For Patients with Mantle Cell Lymphoma

EA4181 Available Through ECOG-ACRIN Cancer Research Group
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

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**Cycle= 28 days; doses based on actual body weight**

**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 66-70 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 66-70 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:**
- Rituxan Hycela 1400 mg/23,400 UNITS SQ/ any approved biosimilar at the approved dose can be used instead of rituximab
- Cytarabine may be given on day 2 or 3 if rituximab is given as outpatient on day 1
- Rituximab/bendamustine/cytarabine administration is per institutional standard of care (see protocol for details)
- 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
- See protocol for criteria for initiating a new course of treatment (on scheduled day 1 of a new cycle)

**Patient Enrollment**
All Sites: Oncology Patient Enrollment Network (OPEN) https://open.ctsu.org

**Protocol Information**

Please Enroll Your Eligible Patients!
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Schema

Arm A
- Cycles 1-3
  - Rituximab 375 mg/m² IV D1 or D2 or rituxan hyceia 1400 mg/23,400 units SQ for cycles 2-6
  - Bendamustine 90 mg/m² IV D1,2

- Cycles 4-6
  - Rituximab 375 mg/m² IV D1 or rituxan hyceia 1400 mg/23,400 units SQ for cycles 2-6 followed by Cytarabine 2000 mg/m² IV Q12 D1,2
  - *Dose reductions for age and Creatinine Clearance (CrCl)

Arm B
- Cycles 1-3
  - Rituximab 375 mg/m² IV D1 or D2 or rituxan hyceia 1400 mg/23,400 units SQ for cycles 2-6 followed by Bendamustine 90 mg/m² IV D1,2
  - Acalabrutinib 100 mg po BID D1-28

- Cycles 4-6
  - Rituximab 375 mg/m² IV D1 or rituxan hyceia 1400 mg/23,400 units SQ for cycles 2-6 followed by Cytarabine 2000 mg/m² IV Q12 D1,2
  - *Dose reductions for age and Creatinine Clearance (CrCl)
  - Acalabrutinib 100 mg po BID D1-7 and Days 22-28

Arm C
- Cycles 1-6
  - Rituximab 375 mg/m² IV D1 or D2 or rituxan hyceia 1400 mg/23,400 units SQ for cycles 2-6
  - Bendamustine 90 mg/m² IV D1,2
  - Acalabrutinib 100 mg po BID D1-28

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 cycle 6, d28 (+ 5 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.