Patient Population

- Age ≥ 18 and ≤ 70; ECOG PS 0-2; adequate lab values
- Baseline evaluations must be obtained within 6 weeks of randomization; abnormal PET/CT scans may constitute evaluable disease; patients must have at least 1 objective measurable disease parameter (see protocol re: liver)
- MIPI score: calculated and entered in OPEN per protocol
- Must have untreated histologically confirmed mantle cell lymphoma, with cyclin D1 (BCL1) expression by immunohistochemical stains and/or t(11;14) by cytogenetics/FISH; the diagnosis must be confirmed by formal hematopathology review at the enrolling center
- Patients being treated with gastric reducing agents proton pump inhibitors must be switched to an alternative drug before starting acalabrutinib
- Patients with HIV/HBV/HCV are permitted per protocol
- Patients with known history/current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the NYHA Functional Classification; to be eligible for this trial, patients should be class 2B or better
- Patients are not eligible if they require treatment with a strong cytochrome P450 (CYP) 3A inhibitor; may not have received strong/moderate CYP3A inhibitors/inducers within 7 days prior to the first dose of study drug
- No patients with malabsorption syndrome/disease significantly affecting GI function, active bleeding/history of bleeding diathesis, uncontrolled AIHA/ITP, history of significant cerebrovascular disease/event within 6 months of the first dose of study drug, known active infections (per protocol) at study enrollment, history of severe allergic reaction attributed to compounds of similar chemical/biologic composition to study drugs
- No warfarin/Equivalent vitamin K antagonists with 7 days of first dose of study drug
- Able to provide FFPE tumor tissue/peripheral blood

Treatment Plan

Cycle= 28 days

Arm A:
- Cycles 1, 2, 3: Rituximab 375 mg/m² IV Day 1 or 2; Bendamustine 90 mg/m² IV Day 1, 2
- Cycles 4, 5, 6: Rituximab 375 mg/m² IV Day 1 followed by Cytarabine 2000 mg/m² IV Q12 hours Day 1, 2 (for age 60-70 years: 1500 mg/m² IV Q12 hours days 1 and 2, starting dose)

Arm B:
- Cycles 1, 2, 3: Rituximab 375 mg/m² IV Day 1 or 2; Bendamustine 90 mg/m² IV Day 1, 2; Acalabrutinib 100 mg orally twice daily days 1-28
- Cycles 4, 5, 6: Rituximab 375 mg/m² IV Day 1 followed by Cytarabine 2000 mg/m² IV Q12 hours Day 1, 2 (for age 60-70 years: 1500 mg/m² IV Q12 hours days 1 and 2, starting dose); Acalabrutinib 100 mg orally twice daily days 1-7 and days 22-28

Arm C:
- Cycles 1-6: Rituximab 375 mg/m² IV Day 1 or 2; Bendamustine 90 mg/m² IV Day 1, 2; Acalabrutinib 100 mg orally twice daily on days 1-28

Notes:
- Doses are based on actual body weight
- Rituximab/bendamustine/cytarabine administration is per institutional standard of care
- Acalabrutinib should be taken whole with water, with/without food. If a dose is missed by more than 3 hours, acalabrutinib should be skipped and the next dose taken at the regular scheduled time
- For cycle 1, rituximab can be split over 2 days and/or delayed per investigator discretion up to day 3
- See protocol for criteria for initiating a new course of treatment (on scheduled day 1 of a new cycle)
A Randomized 3-Arm Phase II Study Comparing 1.) Bendamustine, Rituximab, and High Dose Cytarabine (BR/CR) 2.) Bendamustine, Rituximab, 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

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 enrolment.
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.