Cancer Research Consortium of West Michigan
P: 616.391.1230 | www.crcwm.org



# Fast Facts

**CTSU E1411 - Intergroup Randomized Phase II Four Arm Study In Patients ≥ 60 With Previously Untreated Mantle Cell Lymphoma Of Therapy With:**
**Arm A = Rituximab + Bendamustine Followed By Rituximab Consolidation (RB → R);**
**Arm B = Rituximab + Bendamustine + Bortezomib Followed By Rituximab Consolidation (RBV→ R),**
**Arm C = Rituximab + Bendamustine Followed By Lenalidomide + Rituximab Consolidation (RB → LR) or**
**Arm D = Rituximab + Bendamustine + Bortezomib Followed By Lenalidomide + Rituximab Consolidation (RBV → LR)**

**Patient must sign consent before the collection of bone marrow.**
Bortezomib and Lenolidomide provided

**Step 1 Registration:**

1. MIPI score must be calculated and entered in OPEN (see section 4.1.5.1) ***NOTE:*** For this calculation WBC 7,500/mm3 = 7,500/uL = 7.5 x 10^9/L should be entered as 7500.
2. Age ≥ 18 years
3. Female of childbearing potential must not be pregnant or breast-feeding due to the risk of fetal harm by the chemotherapeutic agents prescribed in this protocol. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

   A female of childbearing potential (FCBP) is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie has had menses at any time in the preceding 24 consecutive months).
4. Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception.
5. Patients must have measurable disease as defined in Section 6.
6. Histologically confirmed untreated mantle cell lymphoma, with documented cyclin D1 (BCL1) by immunohistochemical stains and/or t(11;14) by cytogenetics or FISH
7. Patients must have at least one objective measurable disease parameter. Baseline measurement and evaluations must be obtained within 4 weeks of registration to the study. Abnormal PET scans will not constitute evaluable disease unless verified by CT scan or other appropriate imaging. Measurable disease in the liver is required if the liver is the only site of lymphoma.
8. ECOG performance status between 0-2.
9. Hematologic parameters (unless due to bone marrow involvement) obtained within 4 weeks prior to registration
   a. ANC ≥ 1500/mm3 ($1.5 \times 10^9$/L)
   b. Platelets ≥ 100,000/mm3 ($100 \times 10^9$/L)
10. Liver/Renal function, obtained within 4 weeks prior to registration
    a. AST/ALT ≤ 2 x upper limit of normal (ULN)
    b. Total Bilirubin ≤ 2 x upper limit of normal (ULN) or, if total elevated, direct bilirubin ≤ 2 x upper limit of normal (ULN)
    c. Calculated creatinine clearance by Cockroft-Gault formula ≥ 30mL/min
11. No evidence of prior malignancy except: adequately treated non-melanoma skin cancer, adequately treated in situ carcinoma, low grade prostate carcinoma (Gleason grade ≤ 6) managed with observation that has been stable for at least 6 months, or any malignancy treated with curative intent continuously disease free for ≥ 3 years so as not to interfere with interpretation of radiographic response.

12. No prior therapy for MCL, except: < 2 weeks of steroid therapy for symptom control or local radiation therapy for symptom control if there is measurable disease outside the radiation portal. Patients may be on chronic steroids for non-malignant disease if on a stable dose equivalent to ≤ 20mg prednisone per day.
13. Patient must have no known CNS involvement.
14. Patient agrees that if randomized to Arms C or D, and proceeding onto Arms G or H, they must register into the mandatory RevAssist program, and be willing and able to comply with the requirements of RevAssist.
    Patients must have no medical contra-indications to, and be willing to take, DVT prophylaxis as all patients registering to the lenalidomide/rituximab Arms G and H will be required to have deep vein thrombosis (DVT) prophylaxis. Patients randomized to Arms G or H who have a history of a thrombolic vascular event will be required to have therapeutic doses of low molecular weight heparin or warfarin to maintain an INR between 2.0 – 3.0. Patients on Arms G and H without a history of a thromboembolic event are required to take a daily aspirin (81 or 325 mg) for DVT prophylaxis. Patients who are unable to tolerate aspirin should receive low molecular weight heparin therapy or warfarin treatment.
    Ways to minimize risk of DVT should be discussed with patients, including, but not limited to, avoiding smoking, minimizing pro-thrombotic hormone replacement, avoiding prolonged periods of inactivity (eg uninterrupted long car or plane trips).
15. HIV positive patients are <u>not</u> excluded, but to enroll, must meet <u>all</u> of the below criteria:
    a. HIV sensitive to antiretroviral therapy
    b. Must be willing to take effective antiretroviral therapy if indicated
    c. CD4 count at screening ≥ 300 cells/$mm^3$.
    d. No history of AIDS-defining conditions.
    e. If on antiretroviral therapy, must not be taking zidovudine or stavudine.

    Must be willing to take prophylaxis for Pneumocystis jiroveci pneumonia (PCP) during therapy and until at least 2 months following the completion of therapy or until CD4 cells recover to over 250 cells /$mm^3$ whichever occurs later.
16. Patients must not have grade 2 or greater peripheral neuropathy.
17. Patients must not have hypersensitivity to bortezomib, boron, or mannitol.
18. Patients must not have a serious medical or psychiatric illness likely to interfere with study participation.
19. Patients must not be participating in any other therapeutic clinical trial or taking any other experimental medications with 14 days prior to registration.

**Step 2 Registration**

1. ECOG performance status between 0-2
2. CR, PR or SD after Step 1.
3. Prior to beginning consolidation, patients must meet the following criteria:

Hematologic parameters:

a) ANC ≥ 1000 cells/mm3 (1.0 x 109/L)
b) Platelets ≥ 75,000 cells/mm3 (75 x 109/L)
c) AST/ALT ≤ 2 x upper limit of normal (ULN)
d) Total bilirubin ≤ 2 x upper limit of normal (ULN) or, if total elevated, direct bilirubin ≤ 2 x upper limit of normal (ULN)
e) Calculated creatinine clearance by Cockroft-Gault formula ≥ 30 ml/min

4. Patient agrees that if randomized to Arms C or D, and proceeding onto Arms G or H, they must register into the mandatory RevAssist program, and be willing and able to comply with the requirements of RevAssist.
   a) Pregnancy tests must occur within 10 - 14 days and again within 24 hours prior to initiation of Cycle 1 of lenalidomide. *Females of childbearing potential (FCBP)* with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on lenalidomide therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on lenalidomide therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

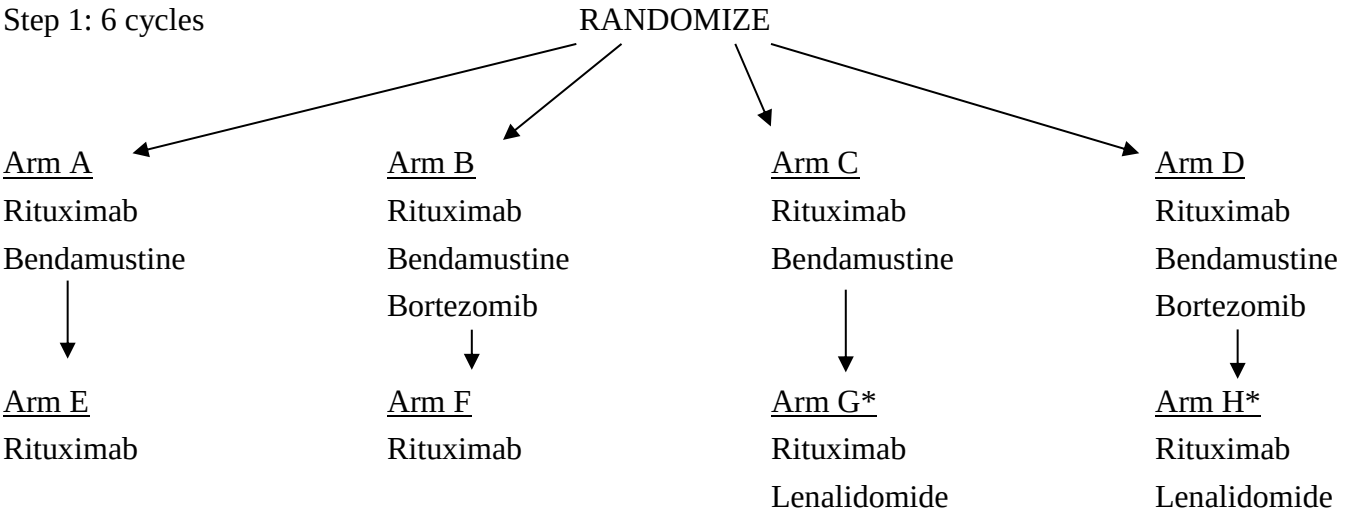
      *Females of childbearing potential (FCBP)* must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 - 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix XIV: Lenalidomide Information Sheet.

      *A female of childbearing potential is any sexually mature female, regardless of sexual orientation of whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) 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).
   b) Females of childbearing potential (FCBP) must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study/lenaliomide: 1) for at least 28 days before starting lenalidomide; 2) while participating in the study including interruptions in therapy; and 3) for at least 28 days after discontinuation/stopping lenalidomide. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.
   c) Women must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from protocol treatment.
   d) Males must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from protocol treatment. All males, regardless of whether they have undergone a successful vasectomy, must agree to use a latex condom during sexual contact with a female of childbearing potential, or to practice complete abstinence from heterosexual

intercourse with any female of childbearing potential during all cycles of study treatment and for at least 28 days following discontinuation of protocol treatment

e) Patients must have no medical contra-indications to, and be willing to take, DVT prophylaxis as all patients registering to the lenalidomide/rituximab Arms G and H will be required to have deep vein thrombosis (DVT) prophylaxis. Patients randomized to Arms G or H who have full anticoagulation, a history of a thrombotic vascular event will be required to have therapeutic doses of low molecular weight heparin or warfarin to maintain an INR between 2.0 – 3.0, or any other accepted full anticoagulation regimen (e.g. direct thrombin inhibitors or Factor Xa inhibitors) with appropriate monitoring for that agent. Patients on Arms G and H without a history of a thromboembolic event are required to take a daily aspirin (81 mg or 325 mg) for DVT prophylaxis. Patients who are unable to tolerate aspirin should receive low molecular weight heparin therapy or warfarin treatment or another accepted full anticoagulation regimen.

   Ways to minimize risk of DVT should be discussed with patients, including, but not limited to, avoiding smoking, minimizing pro-thrombotic hormone replacement, avoiding prolonged periods of inactivity (e.g. uninterrupted long car or plane trips).




**Pre-Study Parameters**

1. Assignment of MIPI scores
2. History and physical including performance status and tumor measurement by physical exam (if applicable)
3. Labs including CBC with differential, CMP including LDH, direct bilirubin if total bilirubin is high, β-2 microglobulin, uric acid, pregnancy test for WOCBP, TSH, Hepatitis B surface antigen and core antibody testing, CD4 and HIV viral load (HIV+ patients only)
4. Bone marrow aspirate biopsy (if baseline bone marrow is positive only by flow cytometry, aspirate and flow cytometry should be completed)
5. CT neck, chest, abdomen, pelvis; FDG-PET/CT