

FAST FACTS

EA4181 - A Randomized 3-Arm Phase II Study Comparing 1.) Bendamustine, Rituximab and High Dose Cytarabine (BR/CR) 2.) Bendamustine, ituximab, High Dose Cytarabine and Acalabrutinib (BR/CR-A), and 3.) Bendamustine, Rituximab and Acalabrutinib (BR-A) in Patients ≤ 70 years old with Untreated Mantle Cell Lymphoma

Eligibility Criteria

1. Baseline measurements and must be obtained within 42 days prior to randomization to the study. Abnormal PET or CT scans may constitute evaluable disease. Patient must have at least one objective measurable disease parameter. Per Section 6.1, measured dominant lesions are defined as nodes, nodal masses, and extranodal lesions that are clearly measurable in two diameters.. Measurable disease in the liver is required if the liver is the only site of lymphoma.
2. MIPI score must be calculated and entered in OPEN.

MIPI calculator must be accessed using the website provided below:

https://qxmd.com/calculate/calculator_149/mipi-mantle-cell-lymphoma-prognosis

NOTE: For this calculation, $WBC\ 7,500/mm^3 = 7,500/\mu L = 7.5 \times 10^3/\mu L = 7.5 \times 10^9/L = 7.5 / K\ cumm$ **should be entered as 7.5.**

3. Patient must be age ≥ 18 years and ≤ 70 years of age.
4. Patient must have an ECOG Performance Status score of 0-2.
5. Patient must have untreated 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. The diagnosis must be confirmed by formal hematopathology review at the enrolling center.
6. Patients being treated with gastric reducing agent proton pump inhibitors must be switched to an alternative drug before starting acalabrutinib.
7. Patient must have adequate organ and marrow function, as defined below, obtained within 14 days of randomization:
 - Absolute neutrophil count (ANC) $\geq 1,000/mcL$
ANC: _____ Date of test: _____
 - Platelets $\geq 75,000/mcL$
Platelets: _____ Date of test: _____
 - If disease includes marrow involvement or hypersplenism, please reference the below revised ANC and platelet requirements:
ANC $\geq 500/mcL$
Platelets $\geq 25,000/mcL$
 - Total bilirubin $\leq 2 \times$ institutional upper limit of normal (ULN)
Bilirubin: _____ Date of test: _____
Institutional ULN (bilirubin): _____
 - Aspartate aminotransferase (AST) and alanine transaminase (ALT) $\leq 2.5 \times$ institutional ULN
AST: _____ Date of Test: _____
Institutional ULN (AST): _____
ALT: _____ Date of Test: _____

Institutional ULN (ALT): _____

- If disease includes hepatic infiltration or is causing biliary obstruction, or if elevated bilirubin is due to Gilbert's disease, please reference the below revised bilirubin and AST/ALT requirements:

Bilirubin \leq 3 x institutional ULN

AST/ALT \leq 5 x institutional ULN

- PT/INR and aPTT (in the absence of lupus anticoagulant) $<$ 2x institutional ULN

PT/INR: _____ Date of Test: _____

Institutional ULN (PT/INR): _____

aPTT: _____ Date of Test: _____

Institutional ULN (aPTT): _____

- Patients receiving anticoagulant therapy (other than warfarin or equivalent Vitamin K antagonists which are excluded), higher INR/aPTT may be permitted to enroll to this study after discussion with the Study Chair and discussion must be uploaded and documented on the baseline forms within Medidata Rave
- Creatinine \leq institutional ULN, OR glomerular filtration rate (GFR) \geq 40 mL/min/1.73 m² (see Appendix VIII).

Creatinine Clearance: _____ Date of test: _____

Creatinine: _____ Institutional ULN: _____

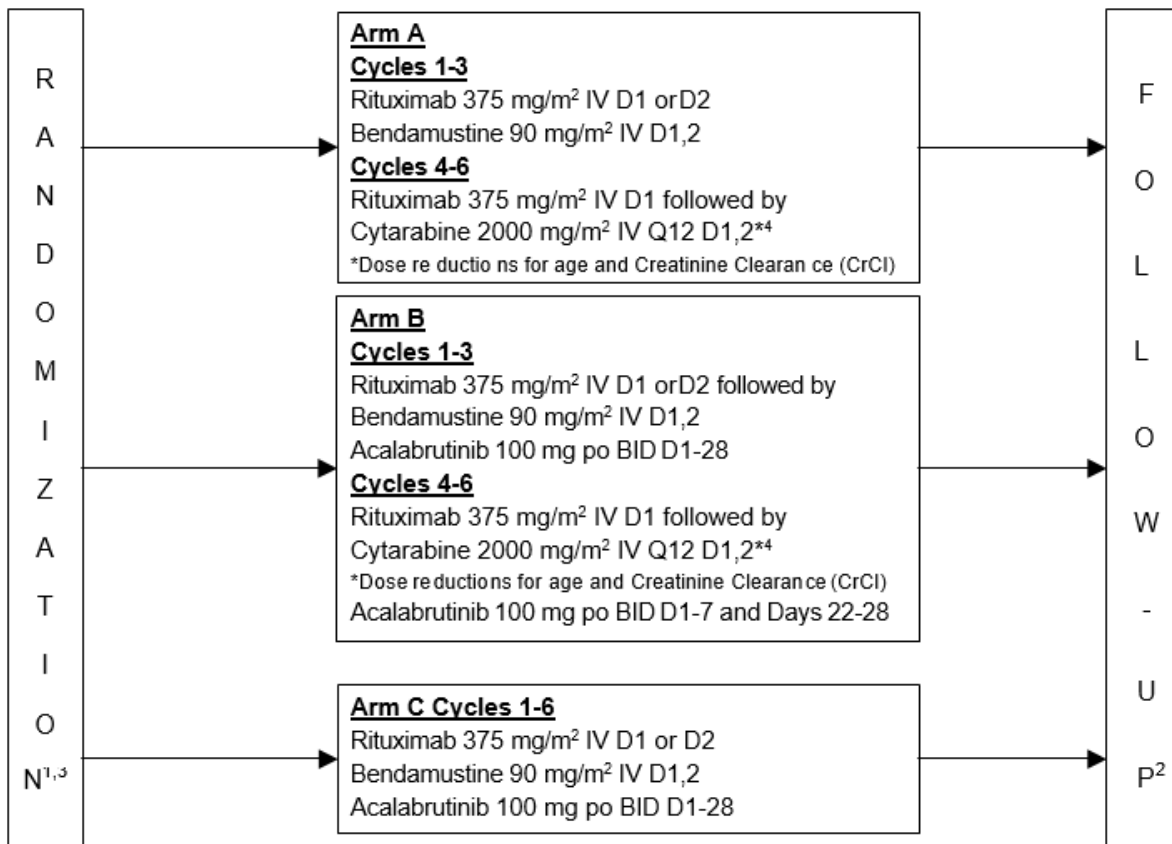
Date of Test: _____

- Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- For patient with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Per the CDC, chronic is defined as (+)HepBsag, (+)HepBcab, (-)IgM Hepbcab, and (-)HepBsab.
- Patient with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
- Patient 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.
- Patient with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
- Women must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used. Patients must also not expect to conceive or father children from the time of randomization, while on study treatment, and until 12 months after the last dose of study treatment. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy. A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
 - Female of child bearing potential? _____ (Yes or No)
 - Date of blood test or urine study: _____

14. Women of childbearing potential and sexually active males must agree to use accepted and effective method(s) of contraception or to abstain from sexual intercourse for the duration of their participation in the study and for 12 months after treatment ends.
15. Patient is not eligible if he/she requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor. For additional information regarding strong inhibitors and use of moderate CYP3A4/5 inhibitors see [Appendix V](#).
16. Patient may not have received the following within 7 days prior to the first dose of study drug:
 - Strong and Moderate CYP3A inhibitors (see Appendix V for details)
 - Strong and Moderate CYP3A inducers (see Appendix V for details)
17. Patient is are ineligible if they have any of the following:
 - Malabsorption syndrome or disease significantly affecting gastrointestinal function.
 - Active bleeding or history of bleeding diathesis (e.g. hemophilia or von Willebrand disease).
 - Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenia purpura).
 - Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon) within 7 days prior to first dose of study drug.
 - History of significant cerebrovascular disease/event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug.
 - Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infections at study enrollment (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
 - History of severe allergic reaction attributed to compounds of similar chemical or biologic composition to rituximab, bendamustine, cytarabine, or acalabrutinib.
18. Patient must be able to fulfill one of the following eligibility requirements pertaining to biospecimen availability for submission following randomization as outlined in Section 10.1:
 - Archived formalin-fixed paraffin-embedded (FFPE) tumor tissue specimen from the original diagnostic biopsy (i.e. LN, BM Bx, etc.) is available for submission
OR
 - If tumor tissue is not available and patient has circulating mantle cells in the peripheral blood, then peripheral blood collected prior to initiation of protocol therapy may be submitted

NOTE: Biospecimens must be submitted within 60 days following randomization to Adaptive Biotechnologies for ClonoSEQ® ID molecular marker identification of unique clonal immunoglobulin DNA sequence. If peripheral blood will be submitted, Adaptive Biotechnologies should be contacted prior to patient randomization for guidance pertaining to collection and submission requirements.

Schema



1 Cycle= 28 days

Accrual Goal: 369

1. Stratify using the MIPI risk score: high vs. intermediate vs. low. Diagnostic FFPE tumor tissue (or involved bone marrow) must be sent to Adaptive within 60 days of enrollment.
2. Patients will be followed per Section 5.5. MRD will be assessed 3-8 weeks after completion of study treatment and specimen submissions should follow guidelines in Section 7.2.
3. Randomization will occur 1:1:1 between Arms A, B, and C.
4. If treatment initiation is urgent and acalabrutinib is not available for cycle 1, treatment with bendamustine and rituximab may begin up to 4 days prior to acalabrutinib start.