adverse events and adverse events of special interest for patients in the safety population by MEDRA preferred term and CTCAE grade.

Descriptive statistics will be used to summarise patient characteristics at baseline and other data. For continuous variables, number of observations, means, standard deviations, medians, inter-quartile ranges and ranges will be used. For categorical variables, frequency counts will be summarised with percentages.

Analyses of best overall and complete response and progression free survival will be performed by the following subgroups: sex; age group; ECOG performance status; number of prior lines of systemic therapy (<3, >=3); time since last anti-lymphoma therapy (<=2, >2 years); baseline extranodal disease; relapsed/refractory to last treatment; prior treatment; bulky disease; baseline LDH elevation; bone marrow involvement; MZL subtype and disease stage. Analyses of outcomes and safety data by treatment frequency and duration will be presented.

9.2 Sample Size

The study aims to include all patients who accessed BeiGene's Pre-reimbursement Access Programme for Zanubrutinib between January 2022 - July 2024. This is anticipated to be approximately 160 patients. The main analyses for the study will be descriptive therefore no power calculations are required.

10) MONITORING AND QUALITY ASSURANCE

Sites will be responsible for the accuracy of data.

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data queries will be raised by the SCTU on the trial database for resolution by site. Sites will respond to the queries on the trial database providing an explanation/resolution to the discrepancies within the required timeframe. There are a number of monitoring principles in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan. There will be no source data verification so as to preserve the anonymity of the patients.

The trial may be subject to inspection and audit by University of Manchester (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group (TMG).

The TMG is responsible for overseeing progress of the trial, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the trial. The TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

11) PEER REVIEW

The proposal has been reviewed by the UK Low grade lymphoma Group of multidisciplinary experts in the field. In addition, the scientific quality of the research and proposal has been assessed within the Chief Investigator's institution (University of Manchester), within the company (BeiGene), and within the research team.

12) ETHICAL and REGULATORY CONSIDERATIONS

12.1 Approvals

Approval for this study will be sought from the University of Manchester Research Ethics Committee and Health Research Authority as well as the R and D Departments of all relevant NHS Trusts before commencing this research. The study will be conducted according to relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

12.2 Risks

The study is a retrospective non-interventional, observational study and so does not pose any significant ethical, legal or risk issues to participants or researchers.

13) STATEMENT OF INDEMNITY

The University of Manchester has insurance for research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students, subject to policy terms and conditions. The CI is acting in their capacity as a University of Manchester staff member

14) FUNDING and RESOURCES

Funding for the study is provided by BeiGene Ltd.

15) PUBLICATION POLICY

The results of the study will be published in peer review journal and presented at relevant conferences. Results will also be disseminated through patient lymphoma organisations and charities to inform the wider lymphoma community. Study investigators will be acknowledged on all presentations and publications arising from this study.

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the study. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

In order to meet the ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. At a minimum,

anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in the data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

16) REFERENCES

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