A RANDOMIZED PHASE 3 TRIAL OF CONTINUOUS VS. INTERMITTENT MAINTENANCE THERAPY WITH ZANUBRUTINIB AS UPFRONT TREATMENT IN OLDER PATIENTS WITH MANTLE CELL LYMPHOMA

Eligibility Criteria (see Section 3.2)

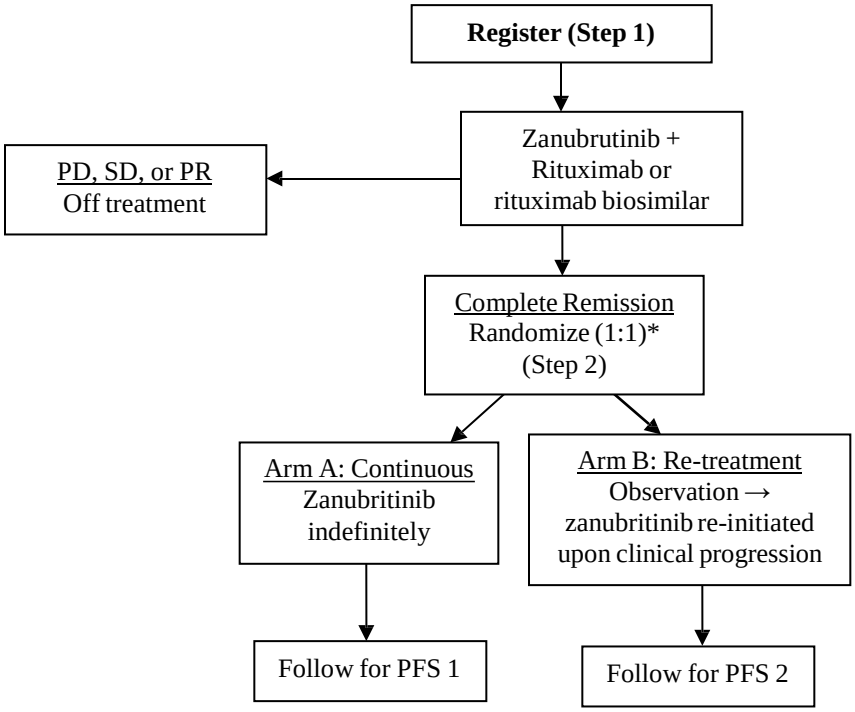
- Histologically confirmed mantle cell lymphoma (see Section 3.2.1)
- Presence of measurable disease (see Section 3.2.2)
- No prior systemic treatment for mantle cell lymphoma
- No prior exposure to a BTK inhibitor or anti CD-20 monoclonal antibody
- No prior stem cell transplant
- Not pregnant and not nursing
- Age ≥ 70 years OR age ≥ 60 to < 70 years with comorbidities precluding autoSCT (see Section 3.2.4)
- ECOG Performance Status 0-2
- No clinically significant cardiovascular disease (see Section 3.2.9)
- No history of severe bleeding disorder (see Section 3.2.7)
- No history of stroke or intracranial hemorrhage within 6 months prior to registration

Required Initial Laboratory Values

ANC	≥ 750/mm^3
Platelet count:	≥ 75,000/mm^3 (or ≥ 50,000/mm^3 for patients with bone marrow involvement of lymphoma)
Creatinine clearance*:	≥ 30 mL/min
Total bilirubin:	≤ 1.5 x ULN (unless documented Gilbert's syndrome)
AST/ALT:	≤ 3 x ULN

**Determined by either: a) estimation using the Cockcroft-Gault equation or b) measurement by nuclear medicine scan or 24 hour urine collection*

Schema



* Patients will be stratified by age (60-69 years vs. ≥70 years) and MCL IPI score (low, intermediate, or high)

Treatment is to continue until disease progression or unacceptable adverse event. Patients will be followed for 10 years or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

3.1 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.2 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Clinicians should consider whether any conditions would make this protocol unreasonably hazardous for the patient.
- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.3 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.2.1 Documentation of Disease

Histologic Documentation: Histologically confirmed mantle cell lymphoma with cyclin D1 (BCL1) expression by immunohistochemical stains and/or t(11;14) by cytogenetics or FISH as confirmed by the enrolling center.

Stage: Any stage allowed (stage I-IV)

3.2.2 Measurable disease as defined in Section 11.0.

Presence of measurable disease, defined as ≥ 1 nodal lesion that is > 1.5 cm in longest diameter or ≥ 1 extranodal lesion that is > 1 cm in longest diameter

3.2.3 Prior Treatment

- Steroids for management of mantle cell lymphoma are allowed up to a dose of prednisone 100mg/day (or equivalent) for up to 7 days.
- No prior systemic treatment for mantle cell lymphoma.
- No prior radiation treatment for stage I MCL
- No prior exposure to a BTK inhibitor or anti-CD20 monoclonal antibody
- No prior stem cell transplant

3.2.4 Age ≥ 70 years OR age ≥ 60 to < 70 years with comorbidities precluding autoSCT including at least one of the following: a) cardiac EF ≤45%, b) diffusing capacity for carbon monoxide ≤60% predicted; c) creatinine clearance <70 but ≥30ml/min; d)Eastern Cooperative Oncology Group (ECOG) performance status of 2, which poses an unacceptable risk of toxicity for high-dose therapy and stem cell transplantation; or e) Cumulative Illness Rating Scales (CIRS) total score >6 (see Appendix IV) [13].

3.2.5 ECOG Performance Status 0-2 (Appendix II)

3.2.6 Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 750/mm^3 (without growth factor support within 7 days)
Platelet Count	≥ 75,000/mm^3 (or ≥ 50,000/mm^3 for patients with bone marrow involvement of lymphoma) without growth factor support or transfusion within 7 days
Creatinine Clearance	≥ 30 mL/ min determined by either: a) Estimation using the Cockcroft-Gault equation (see Appendix I) or b) Measurement by nuclear medicine scan or 24 hour urine collection
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN) (unless documented Gilbert's syndrome)
AST / ALT	≤ 3 x ULN

3.2.7 Comorbid conditions

- Patients should not be considered candidates for stem cell transplant or must have declined a stem cell transplant strategy
- No clinically significant cardiovascular disease including the following:

  a. Unstable angina within 3 months before registration

  b. New York Heart Association class III or IV congestive heart failure (see Appendix III)

  c. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)

  d. QTcF > 480 msecs based on Fredericia's formula

  e. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
- HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- No active Hepatitis B or Hepatitis C infection. Patients with prior HBV exposure (positive HBV core antibody and/or surface antigen) are eligible if they have no detectable viral load, and are taking appropriate prophylactic antiviral therapy to prevent reactivation. Patients with history of HCV are eligible if they have an undetectable HCV viral load.
- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
- No history of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
- No history of stroke or intracranial hemorrhage within 6 months prior to registration
- No disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. Patient must be able to swallow pills.
- Potential trial participants should have recovered from major surgery
- No vaccination with a live vaccine within 35 days prior to registration
- No hypersensitivity to zanubrutinib or rituximab or any of the other ingredients of the study drugs

3.2.8 Concomitant medications

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study. See Section 8.1 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days prior to the start of study treatment. See Section 8.1 for more information.

Avoid use of moderate CYP3A4 inhibitors, PGP inhibitors, and moderate CYP3A4 inducers

___ **3.2.9** Archival tissue must be available for submission in all patients for histopathology review, though participation in correlative substudies is optional.